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SEVEN SCORE ULTRASOUND IN THE ASSESSMENT OF SYNOVITIS IN EARLY RHEUMATOID ARTHRITIS PATIENTS; CORRELATION WITH DISEASE ACTIVITY SCORE (DAS28)

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ABSTRACT

Background: Rheumatoid arthritis (RA) is a common systemic autoimmune disease influencing 0.5–1% of the population. The RA diagnosis is based essentially on clinical and biological parameters, even though the novel American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) sorting standard scomprise MRI and ultra-sound (US) as extra tools to evaluate the objective joint connection. Our study to evaluate the values of Ultra-sound 7 scores in the diagnosis of sub-clinical synovitis in the early RA- Cases and its correlation with the disease activity score (DAS28). **Results:** A significant positive, but moderate association was found between DAS28 score and GSUS synovitis total score ($r = 0.52$, $p < 0.001$) and fair positive association with power Doppler synovitis total score ($r = 0.44$, $p < 0.001$). DAS28 was not connected to total erosion score ($r = 0.045$, $p = 0.754$). **Conclusion:** Ultrasound 7 is simple and practical scoring system and we recommend it for usage in the diagnosis of sub-clinical synovitis in the early RA-cases.

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INTRODUCTION

Rheumatoid arthritis (RA) is a common, systemic autoimmune disease influencing about 0.5–1% of the population. The diagnosis of RA is based essentially on clinical and biological parameters, even though the novel American College of Rheumatology(ACR)/ European League Against Rheumatism(EULAR) sorting standards including MRI and ultra-sound (US) as a supplementary tool to evaluate the objective joint extension.[(1)] The access to musculoskeletal US services varies among hospitals and rheumatology services. Even if a significant part of RA- cases remain to have sub-clinical inflammations, in spite of indication of clinical remission, it is not cost- operative for screening them entirely. General US investigation of exterior joints in RA have a good prognostic value for disease consequence. [(2)] As US examination of multiple joints may be time wasting, numerous US score structures were improved, targeting to evaluate a lesser number of joints with no compromising at the qualities of gathered records.

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The OMERACT (Outcome Measures in RA Clinical Trials) inventiveness defined US anomalies RA characteristics like synovial hypertrophy (SH), with or without power Doppler (PD) signal, tenosynovitis and erosions. [(3)] The existing US scoresystemsutilize different quantitative or semi quantitative measures (including grades of SH or PD) or a dual scoring gadget (including presence/absence of erosions) to define US findings. The fundamental intention of the worldwide and European US expert agencies is to expand a standardized US scoring gadget with a purpose to seize the cases disease activity and which may be hired for guiding the rapeutic decisions. [(4)]

It was proposed that RA treatment should target the control of sub-clinical inflammations (as evaluated through US or MRI), in preference to being completely guided through medical exam and laboratory assesses, and that remission standards for RA- cases have to also consist of joint US exam. [(5)] We aimed in this study to evaluate the role of seven score ultrasound in detecting subclinical synovitis in early RA cases and its association with the disease activity score (DAS28).

METHODS

After the approval from our ethical committeeand after providing detailed information to the patients as regards theaim and procedures of the study, 50 patients with early RA gave their consent and then enrolled in this study. A prospective cross-sectional study included 50 early rheumatoid arthritis Casesviewed in our musculoskeletal US out-patient clinics during the period from (1st of December 2018 to 1stJanuary 2020).

Inclusion criteria

- early Rheumatoid Arthritis patients who satisfy the 2010 American College of Rheumatology(ACR) /European League Against Rheumatism (EULAR) Sorting RA Criteria (diagnosis does not exceed six months from the start of symptoms).
- Age 18 years or older (adult RA patients).

Exclusion criteria

- Age < 18 years.
- Patients on steroids whatever orally intake or locally injected in last 4 weeks.
- Patients on NSAIDs in last 4 weeks.
- Other causes of inflammatory arthritis as endocrinal, hepatic, renal.

