

Correlation of US-7 and US-9 Scores with Disease Activity Score using 28 Joint Counts (DAS28) in Patients with Rheumatoid Arthritis

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What's Known

- The German 7-joint Ultrasound, as a sonographic method, and Disease Activity Score Using 28 Joint Counts, as a clinical method, are the commonly used scoring systems in RA patients.

What's New

- Both the German 7-joint Ultrasound and the novel ultrasound score-based system, US-9 (joints assessed with the German 7-joint Ultrasound plus knees) scores are significantly correlated with the Disease Activity Score Using 28 Joint Counts score. However, there is no significant difference between them. Therefore, adding large joints such as knees into sonographic evaluation does not necessarily improve diagnostic value and clinical correlation.

Abstract

Background: The attentive management of rheumatoid arthritis (RA) has attracted particular attention. The German 7-joint Ultrasound (US-7) is the first scoring system that combines bone erosions and soft tissue lesions in a single composite scoring system. This study aimed to assess the correlation between US-7 and Disease Activity Score Using 28 Joint Counts (DAS28) in clinically active RA patients. The efficacy of a novel ultrasound score-based system, the US-9 score (joints assessed with US-7 plus knees), was also compared with the standard US-7 score.

Methods: All the RA patients referred to the outpatient rheumatology clinic of Ghaem Hospital, Mashhad, Iran, during 2019-2020 were included. 28 joints were clinically examined to calculate DAS28. Nine joints were assessed comprising the German US-7 plus knees using grayscale ultrasonography (GSUS) and power Doppler ultrasonography (PDUS). Retrieved data were analyzed by SPSS software, version 22. The Spearman Correlation test was used to find the correlation between DAS28 and ultrasonographic findings. The statistical significance level was set at $P < 0.05$.

Results: This study was composed of thirty-five RA patients with a mean age of 49.1 ± 12.0 years. US-7 synovitis scores in GSUS and PDUS were significantly correlated with DAS28 ($P = 0.02$, $r = 0.38$ and $P = 0.003$, $r = 0.48$, respectively). US-9 synovitis scores in GSUS and PDUS were also significantly correlated with DAS28 ($P = 0.003$, $r = 0.49$ and $P = 0.006$, $r = 0.45$, respectively). The synovitis score measured by GSUS was significantly correlated with the GSUS knee synovial score ($P = 0.01$, $r = 0.42$).

Conclusion: Ultrasound assessment of large joints such as knees can be an effective approach to determining RA severity. However, it can be proposed that adding more involved joints into the sonographic assessment does not necessarily provide a better clinical correlation.

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Keywords • Arthritis, rheumatoid • Ultrasonography • Joints • Ultrasonography, doppler

Introduction

Considerable progress has been made in our understanding of the underlying pathophysiology and therapeutic approaches of rheumatoid arthritis (RA). Therefore, significant concerns about

early diagnosis, attentive management, and treatment of RA have been raised.^{1, 2} Clinical and imaging scoring systems are developed to monitor clinical findings, disease activity, and treatment response. Indeed, these modalities are used to achieve earlier diagnosis and adjust immunosuppressive therapy in RA patients.³⁻⁵

Disease activity score using 28 joint counts (DAS28) is a useful tool for measuring RA disease activity.⁶ This scoring system was developed by Prevoo and others in 1994.⁷ DAS28 evaluates 28 joints, including shoulders, elbows, wrists, metacarpophalangeal, proximal interphalangeal, and knee joints. Some recent studies have suggested limitations regarding the DAS28, such as identifying some patients as remitted cases despite the presence of subclinical disease activity, which causes erosive radiographic advancement and joint deformity.^{8, 9}

Therefore, more accurate imaging modalities are needed to detect joint destruction at its initiation stage. Ultrasound (US) is one of the most sensitive imaging modalities for evaluating anatomical changes, such as synovitis, tenosynovitis, and bursitis, as well as bone lesions and treatment efficacy in patients with RA.^{10, 11}

