



Simplified vs modified (reduced) ultrasound 6 joint score in assessing disease activity in rheumatoid arthritis patients

Mervat Mamdouh Abo Gabal , Amina Badr Eldin, Maha Ahmed Elserwy,
Mostafa Adel Mohammed

Internal Medicine and Rheumatology, Faculty of Medicine, Ain Shams University, Cairo, Egypt

ABSTRACT

Introduction and aim. With increasing ultrasound US assessment opportunities for tight rheumatoid arthritis (RA) management, more simplified accurate US-assessment is desired in clinical practice. Aim of the work is assessing modified vs simplified ultrasound 6-joint scores relevance in assessing rheumatoid arthritis disease activity.

Material and methods. Fifty-five RA patients were subjected to detailed history, clinical, and musculoskeletal examination with disease activity assessment by clinical disease activity index, simple disease activity index and disease activity score in 28 joints. Complete blood count, erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor, anti-cyclic citrullinated peptide antibodies were done. Patients underwent US examination (gray-scale and power Doppler) for wrist, 2nd and 3rd metacarpophalangeal and knee joints bilaterally. Synovitis composite score was added. Two US indices were constructed: simplified S6 and modified M6 joint scores.

Results. Statistical significant positive correlations were high between S6/M6 score parameters (total, grey-scale (GS), power doppler (PD), Composite) and disease activity markers. Both M6 and S6 scores differentiated mild-moderate and moderate-severe disease activity patients. However, only S6 score differentiated remission from mild disease activity patients.

Conclusion. Ultrasound 6-joint scores (especially simplified S6) were rapid, easy and sensitive ultrasound tools assessing rheumatoid arthritis disease activity in clinical practice.

Keywords. activity, 6-joint score, rheumatoid arthritis, ultrasound

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease, mainly involving the small joints of the hands and feet. In the absence of appropriate treatment, RA leads to irreversible joint and tendon damage, disability and premature death.¹ It has been suggested that some patients may experience radiographic progression of joint disease despite being in clinical remission, although this presumably is a carry-over effect of past disease activity. Nevertheless, if clinical assessment of joint swelling is not a sufficiently reliable method to assess patients with RA in a state

of remission, more sensitive methods for assessment of disease activity might be needed.²

Musculoskeletal ultrasound is capable of evaluating the two elementary findings associated with synovitis: synovial hypertrophy (SH) and synovial fluid/effusion (SF). Both SF and SH are evaluated primarily on gray-scale (GS) ultrasound, while color Doppler (CD) and power Doppler (PD) are utilized to demonstrate activity related to SH. However, a systematic review of the scoring systems used to evaluate synovitis in RA found it difficult to determine the least number of joints that needed to be assessed for a global US score.³

Corresponding author: Mervat Mamdouh Abo Gabal, e-mail: drmervat40@yahoo.com

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The relevance of US for monitoring RA is well reflected in European League Against Rheumatism (EULAR) recommendations for the use of imaging on clinical management of RA.⁴ However, Abo Gabal et al., in their work studying the usefulness of ultrasound 7-joint and 12-joint scores in assessing disease activity in RA patients adding the use of composite synovitis score, reported limitations of both scores and recommended the use of more rapid, objective and sensitive ultrasound score for practical assessment of RA disease activity.⁵

Aim

The aim of the study was to evaluate the relevance of simplified vs modified (reduced) ultrasound 6-joint scores in assessing disease activity in rheumatoid arthritis in clinical practice.

Material and methods

This analytic cross-sectional study was carried out on Fifty-five RA patients fulfilling the 2010 American College of Rheumatology (ACR)/EULAR criteria.⁶ Patients were recruited from the rheumatology outpatient clinic and inpatient rheumatology department at Ain Shams university hospital between January 2019–September 2022. Patients having arthritis/arthropathy due to any other rheumatological or systemic diseases were excluded. All patients were subjected to: detailed history and thorough clinical and musculoskeletal examination with assessment of disease activity by clinical disease activity index (CDAI), simple disease activity index (SDAI) and disease activity score in 28 joints (DAS28-ESR).^{7,8} Laboratory workup included: Complete blood count (CBC) was measured on a Siemens ADVIA 2120i hematology analyzer (Siemens Healthcare diagnostic, Erlangen, Germany), Erythrocyte sedimentation rate (ESR) was placed into sedimentation measurement stand (BD seditainer Manual ESR BD), C-reactive protein (CRP, 0004956842190c501V9.0) was measured by immunoturbidimetric assay on Roche/Hitachi cobas c systems (GmbH, Mannheim, Germany, reference value <5 mg/L). Rheumatoid factor (RF, 0020764574322c501V8.0) was measured by immunoturbidimetric assay on Roche/Hitachi cobas c systems (GmbH, Mannheim, Germany, reference value <14 IU/mL). Anti-cyclic citrullinated peptide (Anti-CCP, 05115671001V4) antibodies were measured by electrochemiluminescence immunoassay “ECLIA” on Roche diagnostic Cobas e411 (GmbH, Mannheim, Germany, reference value <20 IU/mL).

