Can routine clinical measures predict ultrasound-determined synovitis and remission in rheumatoid arthritis patients?

T. Nemoto, M. Ogasawara, Y. Matsuki, G. Murayama, Y. Yamada, N. Sugisaki, S. Ando, K. Minowa, T. Kon, K. Tada, M. Matsushita, K. Yamaji, N. Tamura, Y. Takasaki

Department of Internal Medicine and Rheumatology, Juntendo University School of Medicine, Tokyo Japan.

Abstract

Objective

The purpose of this study was to determine if routine clinical measures can predict the presence and severity of ultrasound synovitis in rheumatoid arthritis (RA) patients.

Methods

Bilateral 1-5 MCP (metacarpopharangeal) and wrist joints were examined using power Doppler (PD) ultrasound (US). Correlations between PD scores and routine clinical measures of RA – swollen joint count (SJC), tender joint count, patient's global assessment (GA), physician's GA, CRP, ESR, MMP-3, RF and anti-CCP antibody – were determined and used to identify significant predictors of PD score. Clinical measures were then compared between two groups (patients with and without PD) and analysed using multiple logistic regression, to derive a model that predicted the absence of PD signals.

Results

SJC was the most significant predictor of PD score (R^2 = 0.4566, p-value <0.0001), but was an inadequate predictor of PD signal remission. However, the combination of Steinbrocker's stage I or II (odds ratio [OR] 9.23, p=0.0049), SJC=0 in 1–5 MCP and wrist joints on both sides (OR 6.60, p=0.0039), and SDAI (or CDAI) remission (OR 5.06, p=0.0450) had a positive predictive value of 100%, predicting the absence of PD signals in all study patients meeting the 3 criteria.

Conclusion

PD score and absence of PD signals can be predicted using routine clinical measures. When used in combination, Steinbrocker's stage, SJC and SDAI (or CDAI) can estimate disease activity and identify patients likely to have synovitis and requiring US.

Key words

rheumatoid arthritis, ultrasound, power Doppler

*Takuya Nemoto, MD**
*Michihiro Ogasawara, MD, PhD**
Yuko Matsuki, MD
Go Murayama, MD
Yusuke Yamada, MD
Nagachika Sugisaki, MD
Seiichiro Ando, MD, PhD
Kentaro Minowa, MD, PhD
Takayuki Kon, MD, PhD
Kurisu Tada, MD, PhD
Masakazu Matsushita, MD, PhD
Ken Yamaji, MD, PhD
Naoto Tamura, MD, PhD
Yoshinari Takasaki, MD, PhD

**These authors contributed equally to this study.*

Please address correspondence and reprint requests to:
Michihiro Ogasawara, MD, PhD,
Department of Internal Medicine and Rheumatology,
Juntendo University School of Medicine,
2-1-1 Hongo, Bunkyo-ku,
Tokyo 113-8421 Japan.
E-mail: miogasaw@juntendo.ac.jp

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Introduction

The goals of rheumatoid arthritis (RA) treatment are the reduction of clinical symptoms as well as improvement in activities of daily living and quality of life without bone destruction (1-3). To achieve these, early treatment, control of symptoms, as well as regular and precise monitoring of disease activity, are necessary (4-7). Disease activity score (DAS), simplified disease activity index (SDAI), and clinical disease activity index (CDAI) are common scales used, within the clinical setting, to rate disease activity (8-11). However, synovitis remains in a small percentage of patients that achieve remission based on the criteria defined by these indices (12-18).

The synovitis persisting in RA patients in clinical remission is referred to as subclinical (12-18). Since subclinical synovitis can result in bone erosion (19-24), its diagnosis and treatment are critical to the long-term health of RA patients, but diagnosis requires a combined approach involving both clinical assessment and ultrasound (US) (16, 25). Unfortunately, time constraints prohibit doctors from conducting US surveys of all RA patients during every visit. Therefore, there is a need to identify and select patients who require US.