Methods

After taking detailed history from each participant in our study, complete clinical examination was done to assess the disease activity score (DAS 28) of each participant by using their number of swollen joints (SJC), number of tender joints (TJC) through the following equation: 0.56 x√(TCJ28) + 0.28 x √(SJC28) + 0.70 x loge (ESR) + 0.014 x GH . Musculoskeletal ultra-sonography: of wrists, hands, and forefeet was done with a 10–18MHz linear scanning device and middle grade to high-end machine US device. All patients were assessed and examined by one medical staff expert in MSUS and doesn't know the pt DAS 28 score using warm gel (at room temperature)as Cooling of the hand should be avoided before PDUS examination of the wrist in patients with RA, because the amount of Doppler activity might be affected by low skin temperatures[6]. US7score includes the joints most expected to be influenced by RA: wrist, meta-carpophalangeal joint (MCP) 2nd and 3rd, proximal inter phalangeal (PIP) 2nd and 3rd, and meta-tarsophalangeal joint (MTP) 2nd and 5th joints. These joints of the most painful hand wereassessed for synovitis, tenosynovitis and superficial bone erosions in accordance to EULAR definitions[7]and Outcome Measures in Rheumatology definition including gray scale ultrasound (GSUS) and power Doppler ultrasound (PDUS) at a very low velocity +/- 2.5 cm/sec. (Table 1). [8]Synovitis and synovial/tenosynovial vascularity were counted semi-quantitatively (scores 0–3) by PDUS in accordance to **Szkudlarek *et al.*[9]**

Detailed joint examination

Each joint was examined in two planes: longitudinal and transverse by gray scale U.S and scored semi-quantitatively (0-3). Searching for synovitis, tenosynovitis (present scored 1or absent scored 0) and superficial bone erosions (present scored 1 or absent scored 0). Wrist joint: examined in dorso-medial, palmo-medial and ulnar aspects. 2nd MCP: examined in dorsal, palmar and radial while 3rd MCP examined in dorsal and palmar aspects only. 2nd, 3rd PIP: examined in dorsal and palmar aspects. 5th MTP: examined in dorsal, planter and lateral while 2nd MTP examined in dorsal and planter only.

Tendons examined for signs of tenosynovitis

- Tendons passed through the six compartments of extensor retinaculum which are : extensor pollicis brevis , abductor pollicis longus , extensor carpi radialis longus , extensor carpi radialis brevis , extensor pollicis longus , extensor digitorum communis , extensor indicis , extensor digit minimi , and extensor carpi ulnaris .
- Tendons passed through carpal tunnel which are: flexor pollicis longus, flexor digitorum profundus,and flexor digitorum superficialis.
- Flexors and extensors of 2nd and 3rd MCPs.

Table 1. Ultrasound 7 score components. [7]

	Wrist	MCP/PIP second and third	MTP second and fifth	Joint regions (range)
US7 synovitis sum score in GSUS (grade 0–3)	Dorsomedian/Ulnar Palmomedian	Palmar	Dorsal	9 (0–27)
US7 synovitis sum score in PDUS (grade 0–3)	Dorsomedian/Ulnar Palmomedian	Dorsal and palmar	Dorsal	18 (0–36)
US7 tenosynovitis/paratenonitis sum score in GSUS (absent=0, present=1)	Dorsomedian Ulnar Palmomedian	Dorsal and palmar (in level of MCP second and third)		7 (0–7)
US7 tenosynovitis/ paratenonitis sum score in PDUS (grade 0–3)	Dorsomedian Ulnar Palmomedian	Dorsal and palmar (in level of MCP second and third)		7 (0–21)
US7 erosion sum score in GSUS (absent=0, present=1)	Dorsomedian Ulnar Palmomedian	Dorsal and palmar (only radial at MCP second)	Dorsal and palmar (only lateral at MTP fifth)	17 (0–17) or 14 (0–14) if wrist not included

GSUS, gray-scale ultrasound; MCP, metacarpophalangeal; MTP, metatarsophalangeal; PDUS, power Doppler ultrasound; PIP, proximal interphalangeal; US7, ultrasound 7.

