# Novel Ultrasound Joint Selection Methods Using a Reduced Joint Number Demonstrate Inflammatory Improvement when Compared to Existing Methods and Disease Activity Score at 28 Joints

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*ABSTRACT.* ***Objective.*** A pilot study testing novel ultrasound (US) joint-selection methods in rheumatoid arthritis.

***Methods.*** Responsiveness of novel [individualized US (IUS) and individualized composite US (ICUS)] methods were compared with existing US methods and the Disease Activity Score at 28 joints (DAS28) for 12 patients followed for 3 months. IUS selected up to 7 and 12 most ultrasonographically inflamed joints, while ICUS additionally incorporated clinically symptomatic joints.

***Results.*** The existing, IUS, and ICUS methods' standardized response means were –0.39, –1.08, and –1.11, respectively, for 7 joints; –0.49, –1.00, and –1.16, respectively, for 12 joints; and –0.94 for DAS28.

***Conclusion.*** Novel methods effectively demonstrate inflammatory improvement when compared with existing methods and DAS28. (J Rheumatol First Release December 1 2015; doi:10.3899/jrheum.150590)

*Key Indexing Term:*
RHEUMATOID ARTHRITIS ULTRASOUND SYNOVITIS

Ultrasonography (US) is increasingly used to monitor joint inflammation in rheumatoid arthritis (RA)[1]. The optimal method of selecting reduced joint counts for US monitoring is not established. Various criteria have been used for reduced joint selection (e.g., frequency of involvement, feasibility, representativeness of joints, logistic regression models)[2]. Scanning fewer joints saves time[3] and yet can be representative of the inflammatory changes using extended scanning[4]. A systematic review studying US joint counts in RA[2] highlighted 2 existing methods[5,6] with good validity: 1 using a predefined 7-joint count[5] and another using a 12-joint count derived out of using US reduction from the frequency of inflammatory involvement from 44 joints[6]. Because the extent and distribution of affected joints differ between individuals, such methods do not ensure selection of the most affected joints or the greatest number of affected joints per individual for US monitoring.

In our pilot study, novel individualized joint selection methods are designed to improve the number of affected joints per patient for US scanning (limited by a target joint number). The novel individualized US (IUS) method selects up to 7 and 12 most inflamed joints detected on US, while the novel individualized composite US (ICUS) method additionally incorporates clinically symptomatic joints. The

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key feature is joint selection dictated by severity, beginning with the most severely affected joint and continuing until the target count is reached. Target joint limits were set at 7 and 12 to maintain consistency with joint counts specified by existing methods[5,6]. We hypothesized that the novel methods would improve experimental efficacy, resulting in greater sensitivity for detecting change when compared with existing methods and the Disease Activity Score at 28 joints (DAS28).

## MATERIALS AND METHODS

*Patients*. Seropositive patients with RA (DAS28 > 3.2) with ≥ 5 tender and/or swollen joints starting or escalating disease-modifying antirheumatic drugs (DMARD) and corticosteroid therapy in the rheumatology unit at the Singapore General Hospital were enrolled from March 2013 to May 2014 and followed up for 3 months. The local institutional review board approved this pilot study. Patients gave written informed consent. Patients were excluded if they had connective tissue diseases, other inflammatory arthritides, pregnancy, Hepatitis B/C, previous joint replacements, or a limb amputation.

At 0 and 3 months, a 44-joint clinical assessment (by a metrologist) and US were performed on the same day. A rheumatologist experienced in musculoskeletal US (blinded to the metrologist's findings) acquired and scored the US images.

*Clinical assessment*. Joints assessed for tenderness and pain included bilateral shoulders, elbows, wrists, metacarpophalangeal joints (MCPJ) 1–5, proximal interphalangeal joints 2–5, thumb interphalangeal joint, hips, knees, ankles, midtarsal, and metatarsophalangeal joints 1–5. Of these 44 joints, 40 were assessed for swelling (hips and midtarsals excluded using the approach of DAS44[7]). Joint tenderness and swelling were scored as 1 = yes and 0 = no. Joint pain was scored as 0 = none, 1 = mild, 2 = moderate, and 3 = severe. These scores form the clinical subscores used in the ICUS method (further described under the section "Individualized methods").

