

Subclinical Synovitis Assessed by Ultrasound Predicts Flare and Progressive Bone Erosion in Rheumatoid Arthritis Patients with Clinical Remission: A Systematic Review and Metaanalysis

Jingjing Han, Yan Geng, Xuerong Deng, and Zhuoli Zhang

ABSTRACT. *Objective.* Subclinical synovitis can be detected by ultrasound in patients with rheumatoid arthritis (RA) who are in clinical remission. We aimed to confirm its predictive value for flare and progressive bone erosion.

Methods. A systematic literature search was performed in Pubmed, Web of Science, Embase, and Cochrane Library on September 7, 2014. Baseline clinical and ultrasonographic characteristics were collected. Methodological quality was assessed. Pooled OR were calculated using Mantel-Haenszel model. We explored the source of heterogeneity through subgroup analysis and completed a cumulative metaanalysis.

Results. Thirteen articles were included (8 with flare, 4 with bone erosion, 1 with both flare and bone erosion). Metaanalysis revealed an association between power Doppler (PD) positivity and the risk of flare (OR 4.52, 95% CI 2.61–7.84, $p < 0.00001$, $I^2 = 21\%$), the risk of progressive bone erosion on patient level (OR 12.80, 95% CI 1.29–126.81, $p = 0.03$, $I^2 = 52\%$) and the risk of progressive bone erosion on joint level (OR 11.85, 95% CI 5.01–28.03, $p < 0.00001$, $I^2 = 0\%$). Further subgroup analysis showed a higher risk of flare in patients with a study period < 1 year (OR 19.98 vs 3.41). No significant differences were observed in the subgroup analysis in duration of remission, disease duration, and medications. Moreover, cumulative metaanalysis indicated the validation and an increasing accuracy of PD positivity in predicting flare since 2012.

Conclusion. Ultrasound-detected subclinical synovitis can predict the risk of flare and progressive bone erosion in RA patients with clinical remission. Additionally, the flare of RA tends to occur within a followup of 1 year. (J Rheumatol First Release October 1 2016; doi:10.3899/jrheum.160193)

Key Indexing Terms:

RHEUMATOID ARTHRITIS
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SYNOVITIS
METAANALYSIS

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease that can lead to joint destruction or even deformity. Since 2010, the widespread treat-to-target strategy, aiming at clinical remission or low disease activity¹, has greatly improved the prognosis of RA. However, in patients

in clinical remission, progressive bone erosion can still be detected^{2,3} and subsequent uncertain relapse can also be observed. Hence, it is indicative of a possibility that clinical remission of RA may not be the true state of remission, and an underlying inflammation may exist in patients with RA who are in clinical remission.

Musculoskeletal ultrasound (US) is a highly sensitive, nonradioactive and easily accessed tool. With the help of US, many studies found subclinical synovitis in patients with RA who were in clinical remission^{4,5}. Our previous study had also shown a prevalence of subclinical US synovitis whatever the criteria we used to define clinical remission⁶. In addition, many studies revealed that the subclinical synovitis assessed by US might have a predictive value for flare and progressive bone erosion^{7,8,9,10}. Further, a related metaanalysis performed in 2012 had already confirmed this conclusion¹¹.

In our current study we performed another metaanalysis to demonstrate the association between subclinical US synovitis and the risk of flare or progressive bone erosion. Compared with the previous metaanalysis, we included

From the Department of Geriatrics, and the Department of Rheumatology and Clinical Immunology, Peking University First Hospital, Beijing, China.

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J. Han, MD, Department of Geriatrics, Peking University First Hospital; Y. Geng, MD, Department of Rheumatology and Clinical Immunology, Peking University First Hospital; X. Deng, MD, Department of Rheumatology and Clinical Immunology, Peking University First Hospital; Z. Zhang, MD, PhD, Department of Rheumatology and Clinical Immunology, Peking University First Hospital.

*Address correspondence to Dr. Z. Zhang, Department of Rheumatology and Clinical Immunology, Peking University First Hospital, No. 8 Xishiku St., Xicheng District, 100034 Beijing, China.
E-mail: zhuoli.zhang@126.com*

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additional articles published in the last 2 years, gave a deeper explanation for heterogeneity using subgroup analysis, and accomplished a cumulative metaanalysis.

MATERIALS AND METHODS

Search strategy. A systematic search was conducted in Pubmed, Embase, Web of Science (including the conference part), and the Cochrane Library, using all spellings of “rheumatoid arthritis,” “ultrasonography,” and “remission” as keywords or medical subject headings. The article search was performed on September 7, 2014. We also manually searched the references of some related articles or reviews and included grey literature.

Selection of articles. We selected articles about the predictive value of subclinical synovitis for relapse or bone erosion in patients with RA who are in clinical remission. Cohort studies of adults (age > 18 yrs) published in English were included. We excluded articles that had different objectives or inaccessible crucial data, as well as cross-sectional studies, case reports, reviews, and consensus reports. The qualities of the enrolled articles were evaluated by the Quality in Prognosis Studies tool in the following 6 areas: study participation, study attrition, prognostic factor measurement, outcome measurement, confounding measurement and account, and analysis¹².