Ultrasound examination

Systematic ultrasound assessment was performed by a rheumatologist (first author of this study who is Eular certified with 7 year experience in performing muscu-

loskeletal ultrasonography) using the Power Doppler PD ultrasound device MyLab™Six (e-Saote company) with 6-18 MH probe for assessment of small joints of hands and wrist and 3-13 MH probe for larger joints (knees). PD pulse repetition frequency was 500-750 Hz; Doppler frequency was 6.7-11.1 MHz; low wall filters were used.

A systematic multiplanar grey-scale and PD examination of 6 joints: wrist, second metacarpo-phalangeal (2nd MCP) and knee of both sides in modified or reduced score (M6), (330 joints in 55 patients) and wrist, 2nd MCP and 3rd MCP in simplified (S6) score (330 joints in 55 patients), was done.^{9,10} The US assessment for each patient, included 12 synovial sites in M6: bilateral wrist (dorsal carpal recesses), bilateral 2nd MCP joint (dorsal and palmar sides) and bilateral knee joint (suprapatellar recess, medial and lateral parapatellar recesses). In case of S6 score 10 synovial sites, bilateral wrist (dorsal carpal recesses), 2nd MCP and 3rd MCP joints (dorsal and palmar sides) were chosen.

Ultrasound scoring system

We then considered each joint as a unique structure, and we assessed the presence of synovitis (synovial proliferation (SP)± synovial effusion (SE)) by B-mode US and PD within the SP in each joint. According to the EULAR/OMERACT definitions, SE and SP were defined. Synovitis (effusion and synovial hypertrophy) on GS images were graded using a 4-grade semiquantitative scale from 0 to 3 as follows: 0 = normal joint (no synovial hypertrophy, no effusion), 1 = mild synovitis (mild synovial hypertrophy, with or without mild effusion), 2 = moderate synovitis (moderate synovial hypertrophy with or without mild or moderate effusion), and 3 = severe synovitis (severe synovial hypertrophy, with or without severe effusion).¹¹

Power Doppler synovitis scoring for 6-joint score was evaluated also using a semiquantitative 4-grade scale from 0 to 3 as follows: grade 0 = absence of signal, no intra-articular flow; grade 1 = mild, 1- or 2-vessel signal (including 1 confluent vessel) for small joints and 2 to 3 signals for large joints (including 2 confluent vessels); grade 2 = moderate confluent vessels (>grade 1) and less than 50% of normal area; grade 3 = marked vessel signals in more than half the synovial area (Fig. 1-4).

We added further modification, the higher score obtained for each of the US elementary lesions (US-Synovitis GS and PD) at each synovial site was then considered for the scoring of each joint as a unique structure (composite score).¹¹

For M6, sum scores for GS synovitis and PD synovitis were computed in 2 separate scores. The scoring range is 36 for each. Total sum for 6-joint score ranges from 0 to 72. Composite score (the higher of GS or PD scores is used for grading the overall synovitis severity) ranges from 0 to 18. For S6 sum scores for GS synovitis

and PD synovitis were computed in 2 separate scores. The scoring range is 30 for each. Total sum for S6 ranges from 0 to 60. Composite score ranges from 0 to 18.

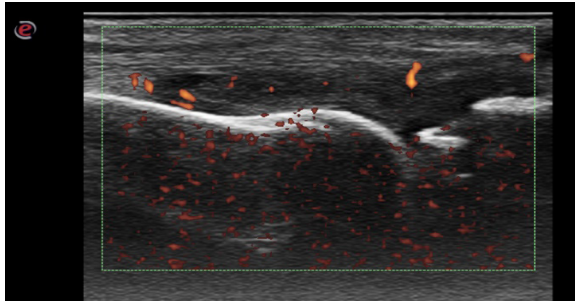


Fig. 1. Ultrasound image (longitudinal power Doppler) of 2nd MCP joint, composite score 2

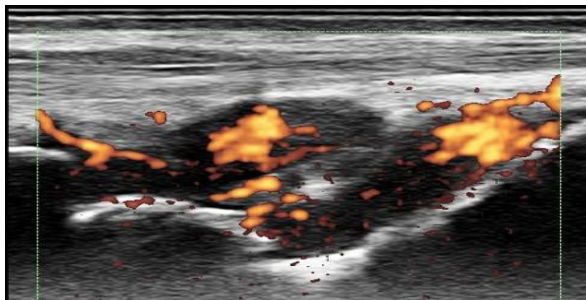


Fig. 2. Ultrasound image (longitudinal power Doppler) of right wrist joint, composite score 3

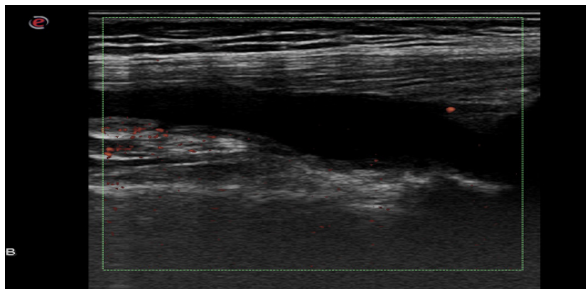


Fig. 3. Ultrasound image (longitudinal power Doppler) of knee suprapatellar recess with effusion and grade 1 synovial thickening, no Doppler signal