*US evaluation*. US was performed with General Electric Healthcare LOGIQe machine with a multifrequency linear array transducer (5–13 MHz) or Philips Medical Systems EPIQ 5G machine with a multifrequency linear array transducer (5–17 MHz). US outpatient facility, machine, probe, and settings were kept the same for each patient. Standardized scanning was based on the European League Against Rheumatism (EULAR) guidelines[8]. The joint/tendon sites scanned are listed in Table 1. US pathology definitions from the EULAR OMERACT (Outcome Measures in Rheumatology) US workgroup were used[1]. Greyscale synovial hypertrophy (SH) and power Doppler (PD) vascularity were scored semiquantitatively (0 = none, 1 = mild, 2 = moderate, 3 = severe) based on US scoring definitions used by Backhaus, *et al*[5]. This method was used at the hand and feet joints (because these joints were included in the study by Backhaus, *et al*) and extrapolated for use in other joints (including the elbow, knee, ankle, midtarsal, shoulder, and hip). However, at certain medium-sized joints (e.g., elbow, knee, and ankle) whereby relevant images from a scoring atlas[9] are available, semiquantitative scoring (0 to 3) was performed based on the relevant images from the scoring atlas. The shoulder and hip joints were not included in the original study by Backhaus, *et al* or the atlas, so where applicable, a score of 0 (normal) was taken to be greyscale SH less than the mean plus 2 SD of normal range[10]. Tenosynovitis was scored as 1 = yes and 0 = no for greyscale and PD findings. These scores form the US subscores used in the existing and individualized methods (further described under the sections "Existing methods" and "Individualized methods").

*Existing methods*. The existing methods include the 7 and 12 joints used by Backhaus, *et al*[5] and Naredo, *et al*[6], respectively (Table 1). The individual joint score (IJS) per joint was calculated as the sum of the US subscores divided by the maximum possible score at that joint, so as to equalize score weights across the joints. The maximum number of affected joints selected by the existing 7- and 12-joint methods are therefore 7 and 12, respectively.

*Individualized methods*. In the 7-joint approach, the individualized methods selected up to a maximum of 7 most affected joints for monitoring. In the 12-joint approach, the individualized methods selected up to a maximum of 12 most affected joints for monitoring. For the IUS method, the IJS at each joint was calculated as the sum of the US subscores divided by the maximum possible score at that joint. For the ICUS method, the IJS at each joint was calculated as the sum of the clinical and US

*Table 1*. Joint and tendon sites used in the individualized and existing methods.

| Joints/tendons Scanned, Bilateral, | Sites/Recesses | 7-joint Approach | | 12-joint Approach | |
|---|---|---|---|---|---|
| | | Individualized | Existing (clinically dominant side) | Individualized | Existing (bilateral) |
| 1. Shoulder | Axillary/posterior | | — | | — |
| 2. Elbow | Humeroradial, humeroulnar, posterior fossa | | — | | Yes |
| 3. Wrist, and ED/ECU/FD tendons | Radiocarpal (dorsal/volar), intercarpal/ulnorcarpal (dorsal) | | Yes | | Yes |
| 4. MCPJ 1–5, and flexor tendons | Dorsal/volar | Selects up to 7 most affected joints for monitoring | Yes, MCPJ 2 and 3 | Selects up to 12 most affected joints for monitoring | Yes, MCPJ 2 and 3 |
| 5. PIPJ 2–5 | Dorsal/volar | | Yes, PIPJ 2 and 3 | | — |
| 6. Thumb IPJ | Dorsal/volar | | — | | — |
| 7. Hip | Anterior | | — | | — |
| 8. Knee | Suprapatellar, lateral/medial recess | | — | | Yes |
| 9. Ankle, and lateral/medial tendons | Anterior tibiotalar | | — | | Yes |
| 10. Midtarsal | Talonavicular, cuneonavicular | | — | | — |
| 11. MTPJ 1–5 | Dorsal | | Yes, MTPJ 2 and 5 | | — |

ED: extensor digitorum; ECU: extensor carpi ulnaris; FD: flexor digitorum; MCPJ: metacarpophalangeal joints; PIPJ: proximal interphalangeal joints; IPJ: interphalangeal joints; MTPJ: metatarsophalangeal joints.

subscores divided by the maximum possible score at that joint. An affected joint for the existing and individualized methods was defined as IJS > 0.