The German 7-joint Ultrasound (US-7) score, is a feasible joint scoring system, which is implemented for the assessment of disease severity in RA patients using ultrasound imaging.¹² The US-7 score evaluates joint lesions, including synovitis, tenosynovitis, and bone erosions based on seven joints of the clinically dominant hand and foot.¹³ However, no US score systems such as US-7 have been established for large joint involvement in RA patients. The current study aimed to assess the value of US-7 as a marker of disease activity and evaluate its correlation with DAS28 in Iranian patients with RA. A new ultrasound score based on nine involved joints (joints assessed with US-7 plus the knees) (US-9) was also introduced and compared with the standard US-7 score.

Materials and Methods

Patients

In this cross-sectional study, after institutional review board approval (ethical code: IR.MUMS.fm.REC.1397.408), all RA patients who were referred to the outpatient rheumatology clinic of Ghaem Hospital, Mashhad, Iran, during 2019-2020, were assessed. All patients were diagnosed by an experienced rheumatologist according to the 2010 American College of Rheumatology/European League Against

Rheumatism (ACR/EULAR) criteria.¹⁴ After the confirmation of RA diagnosis (<7 days), the patient's demographic and socioeconomic data were recorded.

DAS28 was used to measure the disease activity. According to the DAS28, 28 joints, including proximal interphalangeal (PIP) and metacarpophalangeal (MCP), wrists, elbows, shoulders, and knees, were clinically evaluated by a rheumatologist for swelling or tenderness. DAS28 score was calculated by the formula on the DAS website (URL: <https://www.das-score.nl/das28/DAScalculators/dasculators.html>), with erythrocyte sedimentation rate (ESR), patient global health (0-100), and number of swollen and tender joints. Then, eligible patients who were not in the remission phase of RA (DAS28>2.5) signed the informed consent. Patients who had joint pain due to other etiologies, such as trauma, psychosomatic reasons, and degenerative diseases, were excluded from the study.

Ultrasonography

In the next step, patients were referred to the radiology inpatient service of Ghaem Hospital, Mashhad, Iran. They were examined with B-mode (grayscale) and power Doppler by a single radiologist with about seven years of experience who was blind to patients' DAS28 scores and disease severity. The selected joints of the wrist, hand, foot, and knees in all patients were evaluated by ultrasound according to the European League Against Rheumatism (EULAR).¹⁵ Based on the German US-7, the MCP2, MCP3, PIP2, and PIP3 joints in the palmar and dorsal sides, the MTP2 and MTP5 joints in the dorsal and plantar sides, and the wrist joints in the palmar, dorsal, and ulnar sides were examined using grayscale ultrasonography (GSUS) and power Doppler ultrasonography (PDUS).

The method of German US-7 using GSUS and PDUS was previously described by Backhaus and colleagues.¹³ In summary, GSUS was used to evaluate joint lesions, including bone erosions, tenosynovitis, and synovitis. Patients were scored based on the presence (1) or absence (0) of the tenosynovitis and erosions. Erosion was defined as the presence of interruption on the bone surface in two perpendicular planes. Synovitis was scored semi-quantitatively (grade 0: absence, grade 1: mild, grade 2: moderate, and grade 3: severe synovitis). PDUS was used to assess tenosynovitis and synovitis from the palmar and dorsal planes in each joint. Synovitis and tenosynovitis were scored semi-quantitatively (grade 0: no synovial color, grade 1: one or two small synovial color signals, grade

2: less than 50% of synovium filled with color signal, and grade 3: more than 50% of synovium filled with color signal).¹⁶

US-7 and US-9 Calculation

The sum of the GSUS and PDUS scores of each joint side was used to calculate US-7 score in five categories, including synovitis score by GSUS (score 0-27), tenosynovitis score by GSUS (score 0-7), erosion score by GSUS (score 0-14), synovitis score by PDUS (score 0-39), and tenosynovitis score by PDUS (score 0-21). To calculate the knee synovial score, PDUS and GSUS were performed and scored (0 to 3) in the medial, lateral, and superior compartments of both knees, separately. The semi-quantitative GSUS scoring of each knee compartment was as follows: grade 0=synovial thickness between 0- and 1.9-mm, grade 1=synovial thickness between 2- and 3.9-mm, grade 2=synovial thickness between 4 and 5.9 mm, and grade 3=synovial thickness about 6 mm and above. The sum of all three compartments' scores in both knees was assumed as GSUS knee synovial score (score 0-18).