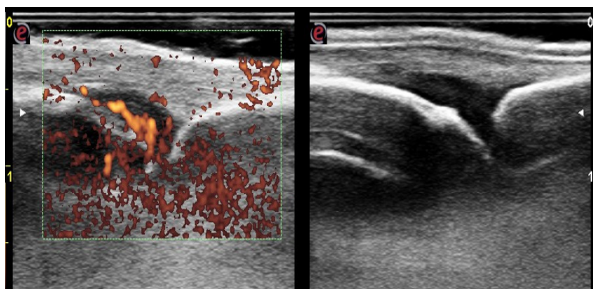


Fig. 4. Ultrasound image of 3rd MCP joint (longitudinal, power Doppler left and gray scale right), composite score 3

Statistical analysis

Data was coded and entered using the statistical package SPSS (IBM, Armonk, NY, USA). Data were summarized using number and percent for qualitative variables, mean and standard deviation for quantitative variables which are normally distributed while median was used for quantitative variables which are not normally distributed. Comparisons of quantitative variables which are not normally distributed between groups were done using nonparametrical Mann-Whitney and Kruskal-Wallis tests. Multiple comparisons between each two groups were done using Mann-Whitney test with Bonferoni correction. Correlations were done to test for relation between quantitative variables. p values less than or equal to 0.05 were considered as statistically significant.

Ethical approval

All subjects gave their informed consent for inclusion before they participated in the study. Approval of Ain Shams University Ethical Committee was obtained.

Results

Our study was performed on 55 Rheumatoid arthritis patients fulfilling the 2010 American College of Rheumatology (ACR)/EULAR criteria.⁶ Table 1 shows RA patients characteristics.

Regarding different extra-articular manifestations among studied patients. Pulmonary fibrosis was diagnosed in 10% of patients, secondary Sjogren's syndrome in 9%, peripheral neuropathy secondary to rheumatoid vasculitis in 7%, carpal tunnel syndrome in 14% (unilateral in 50 % of cases) and rheumatoid nodules in 5.5% of RA patients.

Fifty eight (58.2%) of our patients were on oral corticosteroids and 82% of all patients were on hydroxychloroquine. Concerning conventional synthetic Disease modifying antirheumatic drugs (csDMARDs), 76% of our patients were on leflunomide, 41.8% on methotrexate and 27% on more than one DMARD. None was on biological DMARD. Table 2 presents the total GS synovitis, PD synovitis and composite scores of both S6 and M6 scoring systems.

In Table 3 using ultrasound synovitis composite score, wrist was the commonest joint to be affected in 101/330 examined joints (30.6%) followed by knees in 70/330 (21.21%) then 2nd MCP joints in 55/330 (16.6%) and 3rd MCP joints in 37/330 (11.21%). This was consistent with the known distribution of joint involvement in RA.

Table 4, Figures 5 and 6 show highly statistically significant positive correlations between all M6 score parameters (total, GS, PD, composite) and No TJ, No SJ, VAS, PGA, EGA, ESR, CRP, DAS28, CDAI and SDAI, $p \leq 0.001$. There was statistically significant positive correlation between M6 GS, PD and composite scores and

Table 1. Characteristics of 55 RA patients*

Variable	No (%) / Mean ± SD Range	Variable	No (%) / Mean ± SD Range
Sex	Females 50 (90.9%) Males 5 (9.1%)	RA duration (years)	Mean ± SD 7.35 ± 4.71 Range 1–20
Age (years)	Mean ± SD 41.82 ± 9.09 Range 22–70	No. TJ (0–28)	Mean ± SD 1.84 ± 2.52 Range 1–14
DAS28 (0–9.4)	Mean ± SD 3.44 ± 1.3 Range 1.75–7.2	No. SJ (0–28)	Mean ± SD 1.47 ± 2.64 Range 1–10
DAS28 (activity groups)	Remission <2.6 18 (32.7%) Mild activity ≥2.6 and ≤3.2 11 (20%) Moderate activity >3.2 and ≤5.1 18 (32.7%) Severe activity >5.1 8 (14.5%)	VAS (0–100)	Mean ± SD 32.27 ± 19.86 Range 10–80
CDAI (0–76)	Mean ± SD 10.31 ± 8.49 Range 2–42	PGA (0–10)	Mean ± SD 4.45 ± 1.88 Range 2–10
CDAI (activity groups)	Remission ≤2.8 3 (5.5%) Mild activity >2.8 and ≤10 32 (58.2%) Moderate activity >10 and ≤22 14 (25.5%) Severe activity >22 6 (10.9%)	EGA (0–10)	Mean ± SD 3.29 ± 1.93 Range 1–8
SDAI (0–86)	Mean ± SD 11.03 ± 8.76 Range 2.35–44.4	Rheumatoid F (IU/mL)	Positive 46 (83.6%) Negative 9 (16.4%) Mean ± SD 46.88 ± 49.18 Range 4–250
SDAI (activity groups)	Remission ≤3.3 3 (5.5%) Mild activity >3.3 and ≤11 32 (58.2%) Moderate activity >11 and ≤26 16 (29.1%) Severe activity >26 4 (7.3%)	AntiCCP antibodies (IU/mL)	Positive 50 (90.9%) Negative 5 (9.1%) Mean ± SD 97.13 ± 100.04 Range 4.5–488
TLC (10 ³ /mL)	Mean ± SD 6.9 ± 2.07 Range 3.8–11.3	CRP (mg/L)	Mean ± SD 7.23 ± 4.26 Range 2–24
HGB (gm/dL)	Mean ± SD 11.53 ± 0.95 Range 9–16	ESR (mm/hr)	Mean ± SD 34.71 ± 20.53 Range 9–95
Platelets (10 ³ /mL)	Mean ± SD 308.67 ± 110.42 Range 150–600		