Data extraction. The following data in the selected articles were recorded: general information (sex, age, disease duration, duration of remission before inclusion); baseline clinical characteristics [swollen joint count, tender joint count, erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor, anticyclic citrullinated peptide antibodies, 28-joint Disease Activity Score (DAS), Health Assessment Questionnaire score, shared epitope]; baseline US characteristics [scoring system, scanning region, power Doppler score, greyscale (GS) score, and cutoff points for US synovitis]; followup information (study period, medications); diagnostic criteria and remission criteria of RA; definition and outcome of flare; and definition and outcome of progressive bone erosion. Corresponding authors were contacted if crucial data could not be obtained in the full text.

The literature search, quality assessment, and data extraction were performed independently by 2 authors (J.H. and Y.G.). Differences were discussed and consulted with Z. Zhang.

Statistical analysis. The association of baseline US characteristics and the outcome of flare or progressive bone erosion were calculated by OR in patient level and joint level if data for each joint were available. Mantel-Haenszel model and random effect method were used. I^2 was adopted to represent heterogeneity ($I^2 \leq 25\%$, low; $25\% < I^2 \leq 50\%$, medium; $I^2 > 50\%$, high). Further, in articles related to flare, we analyzed the sources of heterogeneity in 4 subgroups: disease duration, duration of remission before baseline, length of followup period, and medications during followup. We also did a cumulative metaanalysis. A 2-sided $p < 0.05$ ($p < 0.1$ in the test for heterogeneity) was regarded as a significant difference. Metaanalysis was done with Revman 5.2 (The Nordic Cochrane Centre). Cumulative metaanalysis was done with STATA 11.0 (Stata Corp.).

The research protocol was approved by Peking University First Hospital Institutional Review Board for clinical research (2014[785]).

RESULTS

Study characteristics. Our literature search yielded 105 articles in Pubmed, 180 articles in Web of Science, 411 articles in Embase, and 97 articles in the Cochrane Library. In addition, 1 reference and 1 unpublished article (i.e., 1 piece of grey literature) were identified as eligible. After reviewing the titles, abstracts, and full texts, we finally included 13 articles (Figure 1). Among them, 10 articles (including 1 piece of grey literature) were full texts^{3,7,8,9,10,13,14,15,16}, 3 had only abstracts available^{17,18,19}, 8 were related to flare, 4 were related to bone erosion, and 1 was related to both flare

and bone erosion. Compared with the previous metaanalysis, 5 additional articles were written or published in the last 2 years (including 1 piece of grey literature).

The RA diagnostic criteria in 10 of the 13 articles were 1987 American College of Rheumatology (ACR) criteria, while the other 3 (including 1 piece of grey literature) used 2010 ACR/European League Against Rheumatism criteria^{8,16}. As for the remission criteria, all the articles applied DAS criteria, although the cutoff points were different. US examinations of the dominant hand and wrist were done in all study participants, of which 10 studies additionally examined the bilateral hands. Several studies further scanned metatarsophalangeal joints, knees, or other joints. US data were all evaluated by a semiquantitative scale from 0 to 3 except for 1 article using a dichotomous measure¹⁵. Power Doppler scores were obtained in all 13 articles. GS scores were assessed in 5 articles (including 1 piece of grey literature)^{3,7,8,14}. In most of the selected articles, flare was defined as the increase of disease activity, Sharp score was chosen to evaluate the progression of bone erosion, and quality scores calculated by the Quality in Prognosis Studies tool were above 4. The characteristics of the studies and patients in this metaanalysis are described in Table 1 and Table 2; and in Supplementary Table 1 and Supplementary Table 2, available online at jrheum.org.

US and risk of flare. The relapse rate mainly ranged from 22.7% to 51.4% in the 9 selected articles related to risk of flare. The metaanalysis of these 9 studies (including 4 additional studies compared with the previous metaanalysis) showed an association of US PD positivity and risk of flare in patients with RA in clinical remission (pooled OR 4.52, 95% CI 2.61–7.84, $p < 0.00001$; Figure 2). A heterogeneity of $I^2 = 21\%$ was also detected ($p = 0.25$). In the 4 studies that assessed GS scores, metaanalysis showed a risk of flare in patients with US GS positivity (pooled OR 3.69, 95% CI 1.71–7.93, $p < 0.0008$; Supplementary Figure 1, available online at jrheum.org), with a low heterogeneity ($I^2 = 5\%$, $p = 0.37$). Therefore, US PD and GS positivity could increase the risk of flare in patients with RA who are in clinical remission.

