



# Usefulness of ultrasound in the short-term follow-up of rheumatoid arthritis activity

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## Abstract

**Aims:** To compare Ultrasound (US) scores (Naredo score and Backhaus score (NS and BS) to conventional measures (DAS28) in Rheumatoid Arthritis (RA) activity assessment and to evaluate clinical and US score changes after treatment.

**Methods:** Sixty nine RA patients were consecutively assessed at the Rheumatology Department of Monastir Teaching Hospital in Tunisia, from November 1<sup>st</sup>, 2016 to April 30<sup>th</sup>, 2017. All patients underwent clinical, laboratory, radiographic and ultrasonographic assessments at baseline, at one week and at one month after treatment adaptation.

**Results:** Patients mean age was 52 ± 10 years. At baseline, mean DAS 28 was 4.66 ± 1.54. Disease activity was moderate and high in 34.8% and 44.9% of cases respectively. Prevalence of synovitis was 59.4% by physical assessment and 82.6% by US. Mean NS was 17 ± 15 and BS was 21 ± 10. NS and BS were significantly associated with DAS28. The number of erosions found by the BS was superior in 91% of cases to that found by Modified Sharp Score in the same joints. Clinical, biological and US indicators changed significantly after treatment, from baseline to one week and one month. Compared to clinical examination, US was found to better detect synovitis at small joints ( $p < 10^{-3}$ ). NS reactivity with DAS 28 was greater than that of BS.

**Conclusion:** NS and BS are associated with RA disease activity. Ultrasound detects better synovitis and erosions than clinical and radiological assessments. US evaluation is useful in assessing disease activity at baseline and in monitoring treatment efficacy.



## Introduction

Rheumatoid Arthritis (RA) is a chronic inflammatory joint disease in which synovitis causes cartilage destruction and bone erosions, a source of permanent disability [1-3]. The accurate assessment of joint inflammation and close monitoring of disease activity are therefore essential. Hyper-vascularization and angiogenesis of the synovial membrane are the two primary pathogenic mechanisms responsible for the invasive behavior of the rheumatoid pannus. The inflammatory joint activity is then directly related to the synovial vascularization [4].

Synovitis is classically evaluated by subjective clinical examination and laboratory parameters. However, imaging techniques play an important and growing role in its evaluation [4]. In fact, osteoarticular ultrasonography, in RA, has demonstrated greater validity and added value in patient evaluation more than clinical examination and standard radiographs, especially in synovial vascularization assessment through doppler power activity. Therefore, it improves the early diagnosis and disease monitoring under treatment [5,6].

Different clinical, biological and composite indices (DAS 28 ...) are used to evaluate the clinical activity of RA [7-9]. However, subclinical activity may be observed despite clinical remission and may induce radiological progression [10-14]. Ultrasound is of great interest in the detection of asymptomatic or persistent synovitis and in the assessment of the risk of radiological progression as shown by Yin-Chou C et al [4]. Different ultrasound scores have been evaluated [15-18]. The Naredo score (NS) [16] and Backhaus score (BS) [17] are the most interesting for monitoring as they are feasible in daily practice [18,19] and sensitive to change [20].

The objectives of this study were to compare ultrasound synovial scores (NS and BS) with conventional follow-up indices (DAS28, Erythrocyte Sedimentation Rate (ESR), C-reactive protein (CRP)) in the assessment of RA and to evaluate changes in clinical and ultrasound scores at one week and at one month after treatment.

## Methods

This is a prospective, single-center study of patients with RA, conducted in the Rheumatology Department, Fattouma Bourguiba University Hospital, Monastir, Tunisia over a six-month period (November 1st, 2016 to April 30th, 2017).

### Inclusion criteria

Were included in the current study, patients with RA according to the 1987 ACR/EULAR 2010 criteria, seen consecutively and followed at the Rheumatology Department for at least one month. Informed consent was obtained from all patients.

### Non inclusion criteria

If impossibility to achieve ultrasound (US) follow-up 7 days after the initial assessment (on day 7 (D7)) and/or after one month (on day 30 (D30)).

### Data collection and applied definitions

#### For each patient we carried out:

- A detailed interview and a physical examination performed by the same examiner.
- Radiological (dating back to less than one year) and biological examinations.