Current indices for RA-SDAI, CDAI, and DAS use composite measures and were not designed to rate the degree of synovitis (8-11). This is one possible reason for the discrepancy between clinical and US-determined synovitis. We tried to determine whether these traditional indices, SDAI, CDAI, and DAS are the best predictors of power Doppler (PD) signals, or if other traditional clinical measures may serve as more accurate predictors. We hypothesised that if clinical measures can function as predictors of PD signals, we could use these measures to select patients requiring US and improve the diagnosis of synovitis in situations where access to US is limited.

The objective of this study was to identify clinical variables (risk factors) that predict the presence and severity of synovitis, as determined by the degree or absence of PD signals.

Methods

The study consisted of 92 RA patients (75 women and 17 men) between the ages of 22 and 81, who presented at Juntendo University Hospital between August and December 2011 and received stable treatment for at least 4 weeks (Table I). Diagnosis was based on 1987 criteria (26) or new ACR/EULAR criteria (27). The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board at Juntendo University. Informed consent was obtained from the participants. Physical and complete blood examinations were performed on all patients.

These were followed by US examination (ProSound Alpha7 with UST-5411, 10-13 MHz transducer; Hitachi Aloka Medical Ltd., Tokyo, Japan) by 2 well-experienced rheumatologists (T.N, and M.O) with consensus, who were blinded to the physical findings. The US examination was carried out in a darkened room. In total, 1104 joints (both wrists; dorsal carpal recesses; and 1–5 Metacarpopharangeal, MCP; dorsal and palmar recesses) were examined using US. Synovial effusion and/or hypertrophy was defined as abnormal hypoechoic material within joint recesses and graded on a semi-quantitative grey scale (GS) from 0 to 3 (where 0 = absence, 1 = mild, 2 = moderate, and 3 = marked) (28-31) . Synovial blood flow was evaluated by PDUS in each of the intraarticular synovial sites. PD signal parameters were adjusted to the lowest permissible pulse repetition frequency to maximise sensitivity. The intraarticular PD signals were graded on a semi-quantitative scale from 0 to 3 (where 0 = absence, no synovial flow/no signal; 1 = mild, ≤3 isolated signals; 2 = moderate, >3 isolated signals or confluent signal in less than half of the synovial area; and 3 = marked, signals in more than half of the synovial area) (28-31). PD scores represented the sum of PD grades, from 12 joint sites, in each patient.

Candidate predictors of synovitis (PD signals) included the presence of swollen and tender joints. Swollen and tender joint counts (SJC and TJC, respectively) were each determined for 28 joints (proximal interphalangeal; PIP,

Table I. Patient characteristics.

n	92	
Female, n (%)	75	(81.5)
Age[a]	49.5	(22–81)
Disease duration, months[a]	66.1	(2–619)
Steinbrocker's STAGE III/IV, n (%)	38	(41.3)
MTX use, n (%)	64	(69.5)
Biologics use, n (%)	23	(25)
Steroid use, n (%)	30	(32.6)
RF positive, n (%)	53	(57.6)
ACPA positive, n (%)	52	(56.5)
MMP-3 positive, n (%)	60	(65.2)
ESR (mm/h)[a]	25.5	(2–155)
CRP (mg/l)[a]	0.3	(0–8)
Swollen joint count		
Of 28 joints[a]	3	(0–24)
Of 12 joints[a,b]	2	(0–12)
Tender joint count		
Of 28 joints[a]	1	(0–26)
Of 12 joints[a,b]	0	(0–12)
Patient GA[a]	4	(0–10)
Evaluator GA[a]	4.3	(0–9)
DAS[a]	3.9	(0.4–8.2)
CDAI[a]	14	(0–56)
SDAI[a]	15.2	(0–63.5)
DAS remission (<2.6), n (%)	22	(23.9)
CDAI remission (≤2.8), n (%)	12	(13)
SDAI remission (≤3.3), n (%)	12	(13)
Boolean remission, n (%)	9	(9.7)
US variables		
GS score of 12 joints[a,b]	6.5	(0–33)
PD score of 12 joints[a,b]	3	(0–23)