The semi-quantitative PDUS scoring of each knee compartment was as follows: grade 0=no synovial color signal, grade 1=one or two small synovial color signals, grade 2=less than 50% of synovium filled with color signal, grade 3=more than 50% of synovium filled with color signal. The sum of all three compartments' scores in both knees was assumed as PDUS knee synovial score (score 0-18). The acquired scores from the knees were added to the measured GSUS and PDUS US-7 scores. The sum of the US-7 and knee synovial scores was assumed as the US-9 GSUS score (score 0-45) and the US-9 PDUS score (score 0-57).

Sample Size Calculation

As this study was the first that assessed the correlation between the newly introduced US-9 and DAS 28, and there was no previous article using US-9, the estimated sample size according to the possible correlation coefficient of 0.50 between US-9 and DAS 28 was calculated as 29. Since we also examined the correlation between US-7 and DAS 28, our sample size was estimated based on the data given in the article published by Leng and colleagues.¹⁰ In the mentioned article, the correlation coefficient between DAS28 and US7 at the week sixth was reported as 0.45. Considering $r=0.45$, $\alpha=0.05$, and $\beta=0.2$, the sample size was calculated as 36 individuals using the following formula: $C=0.5*\ln[(1+r)/(1-r)]=0.4847$.

The standard normal deviate for $\alpha=Z\alpha=1.9600$

The standard normal deviate for $\beta=Z\beta=0.8416$ (Considering $r=0.45$, $\alpha=0.05$, $\beta=0.2$)

The mentioned formula is accessible at the following address: <http://sample-size.net/correlation-sample-size/>

Statistical Analysis

All the statistical analyses were performed using the SPSS for Windows TM, version 20 software package (SPSS Inc., Chicago, IL, USA). Quantitative data were represented as mean \pm SD. For categorical variables, frequency and percentage were used. Bivariate correlations were performed using Spearman's Correlation test. A $P<0.05$ was considered as statistically significant.

Results

This study was composed of 35 RA patients with a mean age of 49.1 \pm 12.0 years (mean \pm SD). 33 patients were female and two were male. Patients' characteristics and demographic data are shown in table 1. The duration of the disease and the treatment ranged from 0 to 30 years and 0 to 20 years, respectively. The most common comorbidity was hypothyroidism (26.5%). Prednisolone, sulfasalazine, and methotrexate (MTX) were the most commonly used medications by patients. The DAS28 mean \pm SD was 6.1 \pm 1.2, and most patients had severe disease activity (85.7%).

Table 2 summarizes the PDUS and GSUS findings based on the US-7. GSUS and PDUS synovitis scores (US-7) were significantly correlated with DAS28 ($P=0.02$ and 0.003 , respectively) (figures 1-4). Likewise, GSUS and PDUS knee synovial scores showed a statistically significant correlation with DAS28 ($P=0.007$ and 0.02 , respectively). However, no significant correlation between DAS28 and tenosynovitis scores was found in the US-7 scoring system ($P=0.16$ for GSUS and $P=0.19$ for PDUS). There was also a significant correlation between synovitis score measured by GSUS (US-7) and GSUS knee synovial score ($P=0.01$, $r=0.42$). Both GSUS-9 (GSUS synovitis score [US-7] plus knee synovial GSUS score) and PDUS-9 (PDUS synovitis score [US-7] plus knee synovial PDUS score) scores were significantly correlated with DAS28 ($P=0.003$ and 0.006) (figure 5 and table 3).