US and risk of progressive bone erosion. Three articles were related to progression of bone erosion. A pooled OR of 12.80 (95% CI 1.29–126.81, $p = 0.03$) was discovered in the association between US PD positivity and risk of radiological progression (Figure 3A). The heterogeneity was $I^2 = 52\%$ ($p = 0.13$). At joint level, there was also a risk of progression in patients with US PD positivity (pooled OR 11.85, 95% CI 5.01–28.03, $p < 0.00001$; Figure 3B). No evidence of heterogeneity was found in joint level ($I^2 = 0\%$, $p = 0.97$). Hence, whatever the levels in patients or joints, US PD positivity could increase the risk of progressive bone erosion in patients with RA who have clinical remission.

Subgroup analysis of the risk of flare. In consideration of the heterogeneity in 9 articles related to flare, we further performed subgroup analysis based on our clinical experience.

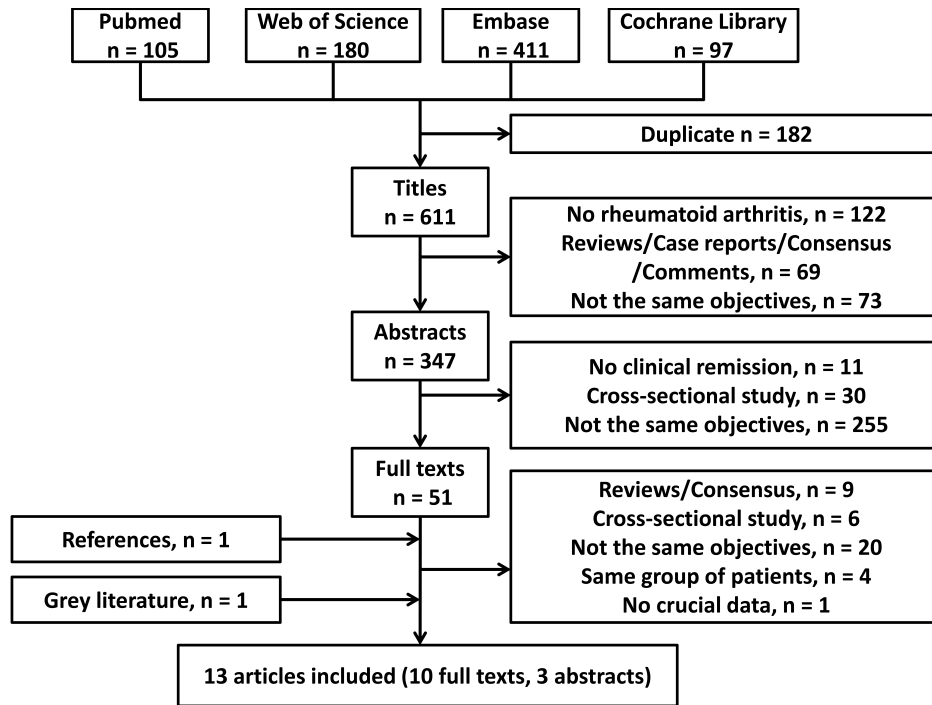


Figure 1. Flowchart of literature search.

The cutoff point in the subgroup of study period was 1 year (Figure 4A). Six of 9 articles had a study period of at least 1 year, while the other 3 were < 1 year. Respectively, in these 2 subgroups, the pooled OR in the association between PD positivity and risk of flare were 3.41 (95% CI 2.07–5.63, $p < 0.00001$) and 19.98 (95% CI 5.65–70.60, $p < 0.00001$). There was no evidence of heterogeneity within either subgroup ($I^2 = 0\%$, $p = 0.74$; $I^2 = 0\%$, $p = 0.63$). The OR value in the group with the shorter study period was greater than that in the group with the longer study period, with a high and significant heterogeneity ($I^2 = 84.6\%$, $p = 0.01$) and no overlap in CI between subgroups. This indicates that patients with PD positivity in clinical remission were much more likely to relapse within 1 year of followup.

Six articles presented data about the duration of remission before baseline. They were divided into 2 subgroups at the cutoff point of 1 year (Figure 4B). Two studies having duration of remission longer than 1 year showed a risk of flare in patients with PD positivity (pooled OR 7.40, 95% CI 1.48–37.09, $p = 0.01$). Meanwhile, the metaanalysis of 4 studies with duration of remission < 1 year revealed a pooled OR of 4.89 in the association between US PD positivity and risk of flare (95% CI 1.48–16.18, $p = 0.009$). The heterogeneity was moderate to high ($I^2 = 45\%$, $p = 0.18$; $I^2 = 60\%$, $p = 0.06$) within each subgroup and was 0 between 2 subgroups ($I^2 = 0\%$, $p = 0.69$). Moreover, there was even an overlap in the CI of OR between 2 subgroups. Hence, no significant effect was found on the risk of flare in the subgroup of duration of remission.

