Predictive grade of ultrasound synovitis for diagnosing rheumatoid arthritis in clinical practice and the possible difference between patients with and without seropositivity

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

Department of Internal Medicine and Rheumatology, Juntendo University Faculty of Medicine, Tokyo, Japan

Abstract

Objective. To determine the degree of contribution and the contributing factors of ultrasound in the diagnosis of rheumatoid arthritis (RA) in daily clinical practice and the predictive differences depending on seropositivity.

Methods. We included 122 patients who presented with the main complaint of finger and/or wrist joint pain but for whom no definite diagnosis was reached or treatment strategy was provided. Ultrasound was performed on at least 22 joints (both wrist joints, proximal interphalangeal joint, and metacarpophalangeal joints), and patients were followed for ≥6 months. Factors contributing to RA diagnosis were determined and compared between seropositive and seronegative RA patients.

Results. RA was diagnosed in 52 of 122 patients, in whom the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria (odds ratio [OR] = 4.74, P = 0.01) and gray scale (GS) grade of 3 (OR = 3.64, P = 0.04) for ≥1 joint were the contributing factors. In seropositive RA, the ACR/EULAR criteria (OR = 15.53, P < 0.001) and power Doppler (PD) ≥2 for ≥1 joint (OR = 10.48, P = 0.0048) were the contributing factors. In seronegative RA, PD ≥1 for ≥1 joint contributed the most (OR = 20.00, P = 0.0044), but the ACR/EULAR criteria did not contribute to RA diagnosis (P = 0.57).

Conclusion. Ultrasound findings contributed to RA diagnosis in clinical practice. The contributing factors are different in the presence or absence of seropositivity, and ultrasound complementation was particularly useful in seronegative RA patients.

Introduction

Articular pain is a common clinical manifestation found in various diseases [1]. Despite the presence of expert rheumatologists, many of them take a long time to provide definitive diagnosis and initiate treatment, as it is difficult to narrow differential diagnoses using only blood examination results and physical examination in patients with joint pain. Rheumatoid arthritis (RA) and osteoarthritis (OA) are the two most common diseases with articular pain, and the prevalence of RA ranges from 0.5% to 1.0% [2], causing a major burden on the economy and the society. In order to improve the prognosis of RA, it is crucial to conduct early diagnosis and treatment. Physical examination is still the gold standard for diagnosing arthritis, and joint involvement is the most skill-dependent and irreproducible domain compared with others, especially when joint manifestation is modest.

It is apparent that modern imaging techniques, such as musculoskeletal ultrasound (US), are more sensitive for detecting arthritis than physical examination. Numerous studies have validated the use of US as a helpful diagnostic tool for RA, spondyloarthropathies, crystal diseases, OA, and other rheumatic diseases [3–6]. Nakagomi et al. studied pathognomonic findings in RA diagnosis, in which if gray scale (GS) ≥2 or power Doppler (PD) ≥1 was found, the chance of progression from undifferentiated arthritis (UA) to RA was high [7]. Freeston et al. reported that the presence of GS 3 or PD ≥1 increased the probability of RA [8]. Kawashiri et al. reported that a finding of PD ≥2 was more useful for the early diagnosis of RA than the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for RA [9] and bone edema on MRI [10].

The 2010 ACR/EULAR classification criteria for RA are utilized to make a diagnosis of RA in patients with newly presenting inflammatory arthritis. However, its specificity is lower than that of the 1987 criteria [11]. Distinguishing RA from other diseases is important, but diagnosing RA in seronegative cases is often difficult [12,13].

The number of studies showing the advantage of US in regular clinical practice is still insufficient to construct robust evidence.

Keywords

Predictive factor, Rheumatoid arthritis, Ultrasound
On the basis of various pieces of information and comprehensive judgment, attending physicians perform various diagnoses and start treatment; thus, the principal aims of the present study were to examine among conventional laboratory findings, the various classificatory criteria, and US findings of RA what contributes to forming diagnoses in the diagnostic process for patients with joint pain and to assess the usefulness of intentional US in combination. Particularly with regard to the difference of seropositivity, the aim of the present study was to provide further supportive evidence of US use for seropositive and seronegative RA diagnoses separately and to evaluate the presence or absence of superiority compared with other clinical information, including ACR/EULAR criteria for RA diagnosis in the regular clinical practice.