* No TJ – number of tender joints, No SJ – number of swollen joints, VAS – visual analogue scale, PGA – patient global assessment, EGA – evaluator global assessment, ESR – erythrocyte sedimentation rate, CRP – C reactive protein, DAS28 – disease activity score, CDAI – clinical disease activity index, SDAI – simple disease activity index, TLC – total leukocyte count, HGB – hemoglobin, AntiCCP – anti cyclic citrullinated protein antibodies

Table 2. Description of ultrasound S6 and M6 scores parameters

S6 score		M6 score	
Variable	Mean ± SD Range	Variable	Mean ± SD Range
Total S6	11.65 ± 11.28 0–60	Total M6	12.89 ± 10.99 0–72
GS synovitis	7.38 ± 6.21 0–30	GS synovitis	8.95 ± 6.54 0–36
PD synovitis	4.27 ± 5.27 0–30	PD synovitis	3.95 ± 4.9 0–36
Composite score	6.35 ± 4.38 0–18	Composite score	6.86 ± 3.77 0–18

Table 3. Examined areas and graded (0-3) parameters of M6 and S6 scores

Examined area	score	Right		Left			
		No./Percent	score	No./Percent			
Wrist	Dorsal	GS	0	3 (5.5%)	0	6 (10.9%)	
			1	21 (38.2%)	1	22 (40%)	
			2	19 (34.5%)	2	19 (34.5%)	
		3	12 (21.8%)	3	8 (14.5%)		
		PD	0	23 (41.8%)	0	26 (47.3%)	
			1	18 (32.7%)	1	15 (27.3%)	
	2		6 (10.9%)	2	7 (12.7%)		
	Composite	3	8 (14.5%)	3	7 (12.7%)		
		0	3 (5.5%)	0	6 (10.9%)		
		1	21 (38.2%)	1	20 (36.4%)		
	2nd metacarpophalangeal	Dorsal	GS	2	18 (32.7%)	2	19 (34.5%)
				3	13 (23.6%)	3	10 (18.2%)
0				36 (65.5%)	0	35 (63.6%)	
PD			1	7 (12.7%)	1	11 (20%)	
			2	4 (7.3%)	2	4 (7.3%)	
			3	8 (14.5%)	3	5 (9.1%)	
Palmar		GS	0	43 (78.2%)	0	39 (70.9%)	
			1	6 (10.9%)	1	8 (14.5%)	
			2	3 (5.5%)	2	7 (12.7%)	
		PD	3	3 (5.5%)	3	1 (1.8%)	
			0	38 (69.1%)	0	33 (60%)	
			1	9 (16.4%)	1	12 (21.8%)	
3rd metacarpophalangeal	Dorsal	GS	2	4 (7.3%)	2	6 (10.9%)	
			3	4 (7.3%)	3	4 (7.3%)	
			0	46 (83.6%)	0	45 (81.8%)	
		PD	1	4 (7.3%)	1	3 (5.5%)	
			2	2 (3.6%)	2	3 (5.5%)	
			3	3 (5.5%)	3	4 (7.3%)	
	Composite	0	31 (56.4%)	0	24 (43.6%)		
		1	11 (20%)	1	19 (34.5%)		
		2	3 (5.5%)	2	5 (9.1%)		
		3	10 (18.2%)	3	7 (12.7%)		
		Dorsal	GS	0	38 (69.1%)	0	37 (67.3%)
				1	7 (12.7%)	1	7 (12.7%)
2	7 (12.7%)			2	6 (10.9%)		
PD	3		3 (5.5%)	3	5 (9.1%)		
	0		44 (80%)	0	45 (81.8%)		
	1		8 (14.5%)	1	4 (7.3%)		
Knee	Suprapatellar	GS	2	2 (3.6%)	2	3 (5.5%)	
			3	1 (1.8%)	3	3 (5.5%)	
			0	46 (83.6%)	0	44 (80%)	
		PD	1	7 (12.7%)	1	10 (18.2%)	
			2	1 (1.8%)	2	1 (1.8%)	
			3	1 (1.8%)	3	1 (1.8%)	
	Medial Parapatellar	GS	0	50 (90.9%)	0	50 (90.9%)	
			1	4 (7.3%)	1	3 (5.5%)	
			2	1 (1.8%)	2	2 (3.6%)	
		PD	0	38 (69.1%)	0	35 (63.6%)	
			1	7 (12.7%)	1	9 (16.4%)	
			2	7 (12.7%)	2	4 (7.3%)	
lateral Parapatellar	Suprapatellar	GS	3	3 (5.5%)	3	7 (12.7%)	
			0	40 (72.7%)	0	39 (70.9%)	
			1	11 (20%)	1	11 (20%)	
		PD	2	2 (3.6%)	2	3 (5.5%)	
			3	2 (3.6%)	3	2 (3.6%)	
			0	52 (94.5%)	0	53 (96.4%)	
	Medial Parapatellar	GS	1	2 (3.6%)	1	1 (1.8%)	
			2	1 (1.8%)	2	1 (1.8%)	
			0	35 (63.6%)	0	37 (67.3%)	
		PD	1	14 (25.5%)	1	14 (25.5%)	
			2	5 (9.1%)	2	3 (5.5%)	
			3	1 (1.8%)	3	1 (1.8%)	
lateral Parapatellar	GS	0	51 (92.7%)	0	54 (98.2%)		
		1	3 (5.5%)	1	1 (1.8%)		
		2	1 (1.8%)	2	1 (1.8%)		
	PD	0	21 (38.2%)	0	26 (47.3%)		
		1	26 (47.3%)	1	21 (38.2%)		
		2	7 (12.7%)	2	7 (12.7%)		
Knee	Suprapatellar	GS	3	1 (1.8%)	3	1 (1.8%)	
			0	52 (94.5%)	0	49 (89.1%)	
			1	2 (3.6%)	1	5 (9.1%)	
		PD	3	1 (1.8%)	3	1 (1.8%)	
			0	19 (34.5%)	0	21 (38.2%)	
			1	25 (45.5%)	1	23 (41.8%)	
	Medial Parapatellar	GS	2	9 (16.4%)	2	9 (16.4%)	
			3	2 (3.6%)	3	2 (3.6%)	
			0	37 (67.3%)	0	37 (67.3%)	