Discussion

In this study, a significant correlation between both US-7 GSUS and PDUS and DAS28 was found. Likewise, there was a significant

Table 1: Patients' characteristics

| Variable | | Patients (N=35) |
|--|--------------------|-----------------|
| Age (year, mean±SD) | | 49.1±12 |
| Sex N (%) | Male | 2 (5.7%) |
| | Female | 33 (94.3%) |
| Duration of disease (month, mean±SD) | | 86.17±81.94 |
| Duration of treatment (month, mean±SD) | | 76.34±67.28 |
| Comorbidities N (%) | Hypothyroidism | 9 (26.5%) |
| | Hypertension | 7 (20.6%) |
| | Hyperlipidemia | 4 (11.8%) |
| | Diabetes mellitus | 2 (5.9%) |
| ESR (mm/h, mean±SD) | | 33±21 |
| DAS28 Score (mean±SD) | | 6.1±1.2 |
| DAS28 grading N (%) | Moderate (3.2-5.1) | 5 (14.3%) |
| | Severe (>5.2) | 30 (85.7%) |
| Pharmacological treatment N (%) | Methotrexate | 29 (89.2%) |
| | Prednisolone | 29 (89.2%) |
| | Sulfasalazine | 29 (89.2%) |
| | Calcium | 21 (60%) |
| | Adalimumab | 3 (8.6%) |
| | Hydroxychloroquine | 4 (11.4%) |

SD: Standard deviation; ESR: Erythrocyte sedimentation rate; DAS28: Disease activity score using 28 joint counts

Table 2: Ultrasonographic findings and scores in the study

| | Variable | Score |
|------|----------------------------|----------|
| GSUS | Tenosynovitis score (0-7) | 1.3±0.7 |
| | Synovitis score (0-27) | 10.4±4.7 |
| | Knee synovial score (0-18) | 4.2±3.9 |
| | US-9 score (0-45) | 14.6±7.4 |
| PDUS | Tenosynovitis score (0-21) | 10±2.2 |
| | Synovitis score (0-39) | 7.5±4.9 |
| | Knee synovial score (0-18) | 2.2±1.5 |
| | US-9 score (0-57) | 9±5.9 |

GSUS: Grayscale ultrasonography; US-9: 9-joint ultrasonography; PDUS: Power Doppler ultrasonography

Table 3: Correlation between DAS28 and ultrasonographic parameters

| | Variable | P value* | Correlation Coefficients (r) |
|---------------------------------------|---|----------|------------------------------|
| GSUS (US-7 score) | Synovitis score (US-7 score) | 0.02 | 0.38 |
| | Tenosynovitis score (US-7 score) | 0.16 | 0.24 |
| PDUS (US-7 score) | Synovitis score (US-7 score) | 0.003 | 0.48 |
| | Tenosynovitis score (US-7 score) | 0.19 | 0.23 |
| Ultrasonographic assessments of knees | GSUS knee synovial score | 0.007 | 0.45 |
| | PDUS knee synovial score | 0.02 | 0.39 |
| | GSUS synovitis score plus knee synovial GSUS score (US-9) | 0.003 | 0.49 |
| | PDUS synovitis score plus knee synovial PDUS score (US-9) | 0.006 | 0.45 |

GSUS: Grayscale ultrasonography; US-7: 7-joint ultrasonography; PDUS: Power Doppler ultrasonography; US-9: 9-joint ultrasonography; *Spearman correlation test was used.