Laboratory assessment

- C-reactive protein (CRP)
- Erythrocyte sedimentation rating(ESR)
- Existence of rheumatoid factor (RF) and anticitrullinated cyclic peptides antibodies (ACPA)

Ethical committee approval: The aim and nature of the study were explained for each patient before inclusion. Written informed consents were obtained from patients.The ethical committee approval No 281/9/18

Statistical analysis of the data: The statistical analysis was done viaSPSS-23 that was employed for data management&analysis. The quantitative data were expressed in the form of Mean ± standard deviation (SD) with median and range. The qualitative data was introduced in the form of numbers with precents. Kruskal-Wallis testing was employed for comparison between three groups of DAS28. Pearson correlation was used to measure strength of association between numerical data and outcome variable. P value was 2-tailed and measured significance at 0.05 level.

RESULTS

A number of 50-cases with early RA were involved in our study, 37 females and 13 males, their age ranged between 21 and 65, with maximum 6 month duration of their symptoms, their RF was positive in 45 patients (90%) and negative in 5 patients(10%), Anti CCP was positive in 35 patients (70%) while negative in 15 patients (30%).

Detailed joint region analysis by ultrasound 7 score: By GSUS, wrists synovitis was determined in 47(94%) of 50 patients in dorso median scan, 19 (38%) in palmo median scan, and 14 (28%) in ulnar scan. MCP joints: synovitis was found in 35 (70%) in MCP II and 36 (72%) in MCP III. PIP II synovitis was found in 20 (40%), and PIP III synovitis was found in 19 (38%), and MTP II synovitis in 48 (96%) and MTP V synovitis in 33 (66%). Different grades of synovitis are shown in Table 3. By PDUS, wrist activity was found in 41 (82%) of patients, MCP joint II and III activity was found in 25 (50%) and very commonly detected in the dorsal feature than in the palmar feature, PIP II and PIP III activity was found in 9 (18%) and very commonly detected in the palmar than in the dorsal aspect, and MTP II and V activity was found in 41 (82%) as shown in Table 4. Tenosynovitis in GS style was noticed in 36 (72%) patients in the wrist joint with PD activity in 28 (56%). Tenosynovitis of the extensor carpiulnaris tendon diagnosed by GSUS was detected in greater than 25 (50%) of the joints studied, with PD activity of 22 (44%). Tenosynovitis in GS mode of MCP joint II was found in 15 (30%) and MCP joint III was found in 8 (16%) with PD activity in 5(10%) MCP II and 5(10%) MCP III as shown in Table 5.

Table 2. Demographic features

	N	Mean	±SD	Median	Minimum	Maximum
Age	50	45.60	9.84	45.50	21	65
ESR	50	52.86	21.75	43.00	15	110
duration(months)	50	5.18	1.21	6.00	2	6

Table 3. Detailed joint region examination for synovitis in gray-scale ultrasound

	Synovitis in GSUS & its grade			
Wrist	No	1	2	3
dorsomedian (n=47) 94%	3	29	13	5
	6.0%	58.0%	26.0%	10.0%
palmomedian (n=19) 38%	31	15	4	
	62.0%	30.0%	8.0%	
Ulnar (n=14) 28%	36	13	1	
	72.0%	26.0%	2.0%	
MCP				
2nd MCP (n=35)70%	15	24	11	
	30.0%	48.0%	22.0%	
3rd MCP (n=36)72%	14	21	13	2
	28.0%	42.0%	26.0%	4.0%
PIP				
2nd PIP (n=20) 40%	30	15	4	1
	60.0%	30.0%	8.0%	2.0%
3rd PIP (n=19) 38%	31	12	4	3
	62.0%	24.0%	8.0%	6.0%
MTP				
2nd MTP (n=48) 96%	2	7	35	6
	4.0%	14.0%	70.0%	12.0%
5th MTP (n=33) 66%	17	27	5	1
	34.0%	54.0%	10.0%	2.0%

MCP: metacarpophalangeal, PIP: proximal interphalangeal, MTP: metatarsophalangeal, GSUS: gray scale ultrasonography.