- US examination within a week of the clinical evaluation, then one week (on day 7 (D7)) and one month (D30) after the first assessment performed by the same sonographer (trained in osteoarticular US for 3 years).

#### We evaluated:

- The epidemiological data (age, sex, educational level, life-style)
- The duration of RA in months.
- Patient's history and current treatments.

We quantified: \* Patient Global Assessment of the disease (PGA), through a visual analogue scale (0-10 mm). \* The tender joint count (TJC) and the swollen joint count (SJC). \* The duration of morning stiffness in minutes. \* The number of nocturnal awakenings from joint pain. \* The Erythrocyte Sedimentation Rate (ESR) at the first hour in mm, C-reactive protein (CRP) in mg/l, and then, we determined the DAS 28 [21]. We specified the presence of extra-articular manifestations (EAM) (type, duration of evolution and treatment), joint deformity and the Tunisian version of the Health Assessment Questionnaire (HAQ) [22]. Moderate handicap is defined by HAQ between 1 and 2 and severe if HAQ > 2. The radiological involvement of the hands and feet was evaluated by analyzing the frontal x-rays of the wrists and hands and forefeet for bone erosions and joint narrowing and calculating the Sharp modified by Van der Heijde score (SS) for each patient [23] at baseline.

Articular US were performed in all patients on D1, D7 and D30 using linear scanning probes: 8-18 MHz frequency. The examination was done by the same physician, trained in musculoskeletal ultrasound for three years, under the same conditions for each patient in three times evaluation. The NS [16] and BS [17] are determined.

Two groups (Gr) were defined according to the RA activity as defined by EULAR [21]:

- Gr1: RA not active: DAS 28 < 3.2
- Gr2: RA moderately or very active: DAS 28 ≥ 3.2

All patients with active RA had treatment adaptation (association of NSAID and/or corticosteroid or dose escalation and/or Disease-modifying anti-rheumatic drugs (DMARD) dose escalation or switch). In those with high disease activity, boluses of corticosteroids (methylprednisolone 125 mg to 250 mg for 1 to 3 days) were administered.

### Statistical analysis

Statistical analysis was performed using SPSS software for Windows (version 17.0). A descriptive study was carried out. We calculated means or medians and we determined range for the quantitative variables. Frequencies and percentages were calculated for the qualitative variables. We searched for associations between US data and RA clinical, biological, radiological and therapeutic data.

For the comparison of averages we used Student's "t" test. For the comparison of the medians we used the Friedman test to compare several parameters and the Wilcoxon test to compare two medians. To study the homogeneity of the cohort parameters, we used the Kolmogorov-Smirnov test. The chi-square test was used to study the correlations between the qualitative variables and in case of non-validity of this test, the Fisher's ex-

act bilateral test was used. Correlations between the quantitative parameters were evaluated by the Spearman test.

For multivariate analysis, we used a binary linear regression. The inclusion of independent variables in the regression models was done when their significance level was less than 0.2 ( $p < 0.2$ ).

For statistical tests, the significance level  $p$  has been set at 0.05.

The study of the responsiveness between the ultrasound scores and DAS28 was performed using the Altaman graph.

## Results

Sixty-nine patients with a mean age of  $52 \pm 10$  years [27-78] and a sex ratio of 0.13 were evaluated. Patients were non smokers in 70% of the cases and of urban origin of the Tunisian Sahel region in 72% of the cases. The educational level did not exceed that of primary education in 76.7% of cases and 53.6% of our patients did not work. The average BMI was  $28 \pm 4.8$  Kg/m<sup>2</sup> [18.03-42.97].

The average age at the disease onset was  $41 \pm 12$  years [11-71]. The mean RA disease duration was  $116 \pm 80$  months [1-333]. The Vander Heijde's modified Sharp score (SS) was  $101 \pm 54$  [17-263]. The mean joint erosion score for both hands was  $50 \pm 37$  [0-161]. The average joint space narrowing score of both hands was  $51 \pm 25$  [3-131].

For the DMARD, 97.1% of the patients were on methotrexate (MTX) with 43.5% at 20 mg/week; 37.7% on sulfasalazine; 36% on hydroxychloroquine (HCQ); 21.7% on leflunomide and 11.6% on biotherapy of whom 50% were on anti-TNF $\alpha$ , 37.5% on rituximab and 12.5% on tocilizumab.