[a]Median (range).
MTX: methotrexate; ACPA: anticyclic citrulinated peptide antibody; MMP-3: matrix metalloproteinase-3; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; GA: global assessment in cm (0-10.0); DAS: disease activity score in 28 joints; CDAI: clinical disease activity index; SDAI: simplified disease activity index; US: ultrasound; GS: grey-scale; PD: power Doppler.
[b]12 joints, bilateral 1-5 MCP and wrist joints.

Table II. Correlation between clinical measures and PD signals.

	r	95% CI		*p*-value
Disease duration (months)	-0.11	-0.30	0.10	0.3184
RF	0.13	-0.08	0.33	0.2271
ACPA	0.02	-0.23	0.25	0.9004
MMP-3	0.25	0.05	0.44	0.0165*
ESR	0.41	0.22	0.57	<.0001***
CRP	0.37	0.17	0.53	0.0003***
Swollen joint count				
Of 28 joints	0.68	0.55	0.77	<.0001***
Of 12 joints[a]	0.67	0.53	0.77	<.0001***
Tender joint count				
Of 28 joints	0.34	0.14	0.51	0.0011*
Of 12 joints[a]	0.40	0.21	0.56	<.0001***
Patient GA	0.31	0.11	0.48	0.0026**
Evaluator GA	0.42	0.24	0.58	<.0001***
DAS	0.55	0.39	0.68	<.0001***
CDAI	0.59	0.44	0.71	<.0001***
SDAI	0.59	0.44	0.71	<.0001***

95% CI: 95% confidence interval; ACPA: anticyclic citrulinated peptide antibody; MMP-3: matrix metalloproteinase-3; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; GA: global assessment in cm (0–10.0); DAS: disease activity score in 28 joints; CDAI: clinical disease activity index; SDAI: simplified disease activity index.
[a]12 joints, bilateral 1-5 MCP and wrist joints.
*p<0.05, **p<0.01, ***p<0.001.

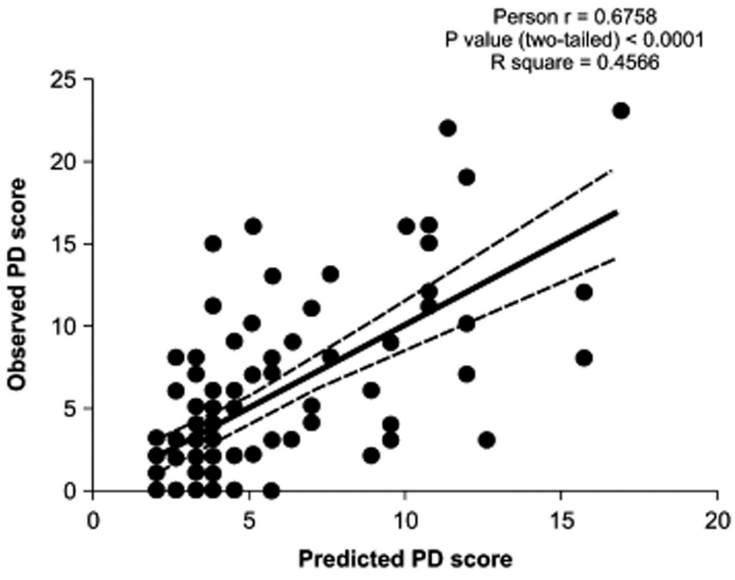

Fig. 1. Linear regression analysis.
SJC was the only variable that was significantly predictive for the PD score. PD score = 1.968 +0.625*SJC, R square = 0.4566, adjusted R square = 0.4506, p-value <0.0001.