Table 4. Detailed joint region examination for synovitis in power Doppler ultrasound

	Synovitis in power Doppler& its grade			
Wrist	No	1	2	3
dorsomedian (n=41) 82%	9	34	7	0
	18.0%	68.0%	14.0%	
palmomedian (n=9) 18%	41	9	0	0
	82.0%	18.0%		
Ulnar (n=4) 8%	46	4	0	0
	92.0%	8.0%		
MCP				
Second MCP Dorsal (n=20) 40%	30	20	0	0
	60.0%	40.0%		
Second MCP palmar (n=13) 26%	37	13	0	0
	74.0%	26.0%		
Third MCP Dorsal (n=25) 50%	25	24	1	0
	50.0%	48.0%	2.0%	
Third MCP palmar (n=19) 38%	31	19	0	0
	62.0%	38.0%		
PIP				
Second PIP Dorsal (n=7) 14%	43	7	0	0
	86.0%	14.0%		
Second PIP palmar (n=7) 14%	43	6	1	0
	86.0%	12.0%	2.0%	
Third PIP Dorsal (n=5) 10%	45	5	0	0
	90.0%	10.0%		
Third PIP palmar (n=9) 18%	41	9	0	0
	82.0%	18.0%		
MTP				
2nd MTP dorsal (n=41) 82%	9	39	2	0
	18.0%	78.0%	4.0%	
5th MTP dorsal (n=5) 10%	45	5	0	0
	90.0%	10.0%		

MCP: metacarpophalangeal, PIP: proximal interphalangeal, MTP: metatarsophalangeal.

A significant positive, but moderate association was found between DAS28 score and GSUS synovitis total score ($r = 0.52$, $p < 0.001$) and fair positive association with power Doppler synovitis total score ($r = 0.44$, $p < 0.001$). DAS28 was not connected to total erosion score ($r = 0.045$, $p = 0.754$) as shown in table 6.

Pearson correlation, P value is significant ™0.05 A significant positive, but moderate association was found between DAS28 score and GSUS synovitis total score ($r = 0.52$, $p < 0.001$) and fair positive association with power Doppler synovitis total score ($r = 0.44$, $p < 0.001$). DAS28 was not correlated to total erosion score ($r = 0.045$, $p = 0.754$)

Table 5. Detailed joint region examination for teno-synovitis in gray-scale ultrasound

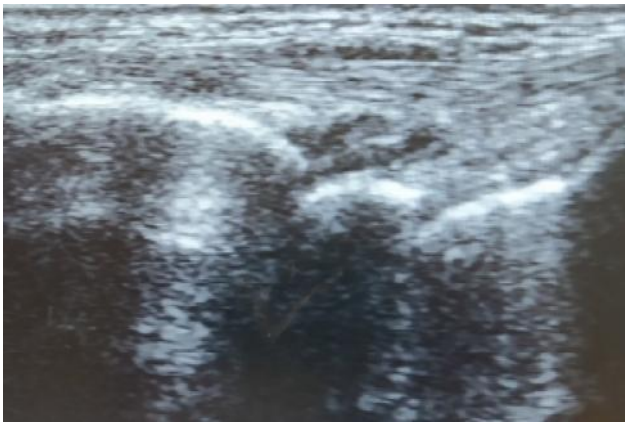
		Count	%
Wrist dosomedian	Yes	36	72.0%
	No	14	28.0%
Palmomedian	Yes	7	14.0%
	No	43	86.0%
Ulnar	Yes	25	50.0%
	No	25	50.0%
2nd MCP dorsal	Yes	1	2.0%
	No	49	98.0%
2nd MCP palmar	Yes	15	30.0%
	No	35	70.0%
3rd MCP dorsal	Yes	7	14.0%
	No	43	86.0%
3rd MCP palmar	Yes	8	16.0%
	No	42	84.0%

MCP: metacarpophalangeal

Table 6. Correlation of DAS 28, GSUS synovitis score, PD synovitis score and total erosion scores

		DAS 28	GSUS synovitis total	PD synovitis total
GSUS synovitis total	r	0.521		
	P value	< 0.001*		
PD synovitis total	R	0.438	0.840	
	P value	< 0.001*	< 0.001*	
erosion total	R	-0.045	-0.081	-0.045
	P value	0.754	0.577	0.755

DAS: disease activity score, GSUS: gray scale ultrasonography, PD: power Doppler, r stands for: result,