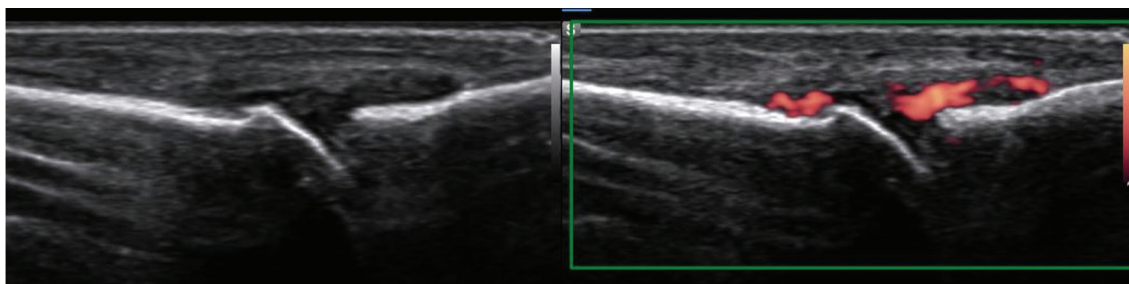


Figure 1: Grayscale ultrasonography (GSUS) and power Doppler ultrasonography (PDUS) of 3rd MCP joint dorsal side show grade 2 synovitis by GSUS and grade 3 synovitis by PDUS.

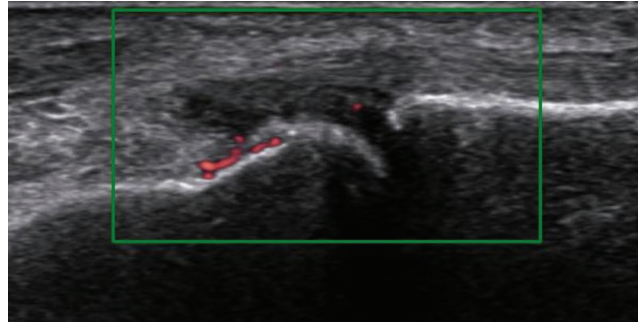


Figure 2: Grayscale ultrasonography (GSUS) and power Doppler ultrasonography (PDUS) of 2nd MCP joint palmar side show grade 3 synovitis by GSUS and grade 1 synovitis by PDUS.



Figure 3: Grayscale ultrasonography (GSUS) and power Doppler ultrasonography (PDUS) of wrist ulnar side show grade 3 synovitis by GSUS and grade 2 synovitis by PDUS.

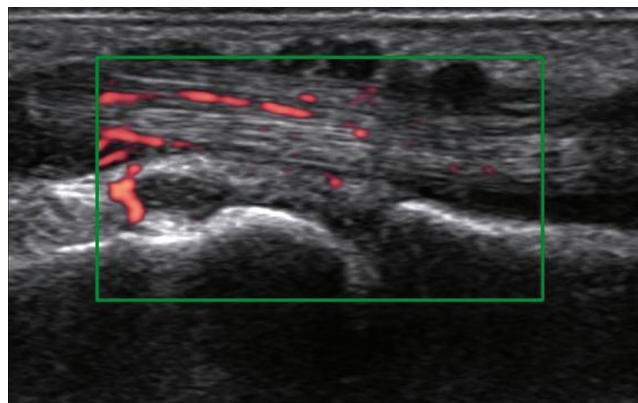


Figure 4: Grayscale ultrasonography (GSUS) and power Doppler ultrasonography (PDUS) of the 3rd MCP joint palmar side show tenosynovitis in the flexor tendon.

correlation between both US-9 GSUS and PDUS and DAS28. However, there was not a remarkable difference regarding their correlation with DAS28.

This study has been conducted to assess the utility of ultrasonography of large joints such as the knee joint in addition to the US-7 ultrasound joint scoring system in RA. To our knowledge, this study was performed for the first time on Iranian patients, as well as the Middle-Eastern population, assessing the correlation of the US-7 score with DAS28 in patients with active RA.