MCP, wrist, elbow, shoulder, and knee on both sides; SJC/TJC), and 12 joints (both wrists and 1–5 MCP; SJC12/TJC12). Additional clinical factors and standard RA indices were also investigated as potential predictors of synovitis. Patient global assessments (GA), and physician GA were conducted. Biochemical indicators included C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), matrix metalloproteinase-3 (MMP-3), rheumatoid factor (RF), and anti-citrullinated protein antibodies (ACPA). Other factors considered were DAS, SDAI, CDAI, Boolean remission rate, treatment (biologics/methotrexate (MTX)/glucocorticoid), disease duration, and Steinbrocker's STAGE. These variables were used for statistical analyses.

Statistical analyses

To determine which variables provided the best predictive power, we used multiple correlation analyses. Candidate biochemical and clinical measures were investigated to determine if they were significantly correlated with PD scores. Model parameters (clinical and biochemical variables) displaying the strongest correlation with PD scores were determined by a stepwise (addition) method and were used in a multiple regression analysis, to determine the model that best predicted the PD score.

We also compared the candidate predictors between the patients with and without PD. We selected the statistically significant measures by a stepwise

Table III. Comparison between two patients' groups.

	PD remission in 12 joints[b]		No PD remission in 12 joints[b]		*p*-value[c]
Number	18		74		
Female, n (%)	16	(88.8)	59	(79.7)	0.36
Age[a]	43	(23-68)	51.5	(22-81)	0.13
Disease dulation, months[a]	58.9	(6-619)	71.6	(2-399)	0.94
Steinbrocker's STAGE III/IV, n (%)	2	(11.1)	36	(48.6)	0.0037**
MTX use, n (%)	10	(55.5)	54	(72.9)	0.14
Biologics use, n (%)	7	(38.8)	16	(21.6)	0.12
Steroid use, n (%)	4	(22.2)	26	(35.1)	0.29
RF positive, n (%)	8	(44.4)	45	(60.8)	0.28
ACPA positive, n (%)	8	(44.4)	44	(59.4)	0.12
MMP-3 positive, n (%)	6	(33.3)	54	(72.9)	0.0023**
ESR (mm/h)[a]	9	(2-59)	31	(2-155)	0.0043**
CRP (mg/l)[a]	0	(0-2.3)	0.4	(0-8)	0.0005***
Swollen joint count					
Of 28 joints[a]	0	(0-6)	4	(0-24)	<0.0001***
Of 12 joints[a,b]	0	(0-4)	2.5	(0-12)	<0.0001***
Tender joint count					
Of 28 joints[a]	0	(0-16)	1	(0-26)	0.05
Of 12 joints[a,b]	0	(0-7)	0	(0-12)	0.0216*
Patient GA[a]	2.4	(0-6)	5	(0-10)	0.012*
Evaluator GA[a]	1.25	(0-4)	5	(0-9)	0.0002***
DAS[a]	2.3	(0.4-5.1)	4.2	(0.5-8.2)	0.0015**
CDAI[a]	5.7	(0-27.5)	16.2	(0-56)	0.0002***
SDAI[a]	6.3	(0-27.5)	17.7	(0.1-63.5)	0.0002***
DAS remission (<2.6), n (%)	9	(50)	13	(17.5)	0.0038**
CDAI remission (≤2.8), n (%)	7	(38.8)	5	(6.7)	0.0003***
SDAI remission (≤3.3), n (%)	7	(38.8)	5	(6.7)	0.0003***
Boolean remission, n (%)	5	(27.7)	4	(5.4)	0.0042**
US variables					
GS score of 12 joints[a,b]	0.5	(0-10)	8	(0-33)	<0.0001***
PD score of 12 joints[a,b]	0	(0-0)	5	(1-23)	<0.0001***