Table 4. Correlations of M6 and S6 score parameters*

		M6 score				S6 score			
		Total S	GSS	PD S	Composite	Total S	GSS	PD S	Composite
No. TJ	Cor.Co.	0.680	0.672	0.562	0.690	0.723	0.696	0.729	0.695
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
No. SJ	Cor.Co.	0.606	0.575	0.641	0.573	0.827	0.797	0.831	0.714
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Dis. Dur.	Cor.Co.	0.121	0.027	0.232	0.073	0.074	0.040	0.111	0.049
	p	0.380	0.843	0.088	0.598	0.592	0.771	0.420	0.720
VAS	Cor.Co.	0.781	0.713	0.744	0.729	0.860	0.834	0.859	0.817
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
PGA	Cor.Co.	0.737	0.673	0.706	0.686	0.742	0.702	0.762	0.705
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
EGA	Cor.Co.	0.789	0.709	0.764	0.716	0.812	0.772	0.829	0.766
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
ESR	Cor.Co.	0.543	0.432	0.612	0.452	0.596	0.555	0.622	0.501
	p	<0.001	0.001	<0.001	.001	<0.001	<0.001	<0.001	<0.001
CRP	Cor.Co.	0.505	0.487	0.479	0.515	0.588	0.574	0.584	0.546
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
RF	Cor.Co.	0.018	0.013	0.057	-0.010	-0.032	-0.054	-0.004	-0.087
	p	0.899	0.924	0.680	0.944	0.818	0.693	0.978	0.526
ACCP	Cor.Co.	-0.103	-0.124	-0.054	-0.136	0.094	0.118	0.061	0.057
	p	0.455	0.368	0.695	0.323	0.496	0.390	0.656	0.680
TLC	Cor.Co.	0.074	0.110	0.146	0.105	0.114	0.080	0.151	0.049
	p	0.592	0.424	0.289	0.446	0.405	0.562	0.271	0.721
HGB	Cor.Co.	0.240	0.226	0.076	0.231	0.030	0.051	0.005	0.074
	p	0.077	0.097	0.580	0.090	0.826	0.712	0.972	0.589
PLT	Cor.Co.	0.357	0.336	0.371	0.318	0.582	0.561	0.585	0.528
	p	0.007	0.012	0.005	0.018	<0.001	<0.001	<0.001	<0.001
DAS28	Cor.Co.	0.772	0.686	0.754	0.708	0.843	0.813	0.849	0.789
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
CDAI	Cor.Co.	0.797	0.727	0.730	0.731	0.888	0.862	0.886	0.834
	P	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
SDAI	Cor.Co.	0.793	0.725	0.726	0.729	0.888	0.863	0.887	0.835
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