Materials and methods

Patients

The study protocol complied with the Helsinki Declaration of 1975/83. We retrospectively studied 122 patients with any finger and wrist joint symptoms who visited our outpatient clinic of our university, from January 2011 to December 2012. Studied these patients are defined as patients who were not made the definitive diagnosis and therapeutic strategy by the attending physician at that point and asked to perform US examination to US examiners to conduct a differential diagnosis and to determine therapeutic strategy. At the time of US examination, patients who had already received medical treatment for joint symptoms, such as disease-modifying anti-rheumatic drugs, biologics, and glucocorticoids, apart from non-steroidal anti-inflammatory drugs, were excluded from the present study. During the follow-up period after US examination—having RA was defined based on a subjective judgment of the attending physician—methotrexate treatment was initiated and diagnosis did not change in at least half year. We assumed that attending physician might make diagnosis reference to the results of US examinations.

US evaluation (ProSound Alpha7 with UST-5411 transducer; Hitachi Aloka Medical, Ltd. Tokyo, Japan) was performed on at least 22 joints: the proximal interphalangeal (PIP) joints, metacarpophalangeal (MCP) joints, and both wrists as well as the dorsal and volar sides. The US examination was performed by either one of the three rheumatologists (KM, SA, and MO) trained to use musculoskeletal US in a temperature-controlled darkened room. US examiners were blinded to clinical and laboratory information. Synovial effusion and/or hypervascularity were graded on a semi-quantitative GS ranging from 0 to 3, and synovial blood flow in each of the intra-articular and peri-articular synovial sites was evaluated using PD US and graded on a semi-quantitative scale from 0 to 3 as mentioned before [14]. The PD signal parameters were adjusted to the lowest permissible pulse repetition frequency to maximize sensitivity, while the Doppler gain was set just below the level to maximize the intra-articular and peri-articular synovial sites was evaluated.

Comparison of Ultrasound Findings of RA and non-RA

Total GS/PD score of the two RA and non-RA groups were compared. In addition, the total GS/PD score of each disease in the non-RA group were compared. Moreover, US findings in each joint part of PIP/MCP/wrist were compared.

Analysis of Factors Contributing to RA Diagnosis

Thirty-six combinations of findings (Supplementary Table 1 to be found online at http://informahealthcare.com/doi/abs/10.3109/14397595.2015.1069457) from PD grade (≥1 or ≥2), GS grade (≥1, ≥2, or ≥3), the joint parts (PIP, MCP, or wrist), and number of joints (≥1, ≥2, or ≥3) were used as inclusion factors of US findings contributing to RA diagnosis. In addition, age, sex, CRP, ESR, RF, anti-citrullinated peptide antibody (ACPA), and ACR/EULAR classification criteria were included as candidate factors. Independent variables were chosen using the stepwise method. Factors contributing to RA diagnosis were analyzed using multiple logistic analysis, and $P < 0.05$ was chosen as the significance level. Factors contributing to diagnosis were extracted in each RA diagnosis in total patients, seropositive, and seronegative group.

Duration from Joint US Examination to RA Diagnosis

Duration from the first visit to our hospital to joint US examination (Visit-US duration month) and from joint US examination to RA diagnosis (US-Diagnosis duration month) of total RA, seropositive RA group, and seronegative RA group were compared.

Statistical analysis

Statistical analysis was performed using SPSS version 16.0 J (IBM Japan, Tokyo, Japan). Non-normally distributed data were analyzed using nonparametric tests (Mann–Whitney U test) for two groups, and Kruskal–Wallis test for three or more groups. Categorical data were analyzed using chi-square test or Fisher’s exact test. A multivariate logistic regression model was constructed using a forward stepwise method. $P$ values less than 0.05 were considered significant unless otherwise specified.

Results

Patients' background and diagnosis results

The patients’ profiles at US examination are shown in Table 1. The established diagnosis from a comprehensive judgment taken by the attending physician was RA in 52 patients and non-RA in 70 patients. The breakdown of non-RA is as follows: polymyalgia rheumatica a (PMR) in 11 patients, Sjogren’s syndrome (SjS) in 10 patients, OA in 8 patients, other conditions in 18 patients (systemic lupus erythematosus in 3 patients, systemic sclerosis in 3 patients, remitting seronegative symmetrical synovitis pitting edema or RS3PE in 2 patients, fibromyalgia in 2 patients, gouty arthritis in 2 patients, synovitis, acne, pustulosis, hyperostosis, osteitis syndrome in 1 patient, reactive arthritis in 1 patient, tenosynovitis in 2 patients, carpal tunnel syndrome in 1 patient, and complex regional pain syndrome in 1 patient), and UA in 23 patients.