The US is one of the most sensitive and reliable approaches to manage and monitor disease activity. In addition, it helps to detect patients with low disease activity, as well as

those who are in the remission phase based on clinical scoring systems such as DAS28. However, the role of the US in the management and treatment of RA is not clear yet.^{8, 9}

A large body of evidence investigated (qualitatively and quantitatively) synovitis by Doppler in patients with RA.¹⁷⁻²⁰ Among proposed US-based approaches, US-7 is one of the most feasible and accurate methods.¹¹ In the current study, we used the German US-7 out of several available US-based scoring systems due to its accuracy and feasibility.^{21, 22} US-7 was the first scoring system that combined bone erosions as well as soft tissue lesions, such as synovitis and tenosynovitis, in a single composite scoring system. Besides, since US-7 can be performed

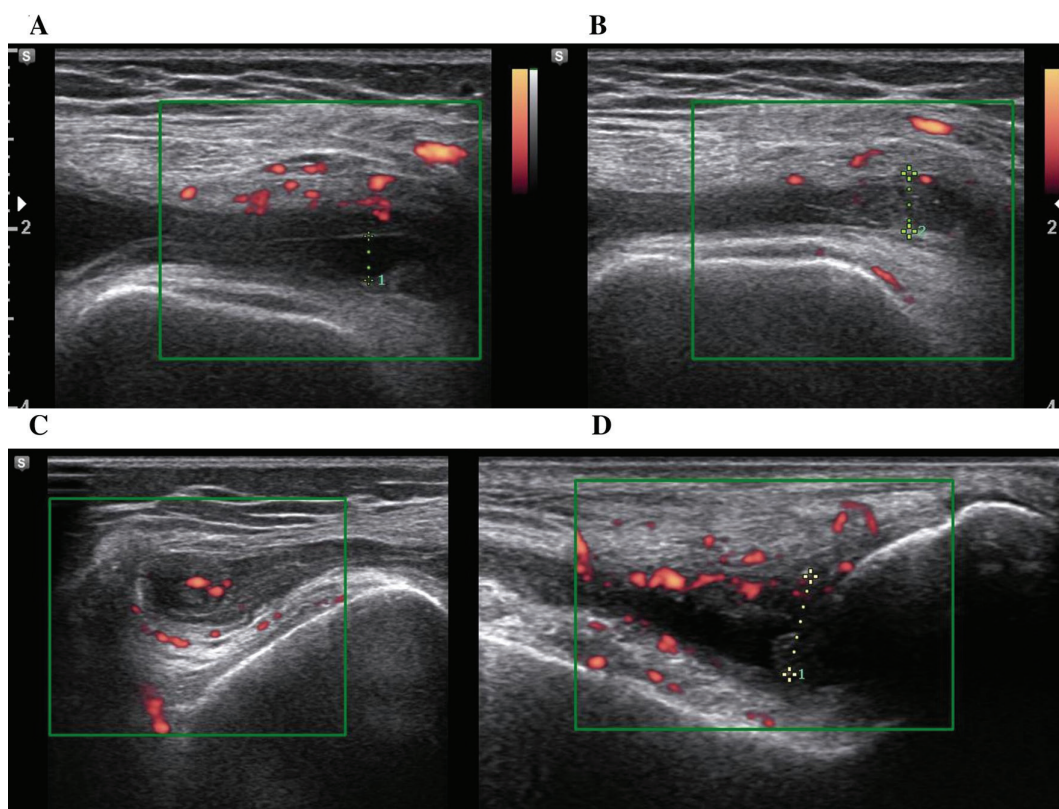


Figure 5: Grayscale ultrasonography (GSUS) and power Doppler ultrasonography (PDUS) measurements of the knee. (A) Shows effusion measurement with GSUS in the medial compartment. (B) shows the same region after compression with grade 1 synovitis by PDUS and GSUS, (C) grade 2 synovitis by GSUS and PDUS, and (D) Grade 3 synovitis by PDUS.

with a limited number of joints (seven joints), assessment with US-7 took approximately 10–20 min for each patient, which is very critical in daily radiologic practice.²² The possible correlation between DAS28, as a clinical scoring system, and US-7 was investigated. A significant positive correlation was found between DAS28 and synovitis scores in the US-7 scoring system measured by GSUS and PDUS. No significant correlation was found between DAS28 and tenosynovitis and erosion scores in the US-7 scoring system.