* Pearson correlation test, No TJ – number of tender joints, No SJ – number of swollen joints, VAS – visual analogue scale, PGA – patient global assessment, EGA – evaluator global assessment, ESR – erythrocyte sedimentation rate, CRP – C reactive protein, DAS28 – disease activity score, CDAI – clinical disease activity index, SDAI – simple disease activity index, TLC – total leukocyte count, HGB – hemoglobin, AntiCCP – anti cyclic citrullinated protein antibodies, Dis. Dur. – disease duration, RF – rheumatoid factor

platelet count, $p \leq 0.05$. Also, there was highly statistically significant positive correlations between all S6 score parameters (total, GS, PD, composite) and no TJ, No SJ, VAS, PGA, EGA, ESR, CRP, DAS28, CDAI, SDAI and platelets, $p \leq 0.001$. However, no statistically significant correlations were noted between any of M6 or S6 components and disease duration, TLC, HGB, rheumatoid factor or ACCP-AB titres, $p \geq 0.05$.

Table 5 shows comparison between different patient groups (classified according to disease activity measured by DAS28, CDAI and SDAI) regarding S6 score

components to determine accuracy and sensitivity in assessing disease activity (when the score differed significantly between patient groups with close disease activities (remission/mild, mild/moderate, moderate/severe). According to DAS28, there was statistical significant difference between patients with remission/mild in total and GS synovitis scores, and between those with moderate/severe in GS synovitis and composite scores, with $p < 0.05$. According to CDAI and SDAI, there was statistical significant difference between patients with mild/moderate disease activity as regard total S6-joint score and all its parameters (GS synovitis, PD synovitis, composite score) with $p < 0.05$.

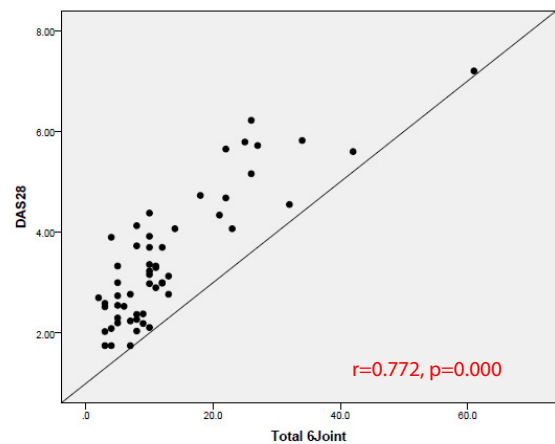


Fig. 5. Correlation between total M6 ultrasound score and DAS-28 ESR

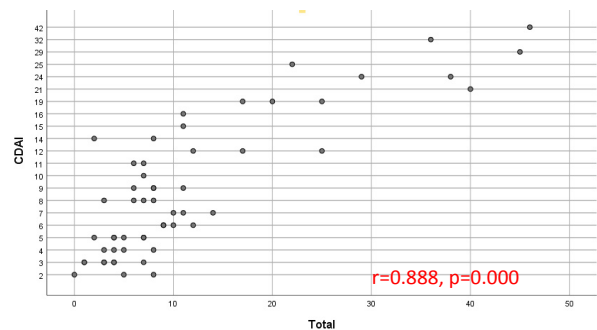


Fig. 6. Correlation between total S6 ultrasound score and CDAI

Table 6 shows that according to DAS28, there was statistical significant difference between patients with moderate-severe disease activity as regard total M6, its GS and PD synovitis scores (but not composite score), with $p < 0.05$. According to CDAI and SDAI, there was statistical significant difference between patients with mild-moderate disease activity in total M6-joint score and all its parameters (GS synovitis, PD synovitis, composite score) with $p < 0.05$.

Table 5. Comparison between patients with different grades of disease activity as regard S6 joint score components (total, GS, PD and composite score)*

	Remission –mild activity	Remission– moderate activity	Remission– severe activity	Mild activity– moderate activity	Moderate– severe activity	Mild activity– severe activity
According to DAS28						
Total S6 score	0.043	0.001	<0.001	1	0.056	0.027
GS synovitis score	0.035	0.006	<0.001	1	0.027	0.046
PD synovitis score	0.256	0.001	<0.001	1	0.066	0.006
Composite score	0.124	0.009	<0.001	1	0.049	0.031
According to CDAI						
Total S6 score	1	0.265	0.009	0.025	0.278	<0.001
GS synovitis	1	0.181	0.007	0.017	0.377	<0.001
PD synovitis	1	0.533	0.015	0.048	0.148	<0.001
Composite score	1	0.228	0.009	0.018	0.348	<0.001
According to SDAI						
Total S6 score	1	0.143	0.018	0.003	0.780	0.002
GS synovitis	1	0.138	0.016	0.009	0.719	0.003
PD synovitis	1	0.229	0.028	0.002	0.747	0.001
Composite score	1	0.162	0.025	0.007	0.912	0.004