At the initial evaluation, the mean PGA was  $4.4 \pm 2.26$  [0-8.9], the mean TJC was  $5.57 \pm 5.7$  [0-27], and the mean SJC was  $5.62 \pm 3.95$  [0-27] (Table 1). Prevalence of synovitis was 59.4% by physical assessment. The mean value of ESR was  $40 \text{ mm} \pm 24$  [4-115]. The mean CRP value was  $15 \text{ mg/l}$  [0-72]. The average DAS28 was  $4.66 \pm 1.54$  [0.97-7.73]. RA was highly active in 44.9% and moderately active in 34.8% of cases. The majority of patients (79%) had a functional impairment with HAQ > 0.5, of whom 41% had a moderate disability and 29% a severe disability. The most difficult tasks involved items 3 (eating) and 5 (catching) with averages of 2.40 and 2.35 respectively.

US assessment revealed that 82.6% of cases had at least one synovitis, the median NS was  $16 \pm 15.4$  [0-64], and the mean BS score was  $17 \pm 7$  [2-34].

The therapeutic adaptation interested 79% of the patients with a good clinical evolution in 56% of the cases.

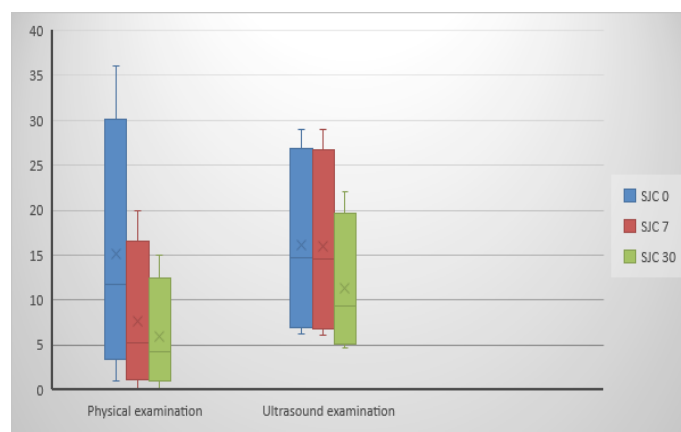
During the 2nd evaluation on D7 and 3rd evaluation on D30, the various indices of disease activity evolved favorably (Table 2). The mustache graphic representation of the evolution in time of the number of synovitis detected by the clinical examination and ultrasonography show a delay in the evolution of ultrasound data in relation to the clinical course, especially in the first week (Figure 1). Indeed, and after therapeutic adaptation, there was a significant decrease in the number of synovitis on clinical examination at D7 greater than that between D7 and D30, while the number of synovitis, was almost the same on ultrasound at D0 and D7 and it was not until D30 that we objectified a fall of the number of ultrasound synovitis.

US detects synovitis better than physical assessment at all the sites explored, especially in small joints. However, there was no statistically significant difference in the assessment of both wrist involvements at the three progressive times (Table 3).

The DAS28 evolution course over time was marked by a statistically significant decrease at the 3 times, D0-D7, D0-D30 and D7-D30 ( $p < 10^{-3}$ , respectively). Similarly, for the evolution of the BS, J0-J7 ( $p < 10^{-3}$ ), J0-J30 ( $p = 0.001$ ) and J7-J30 ( $p < 10^{-3}$ ). The evolution over time of the NS (whose distribution is not homogeneous according to the Kolmogorov-Smirnov test, unlike the DAS28 and BS) was marked by a significant decrease according to the Friedman test ( $p = 0, 05$ ). This decrease was statistically significant between D0-D7 and D0-D30 with respectively  $p < 10^{-3}$  and  $p = 0.05$ . However, the decrease between D7 and D30 was not statistically significant ( $p = 0.107$ ). The improvement in US scores over time was more evident than DAS 28 (Figure 2).

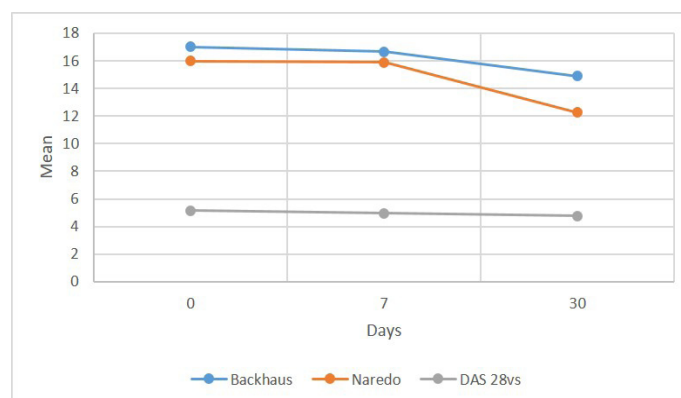
The study of the responsiveness between the US scores and DAS28 by the ALTAMAN graph, shows that the NS follows the DAS28 better than BS (Figure 3).