The joint selection process (Figure 1) was as follows: the IJS from the 44 joints were ranked from largest to smallest score. The target joint count was set at 7 and 12. Joints with the highest IJS were identified. Joint selection progressed from the small to medium and larger joints as described in Figure 1. This process was repeated using joints with decreasing IJS until the target joint count was reached. The rationale for this joint selection process was (1) RA frequently involves the small joints, (2) scanning small joints is often easier, and (3) the semiquantitative scoring method was developed using smaller joints[11].

*Statistical analysis*. For the above methods, the IJS from the selected joints were summed to obtain a total inflammatory score (TIS) per patient. Patients' mean TIS were calculated at 0 and 3 months and were used for deriving the standardized response mean (SRM), calculated as the mean change in the TIS score divided by the SD of the change in the TIS score. The threshold values from Cohen for effect size (ES) are often used for interpretation, i.e., trivial [ES < 0.20, small (0.20 ≤ ES < 0.50), moderate (0.50 ≤ ES < 0.80), and large (ES ≥ 0.80)][12,13,14,15]. The average number of affected joints at baseline by these methods was reported. The SRM (at 3 mos) were calculated for these methods and the DAS28.

## RESULTS

*Patient characteristics*. Twelve patients with RA [mean (SD) age 57.6 (6.5) yrs, 83.3% women, 83.3% Chinese, 8.3% Indian, and 8.3% other ethnic groups] with mean (SD) disease duration at baseline of 55.8 (71.2) months completed the study. All patients were started or escalated with DMARD and corticosteroid therapy prior to the baseline US scans. Within 3 months prior to recruitment, 8 patients (66.7%) were receiving oral DMARD (which included methotrexate, sulfasalazine, hydroxychloroquine, and azathioprine) while 11 patients (91.7%) were receiving prednisolone. The mean DAS28 at baseline and 3 months was 5.21 and 4.32, respectively. The SRM for DAS28 was –0.94.

*Seven-joint and 12-joint approaches*. Using 7 joints, the affected joints (average number) for the existing, IUS, and ICUS methods were 3, 7, and 7, respectively, with corresponding SRM of –0.39, –1.08, and –1.11.

Using 12 joints, the affected joints (average number) for the existing, IUS, and ICUS methods were 7, 11, and 12, respectively. The SRM were –0.49, –1.00, and –1.16, respectively (Table 2).

## DISCUSSION

Our novel methods using a reduced joint number effectively demonstrate inflammatory improvement when compared with existing methods and the DAS28. This is unsurprising, given our emphasis on selecting affected joints (i.e., selecting as many affected joints, beginning with the most severely affected ones, until the target joint limit is reached) for followup scanning.

The SRM of the existing methods was consistent with the SRM reported in 2 RA studies[12,13] using US monitoring. The SRM was –0.2595 at 5 months in 1 study[12] using US of bilateral MCPJ 1–5 and –0.46 at 3 months in another study[13] using US at the dominant wrist.

Our individualized methods required a 44-joint US assessment at baseline to select the target joints. While this means additional time at the baseline scan, followup scans require less time when compared with the baseline scan because only the selected joints need rescanning.