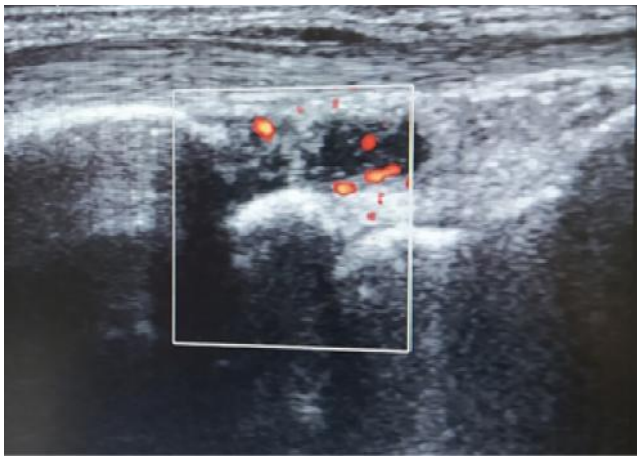
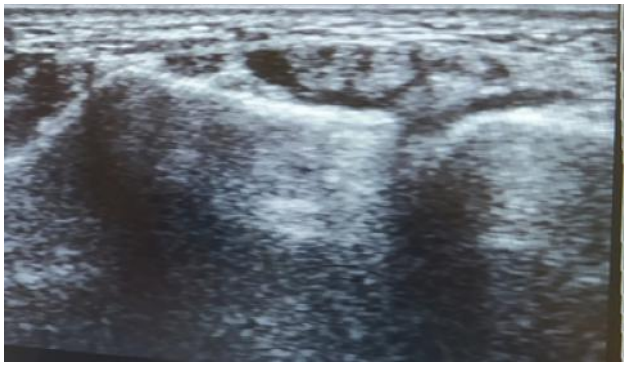


Figure A. Synovitis in wrist joint (grey scale and power Doppler)



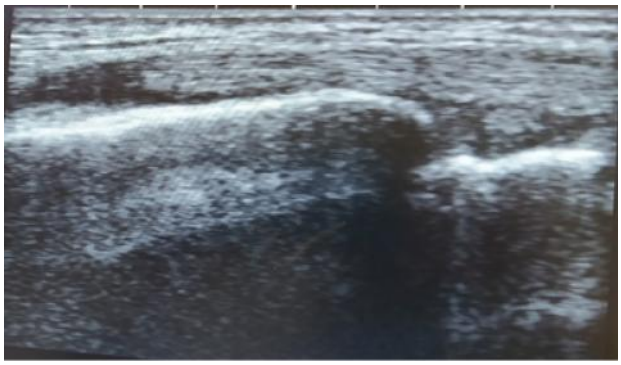


Figure B. tenosynovitis in 4th compartment of extensor retinaculum , longitudinal and transverse planes

Figure C. Bone erosion of the 2nd MCP, longitudinal and transverse planes

DISCUSSION

Of the several validated US scorings, including various joints, we utilized the US7. In spite of including only slight joints of one hand and one foot, the US7 satisfies the Consequence Evaluates in Rheumatology criteria of truth, discernment, and possibility. The US7 is as precise as other confirmed US scorings with a fairly slight number of joints to be evaluated, being an exciting comprehensive US scoring system of synovitis in RA-cases.[3] In the current study,

detailed joint area examination by US7 scoring was performed, and we found that the dorsomedialpart of the wrist (94%) and the dorsum of MTP II (96%) were the most influenced joint areas with synovitis by GSUS. the palmar aspect of MCP II (70%), and the palmar part of MCP III (72%) were affected but to lesser extent early in rheumatoid arthritis. In contrast with our study Kamel *et al.*[10]reported that most joints influenced by synovitis (diagnosed by GSUS) were the wrist in the dorsal aspect, the MCP II in the palmar aspect, and PIP II in the palmar aspect. Scheel *et al*. [11] found that the most joint affected by synovitis was PIP joints followed by MCP joints, synovitis most frequently at the palmar and proximal site of both the MCP and the PIP joints. For the recognition of synovitis by PDUS in our study, dorsomedial part of the wrist, dorsum of MTP II and dorsum of the MCP III were involved, as PD activity was found more on the dorsal than palmar aspect of the joints. Ohrndorf S and BACKHAUSM. [12] Reported that the most joints/joint regions affected by synovitis (detected by GSUS) were the wrist in the dorsal aspect, the 2nd MCP in the palmar aspect, and 2nd PIP in the palmar aspect. *Ohrndrof S; et al:* [13] reported that the most joints affected by synovitis (detected by GSUS) were the wrist in the dorsal aspect and the MCP II in the palmar aspect, whereby the wrist was more severely affected. For the detection of synovitis by PDUS in our study, dorsomedial aspect of the wrist, dorsal aspect of 2ndMTP and dorsal aspect of the 3rd MCP were involved, as PD activity was found more on the dorsal thanpalmar aspect of the joints.