The subgroup analysis of disease duration was done in 8 articles with a cutoff point of 5 years (Figure 4C). In the group of disease duration longer than 5 years, the meta-analysis of 5 related articles showed a risk of flare in patients with US PD positivity (pooled OR 3.99, 95% CI 2.34–6.80, $p < 0.00001$), and without any heterogeneity ($I^2 = 0\%$, $p = 0.62$). However, in the group of shorter disease duration (3 articles < 5 years), we found an association of risk of flare and PD positivity with no statistical significance (pooled OR 5.75, 95% CI 0.84–39.13, $p = 0.07$) and with a high heterogeneity ($I^2 = 72\%$, $p = 0.03$). Apart from that, no evidence of heterogeneity was detected between 2 subgroups ($I^2 = 0\%$, $p = 0.72$). So there was no significant effect on the risk of flare in the subgroup of disease duration.

As for the medications during followup, we grouped the 8 related articles according to the use of biologics (Figure 4D). Four studies admitted the use of biologics. The pooled OR of these 4 articles in the association between risk of flare and PD positivity was 3.94 (95% CI 1.94–8.00, $p = 0.0002$). Accordingly, the other 4 articles in the nonbiologics group had a pooled OR of 6.54 (95% CI 1.53–28.07, $p = 0.01$) and a high heterogeneity ($I^2 = 66\%$, $p = 0.03$). Further, no heterogeneity existed between the 2 subgroups ($I^2 = 0\%$, $p = 0.54$) and there was an overlap in the CI of OR within the 2 groups. As a result, no significant effect of medications on the risk of flare was observed in patients with RA who are in clinical remission.

Cumulative metaanalysis in the risk of flare. To clearly elucidate the effect of PD positivity on risk of flare, we

Table 1. Characteristics of the included studies on flare.

Author, Reference	No. Patients	Diagnostic Criteria	Remission Criteria	Definition of Flare	US Joints	US Evaluation	Cutoff Points in PD/GS	Study Period, mos	Medications	QIPS
Scire, 2009 ¹³	106	1987 ACR	DAS < 1.6	DAS ≥ 1.6	Bilateral wrists, MCP, PIP, shoulders, elbows, sternoclavicular, acromioclavicular, knees, ankles, MTP joints	0-3*	PD > 0	6	cDMARD	5
Saleem, 2010 ¹⁴	27	1987 ACR	DAS28 < 2.6	DAS28 > 2.6 or an increase of 1.2 if DAS < 2.6	Dominant wrist, MCP1-5, PIP1-5	0-3*	GS > 0; PD > 0	24	cDMARD	4
Peluso, 2011 ¹⁵	94	1987 ACR	DAS < 1.6	DAS > 1.6	Bilateral wrists, MCP2-3, PIP2-3	Dichotomy	PD+, GS+	12	66% cDMARD + anti-TNF, others only cDMARD	4
Saleem, 2012 ⁷	93	1987 ACR	DAS28 < 2.6 or SDAI ≤ 3.3 or 1981 ACR criteria or 2010 ACR criteria	Any increase in disease activity that required a change in therapy	Dominant wrist and MCP	0-3*	GS > 0; PD > 0	12	cDMARD	6
Foltz, 2012 ⁹	47	1987 ACR	DAS < 2.4	DAS ≥ 2.4 or an increase in DAS that required a change in therapy or an increase of steroids > 10 mg/day	Bilateral wrists, MCP2/3/5, MTP2/3/5	0-3*	PD > 0	12	cDMARD, biologics, steroids (< 10 mg/day)	6
Iwamoto, 2014 ⁸	42	1987 ACR, 2010 ACR/EULAR	DAS28 < 2.6	DAS > 3.2 and an increase in therapy	Bilateral shoulders, elbows, MCP, PIP, wrists, knees, ankles, MTP	0-3*	GS ≥ 14; PD ≥ 3	6	cDMARD, steroids (≤ 9 mg/day)	4
Geng, 2014	72	2010 ACR/EULAR	DAS28 (ESR) ≤ 2.6	DAS28 (ESR) > 2.6	Bilateral wrists, MCP1-5, PIP 1-5	0-3*	GS > 0; PD > 0	12	NA	4
Ramirez Garcia, 2014 ¹⁷	28	NA	DAS28 < 2.6	NA	Bilateral wrists, MCP, PIP, knees	0-3*	PD > 0	12	cDMARD, 39.3% biologics	6
Van Der Ven, 2014 ¹⁸	67	NA	DAS44 < 2.4 and SJC ≤ 1	DAS44 ≥ 2.4 or SJC > 1	Bilateral wrists, MCP2-5, PIP2-5, MTP2-5	0-3*	PD > 0	3	cDMARD + anti-TNF	4

* Semiquantitative. cDMARD: conventional disease-modifying antirheumatic drugs; NA: not available; US: ultrasound; PD: power Doppler; GS: greyscale; QIPS: Quality in Prognosis Studies tool; ACR: American College of Rheumatology; DAS: Disease Activity Score; MCP: metacarpophalangeal; PIP: proximal interphalangeal; MTP: metatarsophalangeal; DAS28: 28-joint DAS; anti-TNF: tumor necrosis factor inhibitor; SDAI: Simplified Disease Activity Index; EULAR: European League Against Rheumatism; ESR: erythrocyte sedimentation rate; SJC: swollen joint count.

performed a cumulative metaanalysis. Results are shown in Supplementary Figure 2, available online at jrheum.org. Since 2012 there was a sustainable, significant association between risk of flare and PD positivity in patients with RA who are in clinical remission, and also a tendency of a narrow scale of CI on pooled OR. Therefore, the cumulative metaanalysis revealed an increasing predictive accuracy of US PD positivity on risk of flare in patients with RA who are in clinical remission.