* Mann-Whitney and Kruskal-Wallis tests, GS – gray scale, PD – power Doppler, DAS28 – disease activity score, CDAI – clinical disease activity index, SDAI – simple disease activity index

Discussion

Among the different imaging tools described in the European League Against Rheumatism recommendations, US is especially helpful for the following various situations encountered during daily clinical practice: diagnosis of RA, evaluation of disease activity/treatment response/prognosis, and support of remission surveillance.¹² With increasing US assessment opportunities for the tight management of RA, a more simplified, accurate US assessment strategy is desired.¹³ We carried out the present study to evaluate the relevance of modified vs simplified ultrasound 6-joint scores in assessing disease activity in rheumatoid arthritis

Most of our patients in this study were females (91%) and males representing only 9%. Similar demographic data were found in El-Gohary et al., (90% females and 10% males) and in Kamel et al. (92% females and 8% males).^{14,15} In our study, mean and standard deviation (SD) for the age of our patients were 41.82±9.09 years. Similar results were found in El-Gohary et al. (45.3±12.4), and in Kamel et al. (43.9±10.78).^{14,15} Most of the previous figures confirm high incidence of RA in middle aged females. Other studies reported higher

mean ages, 66 years in Endo et al. and 53.52±11.81 in Cerqueira et al.^{13,4} Different ethnicity or disease durations may account for this.

Table 6. Comparison between patients with different grades of disease activity as regard M6 joint score components (total, GS, PD and composite score)

	Remission –mild activity	Remission– moderate activity	Remission– severe activity	Mild activity– moderate activity	Moderate– severe activity	Mild activity– severe activity
According to DAS28						
Total M6 score	0.246	<0.001	0.003	1	0.049	0.007
GS synovitis score	1	0.045	<0.001	1	0.027	0.003
PD synovitis score	0.446	0.005	<0.001	1	0.052	<0.0015
Composite score	0.663	0.010	<0.001	1	0.069	0.007
According to CDAI						
Total M6 score	1	0.087	0.013	0.001	1	<0.001
GS synovitis	1	0.138	0.023	0.001	1	<0.001
PD synovitis	1	0.562	0.034	0.017	0.406	<0.001
Composite score	1	0.235	0.036	0.001	1	<0.001
According to SDAI						
Total M6 score	1	0.056	0.023	<0.001	1	0.002
GS synovitis	1	0.113	0.046	<0.001	1	0.004
PD synovitis	1	0.240	0.048	<0.001	1	0.001
Composite score	1	0.177	0.094	<0.001	1	0.008

* Mann-Whitney and Kruskal-Wallis tests, GS – gray scale, PD – power Doppler, DAS28 – disease activity score, CDAI – clinical disease activity index, SDAI – simple disease activity index

Measuring disease activity with DAS28, 32.7% of our patients were in remission, 20% had low activity, 32.7% had moderate activity and 14.5% showed severe activity. CDAI and SDAI gave similar findings, about 58% of our patients were having mild activity score, only 5.5% in remission according to both scores, 25.5% and 29.1% of patients had moderate activity and 10.9% and 7.3% of patients had severe activity according to CDAI and SDAI respectively. In 2019, Sivakumaran et al., reported 16.5% of patients with remission, 13.3% had low activity, 38.3% had moderate activity and 31.6% had severe activity.¹⁶ El-Gohary et al. found that 26% of their patients were in remission as measured by DAS28. Only 6% and 8% were in remission as defined by and SDAI and CDAI.¹⁴ In study of Kamel et al., 8% of patients were in remission, 12% of low activity, 24% of moderate activity, and 56% of high activity as defined by CDAI.¹⁵ Higher percentage of patients in remission and lower percentage of active disease (especially by DAS 28) in our study may reflect better patient compliance, different disease severity, different response to therapy and different ethnicity.

In our study, significant positive correlations between all M6 score parameters and measures of RA disease activity were evident, $p \leq 0.001$. There was statistically significant positive correlation between M6 GS, PD and composite scores and platelet count, $p \leq 0.05$. Perricone et al., in their study on modified (reduced) 6-joint score reported highly significant positive correlation ($p = 0.001$) between score parameters and DAS28 and CRP.⁹ However, DAS-28 scores usually reflect a combination of active and chronic joint changes, better assessment of disease activity by CDAI and its positive correlation with M6 score was more informative in our study.

On the other hand, there was highly statistically significant positive correlations between all S6 score parameters and CDAI and platelets, $p \leq 0.001$. Rosa et al., in their study on simplified 6-joint score reported similar correlation with DAS28.¹⁰ In Endo et al., although both DAS28-ESR and DAS28- CRP scores were significantly positively correlated with the 6 joint-GS, and PD scores, such correlations tended to weaken with time after therapy initiation.¹³

In our study, despite equal relevance and sensitivities of both ultrasound scores M6 and S6 in differentiating activity groups with mild-moderate and with moderate-severe disease activities in patients with RA, only S6 score was able to differentiate patient groups with remission vs mild disease activity that may reflect its superiority over M6 score. Also, in M6 score, incorporation of knee joint assessment in place of 3rd MCP joint of S6 score was done. And as for GS synovitis in knee, any grade of knee effusion was considered in our study that may account for high frequency of knee involvement by composite score (70/330, 21%).