Vlad *et al.*[14] reported that the maximum prevalence of positive synovitis was found in carpal joints (91%) followed by MCP2 (88%) Our results revealed that tenosynovitis of the extensor carpi-ulnaris tendon noticed by GSUS was detected in at least 25 (50%) of the tested joints, with PD activity of 22 (44%). Erosions were found most in radial aspect of MCP II (64%), ulnar aspect of wrist (22%), planter and lateral aspect of MTP V. Naredo *et al.* [15]reported that the US noticed tenosynovitis on B-mode was detected in 43% of tendons. The positive Correlation of DAS 28, GSUS synovitis score, PD synovitis score and total erosion scores: showed the ability of US7 score to reflect disease activity and severity. But doesn't reflect the extent of erosions. El gohary *et al.* [16] reported that the PD synovitis evaluated by PD US7and sum (PD) US7 exhibiting a significant correlation with disease activity as future evaluated by DAS28 Backhaus *et al.*[17]reported that there was significant correlation among variations in the ultrasound factors for synovitis and the DAS28 variations over 3-months, but there was no significant association among the changes in erosions and the DAS28 variations within 3and 6months of follow up. On the other hand Ciurtin *et al.* [18] found that no significant correlation was existing among somewhat of MSUS scores and the DAS28 score in RA patients. Also Scheel AK; *et al*. [11] didn't find any significant correlation between US scores and clinical findings judged by the DAS28. Ellegaard *et al*. [19] reported that a standardized color Doppler US examination of the wrist joint as the only target joint was very helpful in the detection of disease activity with a high correlation to CRP, ESR, swollen joint count, and DAS28

Conclusion

- Musculoskeletal ultra-sonography detects standard pathologies in RA as Synovitis, tenosynovitis and bone erosion.
- The positive Correlation of DAS 28, GSUS synovitis score, PD synovitis score and total erosion scores: showed the ability of US7 score to reflect disease activity and severity. But doesn't reflect the extent of erosions.
- US7 is simple and practical scoring system and we recommend it for usage in the diagnosis of sub-clinical synovitis in the early RA-cases.

Limitations of our study

- The patients doesn't seek medical adviceearly so patient selection in the 1st six months of symptoms is very difficult.
- Ultrasound is a limited diagnostic modality as:
  - It is an operator dependent and need long –term of training and practice to have experience in detecting abnormalities
  - Limited field of view
  - Time consuming regarding examining each joints and tendons
  - Unable to penetrate bones
  - 2-Quality of image depends on multiple factor such as:
  - Patient position
  - Machine
  - Sonographer skills.

List of abbreviations

- **DAS**: disease activity score
- **RA**: Rheumatoid arthritis
- **ACR**: American colleague of rheumatology
- **EULAR:** European league against rheumatism
- **MRI**: magnetic resonance imaging
- **US**: ultrasound
- **GSUS**: gray scale ultrasound
- **MCP**: metacarpophalangeal joint
- **PIP**: proximal interphalangeal joint
- **MTP**: metatarsophalangeal joint
- **OMERACT:** Outcome Measures in Rheumatoid arthritis Clinical Trials
- **SH:** synovial hypertrophy
- **PD:** power Doppler
- **NSAIDS:** non-steroidal anti-inflammatory drugs
- **SJC:** swollen joint count
- **TJC:** tender joint count
- **CRP:** C-reactive protein
- **ESR:** Erythrocyte sedimentation rate
- **RF:** Rheumatoid factor
- **ACPA:** Anticitrullinated cyclic peptides antibodies
- **SD:** standard deviation
- **PDUS:** Power Doppler ultrasound
- **MSUS:** musculoskeletal ultrasound

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