DISCUSSION

Because the results in the previous single-center studies were inconsistent, the association between US PD positivity and the risk of flare/radiological progression was uncertain. For example, in the predictive value of flare, 3 of 9 articles showed a lack of predictive value of PD positivity on flare while the other 6 showed predictive OR that fluctuated from 3.55 to 28.80. To resolve this question, Nguyen, *et al*¹¹ did a

metaanalysis and demonstrated a predictive value of US PD positivity for flare and progressive bone erosion in patients with RA who are in clinical remission. However, they excluded 1 article with a significant difference when encountering the problems of heterogeneity. In comparison with their work, our metaanalysis added 5 more articles published in recent years (i.e., included the largest number of articles ever before, to our knowledge), confirmed the definite predictive value of US PD positivity, and included a subgroup analysis to deeply explicate the heterogeneity.

The risk of flare in patients with PD positivity was 4.52 times as high as that in patients with PD negativity. This result was quite consistent with the pathogenesis of synovitis. Synovial angiogenesis, which can be sensitively detected by power Doppler US, is known as the essence of active synovitis²⁰. Previous studies had also reported a high correlation between PD positivity and inflammatory cell infiltration or vascularity in synovial tissues ($r = 0.84$,

Table 2. Characteristics of the included studies on progressive bone erosion.

Author, Reference	No. Pts	Diagnostic Criteria	Remission Criteria	Radiographed Joints	Radiography Evaluation	Definition of Progression	US Joints	US Evaluation	Cutoff Points in PD/GS	Study Period, yrs	Medication	QIPS
Brown, 2008 ³	102	1987 ACR	1981 ACR or DAS28 < 2.6	Hands, wrists, feet	Genant-modified Sharp score	$\Delta > \text{SDC}$	Dominant wrist,	0-3*	PD > 0; GS > 0	1	cDMARD, steroids (≤ 5 mg/day)	6
Raffeiner, 2011 ¹⁹	109	NA	DAS28	Hands, feet	van der Heijde/modified Sharp score	$\Delta \text{TSS} > 0$	Bilateral wrists, MCP, PIP, MTP	0-3*	PD > 0	1	Anti-TNF	4
Foltz, 2012 ⁹	47	1987 ACR	DAS < 2.4	Hands, wrists, feet	van der Heijde/modified Sharp score	$\Delta \text{TSS} \geq 1$	Bilateral wrists, MCP2/3/5, MTP2/3/5	0-3*	PD > 0	1	cDMARD, biologics, steroids (< 10 mg/day)	6
Yoshimi, 2013 ¹⁰	31	1987 ACR	DAS28 ESR < 2.6 or DAS28 CRP < 2.3	Hands	van der Heijde/modified Sharp score	$\Delta \text{TSS} > 0.5$ U/yr	Bilateral wrists, MCP, PIP	0-3*	PD ≥ 2	2	cDMARD, anti-TNF, steroids (1-5 mg/day)	4
Ogishima, 2014 ¹⁶	77	1987 ACR or 2010 ACR/EULAR	DAS28 CRP ≤ 2.3	Hands	Erosion and JSN assessment, but not van der Heijde/modified Sharp score or Genant-modified Sharp score	Δ (erosion + JSN) > 0	Bilateral wrists, MCP1-5, PIP2-5	0-3*	PD > 0	282 \pm 150 days	cDMARD, biologics, steroids (5.1 \pm 2.5 mg/day)	3

* Semiquantitative. SDC: smallest detectable change; JSN: joint space narrowing; TSS: total Sharp score (sum of the assessment in erosion and JSN); US: ultrasound; NA: not available; PD: power Doppler; GS: greyscale; QIPS: Quality in Prognosis Studies tool; ACR: American College of Rheumatology; DAS: Disease Activity Score; MCP: metacarpophalangeal; PIP: proximal interphalangeal; MTP: metatarsophalangeal; DAS28: 28-joint DAS; anti-TNF: tumor necrosis factor inhibitor; cDMARD: conventional disease-modifying antirheumatic drugs; EULAR: European League Against Rheumatism; CRP: C-reactive protein.