The PDUS and GSUS of both knees were also assessed and the correlation of our new approach, (US-9), with the clinical assessment using DAS28 was evaluated. A significant correlation was found between knee compartments' synovial thickness and DAS28 score and US-7 synovitis score. This indicates that ultrasound assessment of large joints such as knees can be an effective approach to determine RA severity. According to our findings, US-7 and US-9 revealed similar results. Therefore, including large joints such as the knees in the sonographic assessment does not necessarily provide better diagnostic performance in the assessment of disease activity.

Our results are in agreement with previous reports that indicated the significant positive

correlation between DAS28 and synovitis score in US-7 using GSUS and PDUS.^{11, 13, 23, 24} US is a more sensitive modality than clinical assessments in the detection of synovitis.²² PDUS can assist in distinguishing actively inflamed joints from inactive joints, which is an important issue in RA management.¹⁶ PDUS can also identify patients with well-controlled disease²⁵ and predict relapse within one year in RA patients classified as clinical remission based on DAS28.²⁶ In another study, US-7 is shown to be sensitive to change over a treatment period.¹⁰ The DAS28 scoring system requires some experience by the rheumatologist and is time-consuming in some cases. Thus, the US would be utilized in addition to DAS28 to achieve better differentiation between active and remitted phases of RA disease.

The association between clinical disease activity indices and US-7 was evaluated in previous studies.^{27, 28} Mahesh Wari and his colleagues studied sixty-two RA patients with a mean age of 44 years and a median treatment duration of 7 years. In line with our results, they found a significant correlation between DAS28 and synovitis by GSUS and PDUS scores. Similar to our results, they did not find any correlation between DAS28 and erosion score and tenosynovitis on GSUS and PDUS.¹¹

Kamel and his colleagues studied fifty RA patients in a cross-sectional study with a mean disease duration of 8.7 years. They reported that DAS28 scores were positively correlated with synovitis scores on GSUS and PDUS assessed by US-7.²⁹

Although DAS28 is still a common method for measuring RA activity, its application has been argued recently due to some drawbacks.⁸ For instance, Terslev and coworkers detected subclinical synovitis using US in the majority of RA patients in longstanding DAS28-remission.⁹ There are some other scoring systems for measuring RA activity. Kamel and others evaluated the association between the US-7 and disease activity, based on the Clinical Disease Activity Index (CDAI), global arthritis score (GAS), and the Routine Assessment of Patient Index Data 3 (RAPID 3). All three disease activity indices were found to be significantly correlated with GSUS and PDUS synovitis.²⁹ Future studies can evaluate the correlation between the US-7 scoring system and other clinical disease activity indices.

In the present study, both US-7 and US-9 were significantly correlated with DAS28, but there was no significant difference between these two US methods. Leng and colleagues evaluated US-7 and US-12 in RA patients and reported no significant difference regarding response to therapy.¹⁰ However, new scoring methods may be discovered by further exploration that differ significantly from the previously established systems, regarding disease activity and treatment response.

Our study had some limitations, including the lack of follow-up examinations for the patients to assess the possible alterations in our study variables. We could also use other clinical scoring systems in addition to DAS28. However, based on the literature, DAS28 is the most commonly used method for assessing RA patients in clinical studies and daily practice.³ ³⁰ RA is more prevalent in women, and they usually experience a more severe form of RA.³¹ Consistently, most of the patients were female (94.3%) in the current study. It is recommended to compare the utilization of US-7 in both men and women in future studies. We hope that a new study with more patients may lead to more accurate results.

Conclusion

The US-7 is a simple, accurate, and practical scoring system to predict disease activity in RA patients. Knee ultrasound alone is also effective in determining the severity of the

disease. However, the combination of them and adding large joints' scores such as knees, do not improve its diagnostic value necessarily.

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Authors' Contribution

All authors contributed to the conception and design. M.E contributed to the analysis and interpretation of the data. S.E, A.M.A, H.R.H, and R.G contributed to drafting the article. M.S, M.E, F.K and B.A contributed to the critical revision of the article for important intellectual content. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest: None declared.

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