[a]Median (range).
MTX: methotrexate; ACPA: anticyclic citrulinated peptide antibody; MMP-3: matrix metalloproteinase-3; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; GA: globalassessment in cm (0-10.0); DAS: disease activity score in 28 joints; CDAI: clinical disease activity index; SDAI: simplified disease activity index; US: ultrasound; GS: grey scale; PD: power Doppler.
[b]12 joints, bilateral 1-5 MCP and wrist joints.
[c]Statistical difference between PD remission and no PD remission patients group.
*p<0.05, **p<0.01, ***p<0.001.

method and used these in a multiple logistic regression analysis to determine the predictor that best predicts a PD score of zero. In these analyses, variables (clinical predictors) displaying multicollinearity (those with correlation coefficients >0.8) and patient/physician GA were excluded.

Results

Patient demographics

Average disease duration was 97.2±100.0 months. Of the 92 patients included in this study, 41.3% were classified as having Steinbrocker stage III or IV. MTX was given for 69.5% of the patients, biologics for 25%, and glucocorticoids for 32.6%. Percentage of patients in clinical remission differed according to the index and definition – DAS (23.9%), SDAI (13%), CDAI (13%), Boolean (9.7%) (Table I).

Distribution and prevalence of swollen and tender joints (Supplementary figures 1A–E)

Joint swelling was most common in wrists and 2–3 MCPs. Tenderness was common in wrists, but was also frequently reported in knees. Swelling and tenderness of 1–5 MCPs and wrist joints were observed in 70.6% and 42.3% of patients, respectively. The percentage of patients with swelling and tenderness of other joints was 6.5% and 10.8%, respectively. Positive GS and PD signals were mainly observed in the wrist and 2–3 MCPs, and 2–3 MCPs and PD scores between 0 and 4 were most common.

Clinical predictors of PD

Of the 14 routine clinical measures we investigated as predictors of synovitis, 11 were significantly correlated with PD signals (Table II). SJC (r=0.68, p<0.0001), SJC12 (r=0.67, p<0.0001), CDAI (r=0.59, p<0.0001), SDAI (r=0.59, p<0.0001), DAS (r=0.55, p<0.0001), ESR (r=0.41, p=0.001) had the highest correlation coefficients. A subset of the correlation data (MMP-3, ESR, SJC, TJC12 and SDAI) are shown in the supplementary file (Supplementary figure 2*A–E*). Multiple correlation analysis identified SJC as the only variable that was significantly predictive for the PD score (PD score = 1.968 + 0.625*SJC, R square = 0.4566, adjusted R square = 0.4506, p-value <0.0001, Fig. 1).

Clinical measures associated with the absence of PD

The second phase of our analysis was to identify clinical variables capable of predicting the absence of synovitis (PD score = 0). Of the 25 candidate clinical measures that were compared between patients with and without PD, 16 were found to be significant predictors of the absence of PD signals (Table III). However, even when the values of these predictors were in the normal range (indicating remission), residual PD scores were still present, and the percentage of patients with positive PD scores varied significantly among these predictors, ranging from 38% for negative ESR, to 72% for TJC <1 (Fig. 2A). The mean PD scores, observed among the patients with normal or negative values also varied among the predictors. Patients meeting Boolean remission criteria had the lowest median PD score, while Stage I/II was associated with the largest range (Fig. 2B).

Of the 16 significant clinical measures, we chose 7 – Steinbrocker's STAGE, MMP-3, CRP, SJC12, SJC, TJC12, SDAI (or CDAI) – for the subsequent multiple logistic regression analysis. This analysis identified 3 factors, Steinbrocker's STAGE I/II (OR 9.23, 95% confidence interval (CI); 18–81.4,