Comparative results of US findings between RA and non-RA

The total GS/PD score between 52 RA patients and 70 non-RA patients are compared in Figure 1a. The total GS scores of the RA group and non-RA group were 12.83 ± 1.82 (mean ± SEM) and 3.21 ± 0.66, respectively (Mann–Whitney test, $P < 0.0001$). The total PD scores were 7.94 ± 1.32 and 1.01 ± 0.24, respectively (Mann–Whitney test, $P < 0.0001$), suggesting that the RA group had a significantly higher score in either comparison. Among the non-RA group, the GS/PD score of PMR was high and there were no significant differences ($P = 0.1911/0.0789$, Kruskal–Wallis test). (Figure 1b) Comparative results of US findings in each diagnosis group based on the grouping of joint part of PIP/MCP/wrist are shown in Figure 2. The finding rates of total GS/PD score in either PIP/MCP/wrist in the RA group were significantly higher.

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than those in the non-RA group. US findings of RA and PMR did not show any difference in total GS scores of the wrist and MCP; however, RA showed a higher tendency of finding rate than PMR in the total PD score of the wrist and MCP and the total GS/PD score of PIP. GS/PD of UA/SjS in either PIP/MCP/wrist did not show any or show significantly lower finding rate. OA with total GS score more than 1 or 2 had a lower rate in MCP/PIP.

Results of analysis of factors contributing to RA diagnosis

The results of multiple logistic analyses for each total RA, seropositive RA, and seronegative RA groups are shown in Table 2, and the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of RA diagnosis are shown in Table 3. In the total RA group, ACR/EULAR classification criteria (odds ratio [OR] = 4.74, \( P = 0.01 \)) was the main factor contributing to RA diagnosis, followed by GS grade 3 in the wrist/MCP/PIP joints (OR = 3.64, \( P = 0.04 \)). By combining these two factors, the PPV improved to 95.2%. The comparison of the profiles of RA and non-RA groups is shown in Supplementary Table 2 to be found online at http://informahealthcare.com/doi/abs/10.3109/14397595.2015.1069457.

In the seropositive RA group, similar to the RA group, the ACR/EULAR classification criteria (OR = 15.53, \( P < 0.001 \)) were the main factor contributing to RA diagnosis, followed by PD grade \( \geq 2 \) in either wrist/MCP/PIP joints (OR = 10.48, \( P = 0.0048 \)). In addition, by combining these two factors, the PPV increased to 95.7%. The comparison of the profiles of the seropositive RA and non-RA groups is shown in Supplementary Table 3 to be found online at http://informahealthcare.com/doi/abs/10.3109/14397595.2015.1069457.

In the seronegative RA group, US findings of PD grade \( \geq 1 \) in either wrist/MCP/PIP joints (OR = 20.00, \( P = 0.0044 \)) were the main contributing factor for RA diagnosis, followed by at least one GS grade 3 in PIP (OR = 8.52, \( P = 0.0295 \)). Contribution of the ACR/EULAR classification criteria was not significant in the seronegative group (\( P = 0.5774 \)). The profiles of the seronegative RA and non-RA groups are shown in Supplementary Table 4 to be found online at http://informahealthcare.com/doi/abs/10.3109/14397595.2015.1069457.

Table 1. Patient demographics and clinical laboratory data at the US examination.

|                        | All patients (N = 122) |
|------------------------|------------------------|
| Age (years) mean ± SD  | 55.4 ± 13.5            |
| Female, n (%)          | 95 (77.9)              |
| Tender joint counts mean ± SD | 3.82 ± 10.64         |
| Swollen joint counts mean ± SD | 3.68 ± 5.71        |
| CRP Positive, n (%)    | 67 (54.9)              |
| Value (mg/dL) mean ± SD| 78 (63.9)              |
| ESR Positive, n (%)    | 47 (38.5)              |
| Value (mm/h) mean ± SD | 29 (23.8)              |
| RF Positive, n (%)     | 31 (25.4)              |
| Titer: >×3, n (%)      | 69 (56.6)              |
| ACPA Positive, n (%)   | 156.71 ± 212.87        |
| Titer: >×3, n (%)      |                        |
| MMP-3 Positive, n (%)  |                        |
| Value (ng/mL) mean ± SD|                        |

CRP C-reactive protein, ESR erythrocyte sedimentation rate, RF rheumatoid factor, ACPA anti-citrullinated peptide antibody, MMP-3 matrix metalloproteinase-3.