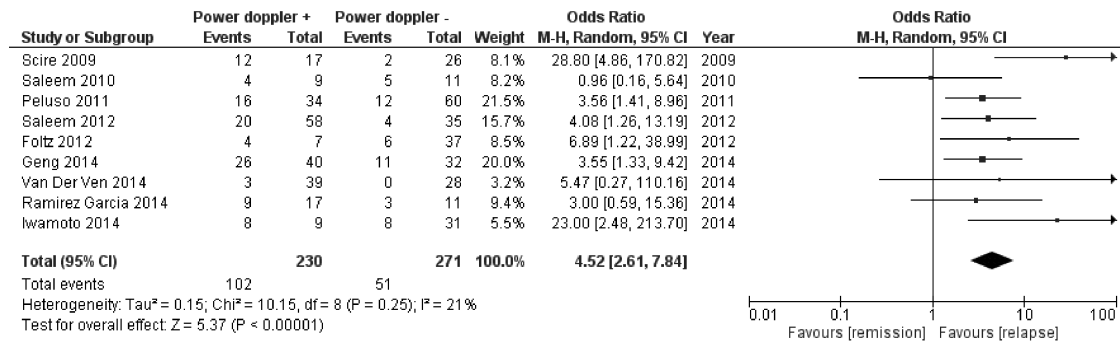


Figure 2. Summary of the association between ultrasonic power Doppler score and risk of flare.

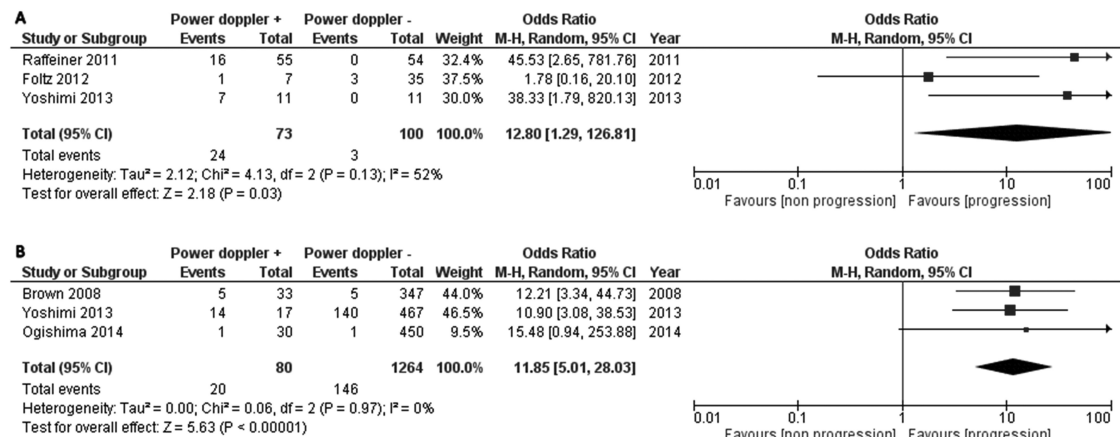


Figure 3. Summary of the association between ultrasonic power Doppler score and risk of progressive bone erosion. A. Patient level. B. Joint level.