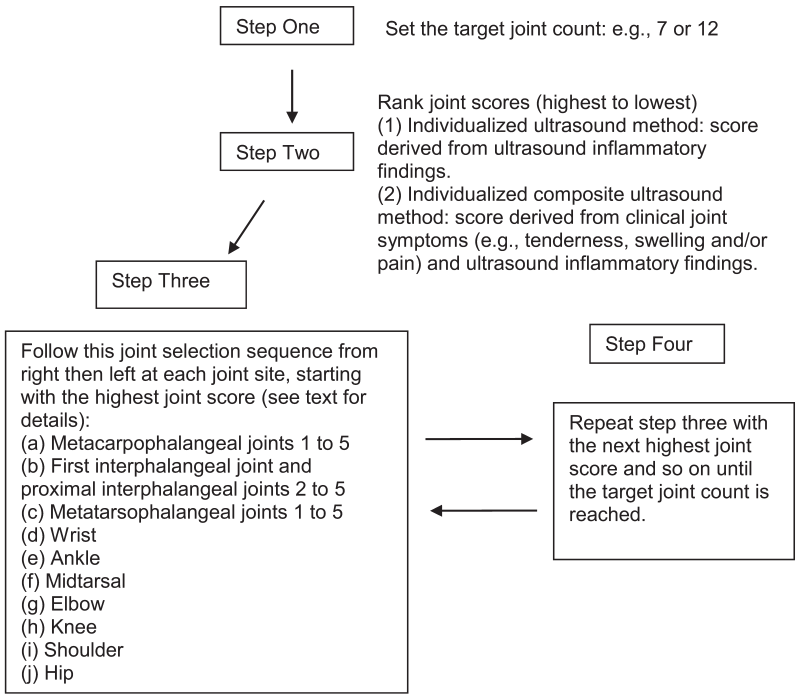


*Figure 1*. Individualized methods of the joint selection process.

*Table 2*. Results of the individualized and existing methods.

| No. Joints | Scoring Method | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | IUS | | ICUS | | Existing | | DAS28 | |
| | Baseline | Third Mo | Baseline | Third Mo | Baseline | Third Mo | Baseline | Third Mo |
| 7-joint[#] | | | | | | | | |
| Average no. affected joints* | 7 | | 7 | | 3 | | | |
| Mean (SD)^ | 2.14 (1.17) | 1.42 (0.76) | 2.06 (0.90) | 1.21 (0.68) | 0.47 (0.32) | 0.38 (0.25) | 5.21 (0.66) | 4.32 (1.00) |
| Median TIS (IQR) | 2.00 (1.45) | 1.42 (0.90) | 2.07 (1.24) | 1.16 (1.31) | 0.42 (0.38) | 0.37 (0.50) | | |
| SRM (95% CI) | | –1.08 (–1.79 to –0.34) | | –1.11 (–1.83 to –0.37) | | –0.39 (–0.97 to 0.21) | | –0.94 (–1.68 to –0.17) |
| 12-joint[#] | | | | | | | | |
| Average no. affected joints* | 11 | | 12 | | 7 | | | |
| Mean (SD)^ | 2.70 (1.61) | 1.76 (0.95) | 2.81 (1.20) | 1.84 (0.82) | 1.46 (0.80) | 1.27 (0.72) | | |
| Median TIS (IQR) | 2.48 (1.99) | 1.60 (1.20) | 2.74 (1.58) | 1.75 (1.25) | 1.55 (1.65) | 1.42 (1.37) | | |
| SRM (95% CI) | | –1.00 (–1.69 to –0.29) | | –1.16 (–1.89 to –0.40) | | –0.49 (–1.09 to 0.12) | | |

[#] Refers to no. joints used in the IUS, ICUS, and existing methods (and not DAS28). * An affected joint is defined as individual joint score greater than 0. ^ For the IUS, ICUS, and existing methods, refers to mean TIS score; for DAS28, refers to the mean DAS28 score. IUS: individualized ultrasound; ICUS: individualized composite ultrasound; TIS: total inflammatory score; SRM: standardized response means; IQR: interquartile range; DAS28: Disease Activity Score at 28 joints.

Our pilot results will need to be confirmed in larger cohorts. Future studies incorporating control group(s) for comparison, as well as correlation with other patient outcomes (e.g., disease remission, structural alteration, functional prognosis) would be necessary. The number of reduced joints to assess during followup could also be explored in larger studies.


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