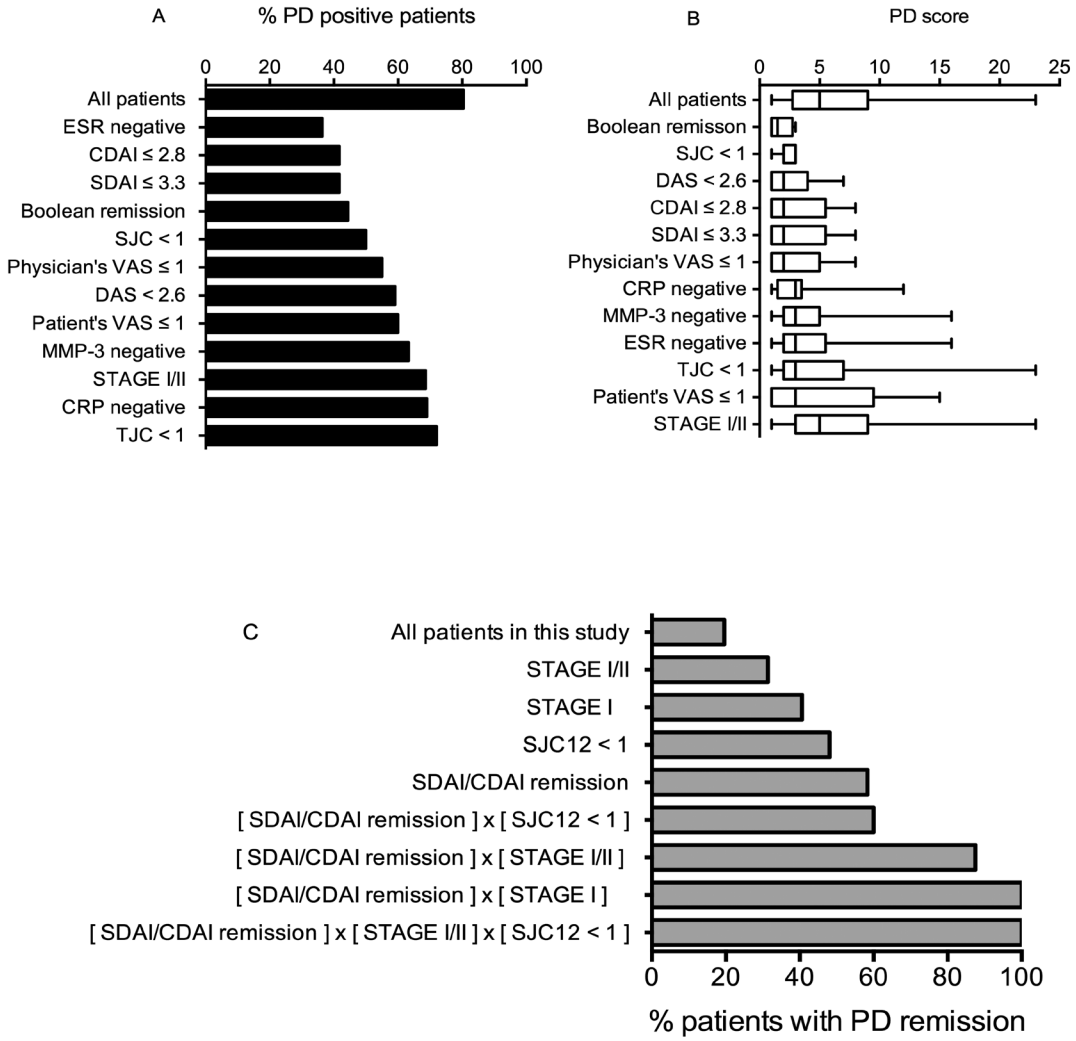

Fig. 2. Residual synovitis (PD signals). **A**-**B**: Each measures in normal range still showed percentage of residual PD score and those orders were different among measures in proportion and average score;
C: percentage of patients with no PD signals. Combination of [SDAI/CDAI remission], [STAGE I/II] and [SJC12<1] were fulfilled only in 6 RA patients who have no PD signals.

p=0.0049), SJC12 <1 (OR 6.60, 95% CI; 1.8–26.2, *p*=0.0039), and SDAI (or CDAI) remission (OR = 5.06, 95% CI; 1.04–28.9, *p*=0.0450), as significant predictors of PD signals. Individually, these had significant predictive power, but when the 3 factors were combined, the positive predictive value (PPV) of the model, for the absence of PD signals, was 1.0 (Table IV). Clinical data showed that the combination of SDAI/CDAI remission, STAGE I/II, and SJC12<1 was only found in 6 RA patients, but all 6 were free of PD signals (Fig. 2B).