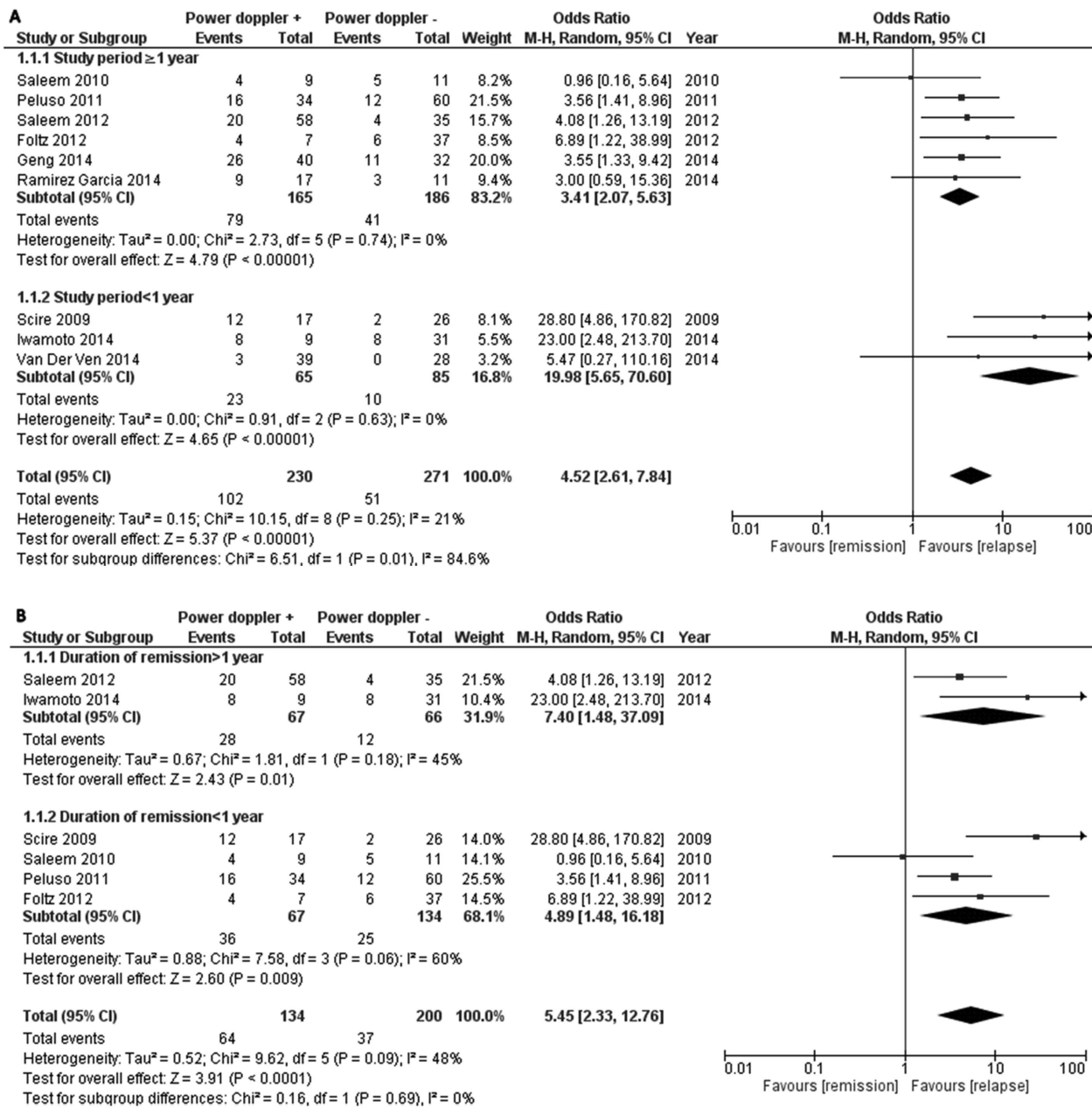


Figure 4A-B. Subgroup analysis of the association between ultrasonic power Doppler score and risk of flare. A. Subgroup of study period (cutoff point of 1 yr). B. Subgroup of duration of remission (cutoff point of 1 yr).

$p < 0.01$)²¹. In other words, US PD positivity is obviously related to histopathological activity in patients with RA who are in superficial clinical remission, which might give a reasonable explanation of the susceptibility to flare. At the same time we also found the risk of flare in patients with GS positivity was 3.69 times as high as that in patients negative for GS. Although it might imply a possible predictive value of GS positivity, the interaction between GS and PD could not be neglected. With little identification between fibrous tissues and active synovitis, GS signals only reflected the presence of synovium tissues²². Thus the

predictive value of GS independent of PD is still unknown.

In bone erosion, the risk of progression in patients with PD positivity was 11.85 and 12.80 times as high as that in patients with PD negativity on joint level and patient level, respectively. In addition, the range of CI of OR in joint level was much smaller than that in patient level. This phenomenon could be explained by the effect of synovial inflammation on each joint. A previous study confirmed that the cause of bone destruction was sustained synovial inflammation²³. Because active synovitis in 1 joint, reflected by PD positivity, led to structural progression in that joint, it was much easier to