Figure 1. (a) Comparative results of the total GS/PD score in 52 RA patients and 70 non-RA patients. Comparison of total GS/PD scores in patients with and without RA. The total GS and total PD scores represent the sum of the GS and PD scores of all 22 joint regions, and the maximum score for each patient is 66. Statistically significant differences are shown. (Mann–Whitney test, \( P < 0.0001 \)). (b). Comparative results of the total GS/PD scores of each pathology groups in the non-RA group. Comparison of total GS/PD scores in patients without RA: UA, SjS, PMR, and OA. There were no significant differences (\( P = 0.1911/0.0789 \), Kruskal–Wallis test).
found to have a high degree of swelling on US images were possibly diagnosed to have RA and initiate treatment. It is thought that in contrast to the PD finding, specialists do not understand the severity of swelling in GS1,2 on a pathological level or do not use the findings that serve as reference for diagnosis. Furthermore, similar to the findings of the present study, Kawashiri et al. reported that a finding of PD/H113502 was detected as an extremely well-balanced contributing factor, but no significant differences were observed [10]. As compared with other studies that were strongly suspected the prevalence of RA, the patients of the present study had widely ranged rheumatic diseases, which may have led to these differences. By the same reason, it is thought that the RA patients of this study had lower sensitivity of seropositivity and the ACR/EULAR classification criteria, and lower US findings of the PIP joints.

In addition, among these two contributors of RA diagnosis, ACR/EULAR classification criteria reflect well the progression of RA diagnosis in clinical practice, and additional use of US has proved useful in the actual clinical practice [7,10,15].

The most interesting points from the results of the present study were that the factors contributing to RA diagnosis were different between the seropositive and seronegative groups, and that the OR

![Comparison of US findings of patients with and without RA: UA, SjS, PMR, and OA in each joint. White, gray, and black bars represent grade 1, grade 2, and grade 3 semi-quantitative GS and PD signals, respectively.](image)

**Analysis results of duration from Joint US examination to RA diagnosis**

The mean of Visit-US duration month and US-Diagnosis duration month were 23.2 ± 46.1 months and 0.65 ± 0.91 months, respectively, in the total RA group; were 12.8 ± 12.6 months and 0.58 ± 0.78 months, respectively, in the seropositive RA group; and were 35.4 ± 65.1 months and 0.72 ± 1.04 months, respectively, in the seronegative RA group.

**Discussion**

In the present study, we investigated the degree of contribution of joint US examination on differential and early RA diagnosis in actual clinical practice, the pathognomonic joint US findings that significantly contribute to RA diagnosis, as well as the duration required to reduce the time taken for RA diagnosis.

Significant factors that differentiate between RA and non-RA in multivariate analysis were ACR/EULAR classification criteria and GS3 in any joint, followed by PD1, which is similar to the results reported by Freeston et al. [8]; and no other factors from the clinical evaluation items was significant. This result suggests that clinically unidentified findings of joints that were subsequently
of each contributing factor in the seropositive and seronegative RA groups was higher than that in the total RA group. Between the two groups, US finding that contributed most to RA diagnosis was PD grade ≥ 1 in the seropositive group and PD grade ≥ 2 in the seropositive group, which was milder in the seronegative group. In previous studies, compared with the seropositive RA group, the seronegative RA had fewer clinically affected joints and lower activity during onset, had larger joints affected than small joints, and lesser bone destruction in the finger and wrist joints [16–19]. The results of the present study highlight, for the first time, clinical differences between the seropositive and seronegative RA groups using US images. Thus, the seronegative RA group had larger joints affected, fewer joints with arthritis, and a mild degree of RA, which indicate the difficulty of diagnosing seronegative RA on physical examination alone. This study also found that Visit-US duration months of the seronegative RA group was longer than that of the seropositive RA group. In order to achieve better sensitivity in RA diagnoses for seronegative patients, it is important to perform joint US in the usual clinical practice. In addition, these results also suggest the importance of US equipment with sufficient Doppler sensitivity and setting and US examiner’s careful judgment on the presence or absence of mild synovitis in seronegative patients. Conversely, US findings of each contributing factor in the seropositive and seronegative RA groups was higher than that in the total RA group.

Table 2. Results of multivariate logistic regression analysis: Predicted contributing factors.