In Figus et al., using M6 ultrasound score, ultrasound detected significant differences in the score of joint effusion (SE), synovial hypertrophy (SH), and Doppler signal and significant differences in the joint score of II MCP and wrist (but not for knee joint scores) between oligoarticular PSA and RA, $p < 0.05$. No differences were found between RA and polyarticular PSA.¹⁷ Moreover, previous studies reported good correlation between hand US scores and DAS-28 assessment using three different US scores, which was replicated in the study of Sivakumaran et al.^{10,16,18} These findings may support the higher value of S6 (hand joint score) versus M6 score.

However, Perricone et al., stated that they obtained a 6-joint US assessment (M6) that was able to detect 97.7% of patients with 12-joint US-SE, 100% of patients with 12-joint US-SP and 100% of those with 12-joint PD and this 6-joint US score showed a highly significant correlation with changes in DAS-28 ($p < 0.001$).⁹

Abo Gabal et al., in their work studying the usefulness of ultrasound 7 and 12-joint scores in assessing disease activity in RA patients adding the use of synovitis composite score, they reported limitations of both scores

as they included assessment of tenosynovitis/paratendinitis which are nonspecific for rheumatoid arthritis, they may result from mechanical injury especially in advanced disease and cannot be used alone as a domain to assess or decide starting, continuing or withdrawing biologics. Twelve score was time consuming and erosions included in 7-joint score were not accurate indicator of disease activity. They reflect structural damage and chronicity of the disease. In contrast, hot erosions or growing erosions over time are the better indicator of pannus activity but were not included in the score.⁵

They also reported that synovitis component of both scores was more informative and accurate in assessing disease activity and combined synovitis score (composite score) recommended by EULAR/OMERACT and Abo Gabal et al., was a significant assessing tool.^{5,19} In their study, Abo Gabal et al., mentioned the need for more rapid, objective and sensitive ultrasound score for practical assessment of RA disease activity.⁵

We think that our choice of 6 joints synovitis (GS and PD) score in the present study had avoided these limitations being rapid, easy, including only synovitis, the most important US-detected elementary lesions in RA that reflects disease activity. As in Abo Gabal et al., we added EULAR-OMERACT combined synovitis score (composite score).^{5,19} However, its use in our study did not show superiority to any of M6 or S6 GS or PD synovitis scores making its addition to the original M6 or S6 scores components non-essential.

On the other hand, Sivakumaran et al., stated that preselected simplified US scores are less reliable in appreciating the disease burden when compared with an extended protocol for 22 joint US examination, raising clinicians' awareness regarding the need to comprehensively assess multiple hand joints to reliably rule out subclinical inflammation. They stated that the scores including 20 and 22 joints captured more information than the eight-, ten-, and 14-joint scores, even if all the eight US scores they explored correlated very well with the DAS-28 assessment.¹⁶ Also Endo et al., stated that their study was limited by US assessments eliminating the possible involvement of the joints other than bilateral wrist and finger joints using simplified 6 joint score.¹³

Our opinion to solve this issue is to add separate variable joint number ultrasound score (from the remaining 22 joints) that assessing current joints (GS and PD synovitis) showing clinical involvement (symptoms or signs) in previous 2 weeks to be added to standardized assessment using simplified 6 joint score in order not to miss or underestimate RA joint activity.

Conclusion

Ultrasound 6-joint scores (whether modified or simplified) were rapid, easy and sensitive ultrasound tool in assessing disease activity in rheumatoid arthritis in clin-

ical practice. S6 score was superior in differentiating remission from mild disease activity groups.

Recommendation: Further studies are needed on larger scale to establish a cutoff value for ultrasound 6-joint score that differentiates RA patients in remission and at different grades of disease activity as in clinical disease activity indices.

Declarations

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Author contributions

Conceptualization, M.M.A.G.; Methodology, M.M.A.G., M.A.M. and M.A.E.; Software, M.A.M.; Validation, M.M.A.G., A.B.E., M.A.M. and M.A.E.; Formal Analysis, M.M.A.G. and M.A.M.; Investigation, M.A.M., M.A.E. and M.M.A.G.; Data Curation, M.A.M., M.A.E. and M.M.A.G.; Writing–Original Draft Preparation, M.M.A.G. and M.A.M.; Writing–Review & Editing, M.M.A.G., M.A.M. and A.B.E.; Visualization, M.M.A.G. and M.A.M.; Supervision, M.M.A.G.; Project Administration, M.M.A.G.; Funding Acquisition, M.M.A.G. and M.A.M..

Conflicts of interest

The author(s) declare no competing interests.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval

All subjects gave their informed consent for inclusion before they participated in the study. Approval of Ain Shams University Ethical Committee was obtained.

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