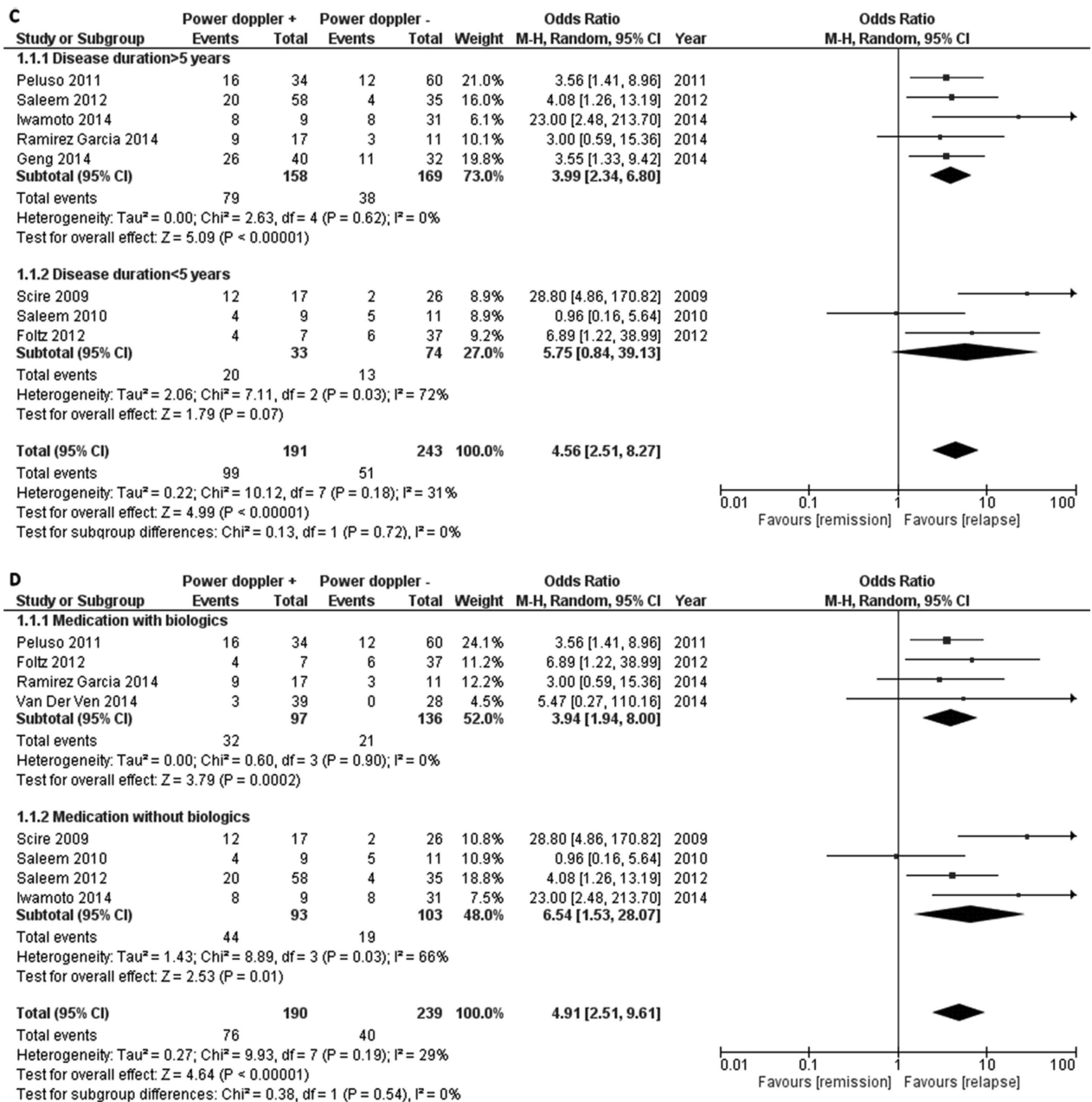


Figure 4C-D. C. Subgroup of disease duration (cutoff point of 5 yrs). D. Subgroup of medication.

understand the higher accuracy of PD positivity in predicting progression on joint level.

Negative results were obtained from the subgroup analyses of disease duration, duration of remission, and medications, indicating no predictive values of these variables for risk of flare. Nevertheless, in the subgroup analysis of shorter study period, a higher risk of flare was observed. After reviewing all the 3 articles that documented the time to relapse, we discovered that an average time to relapse was within 1 year^{7,8}. The probability of relapse remains high within a certain period of time, and there might

be a predisposition to flare in a certain group of patients with RA. Studies focused on the pathogenesis of flare were extremely rare. Some researchers showed that the alteration of popliteal lymph node volume was associated with arthritic flare in mice. The lymph node expanded and subsequently collapsed before and during the flare, accompanied by the migration of a subset of B cells^{24,25}. But this is apparently not enough to clarify the reason for early flare in RA.

Further, musculoskeletal US, the evaluation tool, should also be taken into account. Power Doppler score at remission might have a predictive value for flare only in the short term.

A few studies had begun to address the significance of cumulative PD scores during the study period^{26,27}; however, they mainly focused on the value of cumulative PD scores in the field of structural progression, not the arthritic flare.

Through our cumulative metaanalysis, we reaffirmed the predictive value and the predictive accuracy of US PD positivity on risk of flare in patients with RA who are in clinical remission. RA patients with subclinical synovitis may require a cautious adjustment in medications and frequent surveillance during followup. Hence, achieving US remission and implementing an US-guided treatment strategy are becoming inevitable trends in the management of RA.

Our study had some limitations. First, the accuracy of our study was affected by the exclusion of an eligible abstract with key data inaccessibility. Second, no significant effect was observed in the subgroup analysis of duration of remission, which was in contrast to our clinical experience. However, Tokai, *et al*²⁸ once showed that a longer duration of remission went along with a lower PD score, probably meaning a lower risk of future relapse. We suspected the reason for our negative results was the lack of attention and subsequent sketchy records of this variable in the selected articles. As a result, deeper analysis on the effect of duration of remission still needs to be performed in future studies.

US PD positivity has a predictive value for flare and progressive bone erosion in patients with RA who are in clinical remission. The predictive ability is not influenced by duration of remission, disease duration, or medications. In addition, patients tend to experience an early relapse, mainly within 1 year, for unknown reasons. Therefore, further studies are needed to better understand the pathogenesis of RA flare, to bring about improved prognosis for patients with RA.

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ONLINE SUPPLEMENT

Supplementary data for this article are available online at jrheum.org.

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