|                      | Odds ratio | P value | 95% CI       |
|----------------------|------------|---------|--------------|
| All patients         |            |         |              |
| At least 1 joint with GS 3 | 3.64      | 0.04    | 1.07–13.72  |
| 2010 ACR/EULAR       | 4.74      | 0.01    | 0.92–19.55  |
| classification criteria |          |         |              |
| At least 1 joint with PD ≥ 1 | 4.08 | 0.06 | 0.77–10.45 |
| At least 1 joint with PD ≥ 2 | 2.75 | 0.12 | 1.57–15.37 |
| Seropositive         |            |         |              |
| At least 1 joint with PD ≥ 2 | 10.48 | 0.0048 | 2.06–63.77  |
| 2010 ACR/EULAR       | 15.53     | < 0.001 | 3.04–102.03 |
| classification criteria |          |         |              |
| Seronegative         |            |         |              |
| At least 1 PIP joint with GS 3 | 8.52  | 0.0295 | 1.21–175.28 |
| At least 1 joint with PD ≥ 1 | 20     | 0.0044 | 2.45–431.05 |
| At least 1 joint with PD ≥ 2 | 1.44  | 0.6578 | 0.28–7.85   |
| 2010 ACR/EULAR       | 1.74      | 0.5774 | 0.26–15.59  |
| classification criteria |          |         |              |

Table 3. Performance of ultrasound.

| Contributing factors classification criteria | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|--------------------------------------------|-----------------|-----------------|---------|---------|
| All patients                               |                 |                 |         |         |
| At least 1 joint with GS 3a                | 55.8            | 92.9            | 85.3    | 73.9    |
| 2010 ACR/EULAR classification criteria     | 57.7            | 90              | 81.1    | 74.1    |
| a + b                                      | 38.5            | 98.6            | 95.2    | 68.3    |
| At least 1 joint with PD ≥ 1               | 92.3            | 64.3            | 65.8    | 91.8    |
| At least 1 joint with PD ≥ 2               | 86.5            | 72.9            | 70.3    | 87.9    |
| Seropositive                               |                 |                 |         |         |
| At least 1 joint with PD ≥ 2c              | 82.1            | 83.3            | 85      | 80      |
| 2010 ACR/EULAR classification criteria     | 89.3            | 79.2            | 83.3    | 86.4    |
| c + d                                      | 78.6            | 95.8            | 95.7    | 79.3    |
| Seronegative                               |                 |                 |         |         |
| At least 1 PIP joint with GS 3c            | 37.5            | 97.8            | 90      | 75      |
| At least 1 joint with PD ≥ 1f              | 37.5            | 97.8            | 90      | 75      |
| e + f                                      | 37.5            | 97.8            | 90      | 75      |
| At least 1 joint with PD ≥ 2               | 79.2            | 78.3            | 65.5    | 12.2    |
| 2010 ACR/EULAR classification criteria     | 20.8            | 95.7            | 71.4    | 69.8    |

In this study, patients were followed up for 6 months to 1 year after US examination; 48 patients who received treatment immediately after RA were diagnosed after US examination. In addition, US was also performed in the non-RA group, and the diagnosis of other pathologies and their treatment were initiated immediately after US examination. For the many cases that were included for observation (data not shown) and for suspected cases particularly the seronegative RA group, performing US at an earlier stage contributed to attending physician’s motivation of early diagnosis and treatment, which lead to prognostic improvement.

As previously reported, we found that the objective observation of synovitis during the general diagnosis procedure for patients who present with arthralgia greatly progresses many differential diagnoses. However, the presence of synovitis alone is insufficient to diagnose RA, and it is necessary to consider if the synovitis is sustained and has caused joint destruction, but assessment cannot be made at the time of initial US. In the present study, each attending physician considered the immunologic characteristics and progress of the disease in each patient, even in those with synovitis detected on US, and comprehensively determined if the patient had RA. In the present study, the use of US examination to confirm synovitis has contributed in diagnoses, especially in cases of seronegative RA. However, in addition to the above-mentioned difference in seropositivity, this was thought to be due to not only the fact that the visit-US interval was longer in cases of negative RA, but also the fact that during that period, other diseases had already been excluded and persistent synovitis had already been determined to exist.

In the present study, only factors for RA diagnosis could be determined and differential diagnoses from PMR could not be determined. US findings are included in the PMR classification criteria [20, 21], but differentiating it from RA is difficult using US findings alone [22]. In this study, having PMR was defined based on a subjective judgment of the attending physician in spite of relevance for classification criteria. We observed a trend in the difference of findings for peripheral joints in the present study, but US findings could not be used for differential diagnosis between RA and PMR; therefore, a comprehensive clinical judgment, including other joint findings, is important.

US examination aided RA diagnosis, allowed differentiation of RA from other pathologies, and allowed treatment initiation in the daily clinical practice in patients with joint pain. In addition, this study reported for the first time that pathognomonic US findings contributing to RA diagnosis are possibly different in the presence or absence of seropositivity. It is important to use US in patients with joint pain in usual clinical setting. Accordingly, in order to serve higher degree of medical treatment for rheumatic disease patients, its widespread use is anticipated.
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Conflicts of interest
None.

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Supplementary material available online
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