Discussion

Confirmation of absence of inflammation in RA patients with clinical remission currently requires US as a complement to physical examination. Misdiagnosis of RA remission can result in persistent subclinical synovitis and bone destruction. Unfortunately, US is not available or not performed for all RA patients. In 2008, only 22% of rheumatologists in Japan had access to US (32, 33) and even in clinics that do, time constraints restrict the number of patients that are able to undergo US examinations. Therefore, it is critical to identify clinical variables that can be used to identify RA patients with an elevated risk of synovitis and requiring US. The results of this study identify clinical factors that can be used to identify RA patients requiring US.

It is surprising that none of the other factors – CRP, ESR and MMP-3 – were significant predictors of PD score, and SJC was the factor most highly correlated to PD score. Since SJC is a recommended component of the common RA indices, yet these indices fail to indicate patients with synovitis; this suggests that SJC may be not weighted properly in these indices and highlights the value of clinical examination of the focal joints (34, 35). SJC was strongly correlated with PD; however, its utility is limited at low SJCs. For example, if SJC is zero, the regression formula demonstrates that it is no longer an adequate predictor of PD signals. In other words, it does not adequately indicate the absence of PD signals. In these cases, patients should receive US examinations.

In contrast, under the right circumstances, the combination of SDAI/CDAI remission, STAGE I/II and SJC12 <1 can act as strong predictors of the silence of PD signals in RA patients. While these are not absolute indicators of PD remission, our results indicate that patients meeting these 3

Table IV. Sensitivity, specificity, likelihood ratios and predictive values for PD remission.

Clinical measures			Sensitivity	Specificity	Positive LR	Negative LR	PPV	NPV	Patients n.	(%)	PD remission n	(%)
SDAI/CDAI remission	STAGE I/II	SJC12 <1										
+	-	-	80.0	93.2	11.8	0.2	0.90	0.86	12	(13.0)	7	(58.3)
-	+	-	96.4	50.7	2.0	0.1	0.60	0.95	51	(55.4)	16	(31.4)
-	-	+	90.9	81.1	4.8	0.1	0.78	0.92	27	(29.3)	13	(48.1)
+	+	-	80.0	98.6	59.2	0.2	0.98	0.87	8	(8.7)	7	(87.5)
+	-	+	78.2	94.6	14.5	0.2	0.91	0.85	10	(10.9)	6	(60.0)
-	+	+	90.9	91.9	11.2	0.1	0.89	0.93	19	(20.6)	13	(68.4)
+	+	+	78.2	100.0	Infinity	0.2	1.00	0.86	6	(6.5)	6	(100.0)

LR: likelihood ratio; PPV: positive predictive value; NPV: negative predictive value.

criteria are free of PD signals. By identifying these patients who are unlikely to require US, this composite criteria would increase the accessibility of US to those in need. Remission definitions (36, 37) were not originally designed to detect the presence of or the degree of synovitis. Consequently, a small percentage of patients with SDAI/CDAI remission have residual PD signals. For example, one study found radiographic damage in 23% of patients in SDAI remission while another did not it in 50% of patients without SDAI remission (36, 37). Individually, composite clinical indices may be incapable of predicting a patient's risk of synovitis and bone destruction; however, this study demonstrates that the satisfaction of multiple criteria (in this case, SDAI/CDAI remission, STAGE I/II, and SJC12 <1) can act as a reliable clinical measure and strong predictor of PD signal remission.

This study is an important step toward identifying clinical factors capable of predicting synovitis, but it also has some potential limitations. As this study was conducted in a single medical center and with a limited number of patients, it requires validation in other larger and geographically diverse populations of RA patients. Moreover, this study also needs to be validated through a longitudinal study by repeating the evaluation in a tight control strategy. In particular, we need to confirm that the PPV of the model established in this study, for silence of PD signals is applicable to other patients in SDAI/CDAI remission. Another possible limitation is that US examinations were restricted to joint sites in the patients' hands. However, we feel that this choice is justified. Our results show that swelling and tenderness were most common in the hands of study patients (Supplementary Fig. 1a-b, Supplementary Table I), and joints of the hand are the most examined and affected among RA patients; they are also the easiest to access with US. Although our results must also be applicable to feet, it is more difficult to assess swelling in larger and/or deeper joints (*e.g.* the shoulder, elbow, hip, or knee). As a result, these joints are unlikely to serve as reliably as hands for the clinical prediction of presence and absence of synovitis.

This is the first study showing that routine clinical measures can be used to predict the absence and severity of synovitis (PD signals) in RA patients. We show that the strength of PD signals can be adequately predicted by SJC and silence of PD signals by the combination of 3 common clinical variables SDAI/CDAI, STAGE, and SJC12. Based on these findings, we recommend a clinical protocol for the identification of patients in PD remission, in need of US and with a high probably of synovitis. If used appropriately, we feel that these measures can provide information regarding a patients' disease activity, in terms of the strength or absence of PD signals, and be used as criteria for the selection of patients requiring US (Fig. 3).

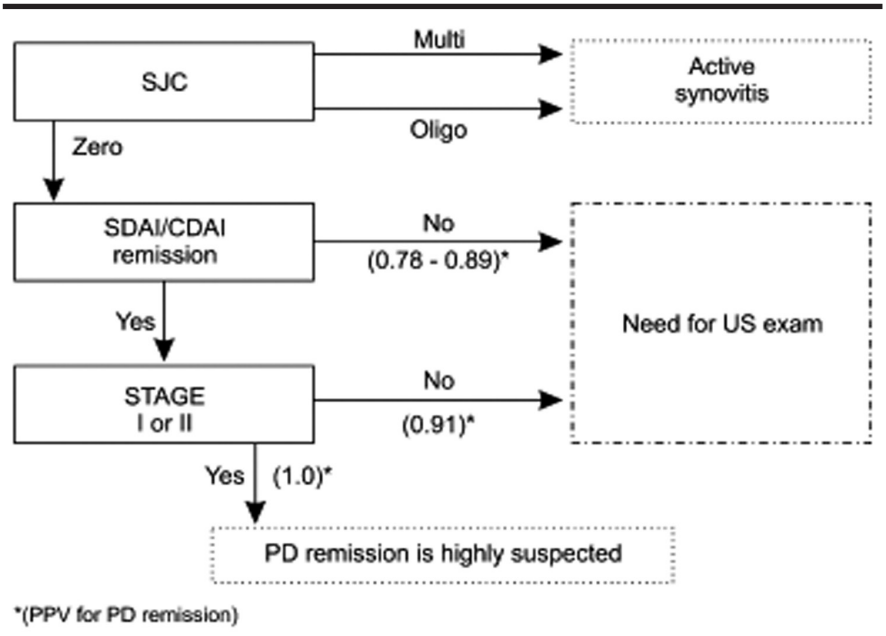

Fig. 3. Flow chart for the application of US in RA patients.
Considering the patients should undergo US to assess disease activity in clinical situation. Condition of SJC, SDAI/CDAI remission and STAGE could lead to correct US indication.

Conclusions

There is a need to identify and select patients with RA who require US. In this study, we found that US imaging synovitis can be predicted by routine clinical measures. Particularly, when used in combination, Steinbrocker's stage, SJC and SDAI (or CDAI) can estimate the probability of remission and facilitate identification of patients likely to have residual synovitis and requiring US.

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