The three disease activity scores (DAS 28, NS, and BS) were correlated with each other on D0 and had the same trend of progression on D7 and D30. For patients with RA remission or weak activity, US were better to detect asymptomatic synovitis mainly in large joints.

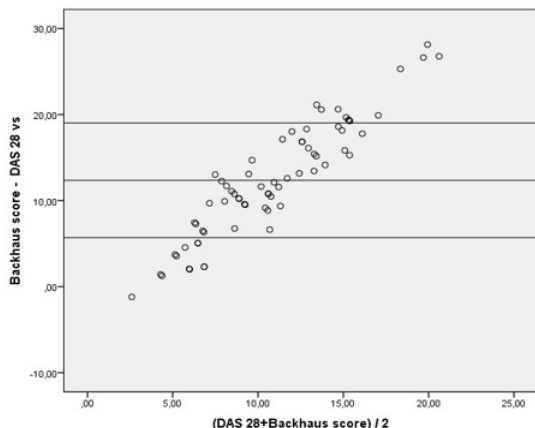


**Figure 1:** Evolution of synovitis detected by physical and ultrasound examination

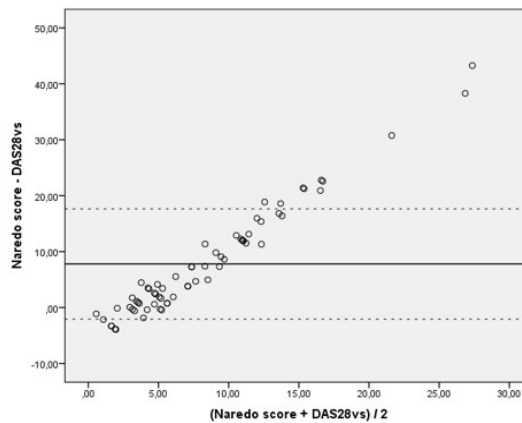
SJC: Swollen joint count at days 0, 7 and 30



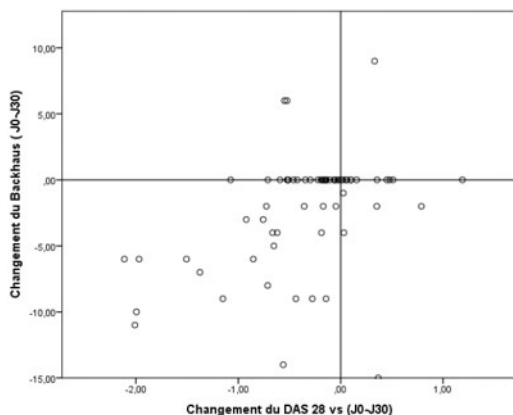
**Figure 2:** Evolution of clinical and ultrasound rheumatoid arthritis disease activity parameters



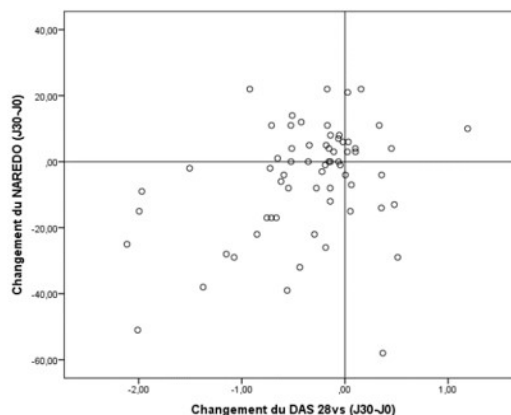
Responsiveness of Backhaus score and DAS28



Responsiveness of Naredo score and DAS28



Correlation between change in BACKHAUS score and DAS28



Correlation between change in NAREDO score and DAS28

**Figure 3:** Correlation between ultrasound scores and DAS28 by Altman graph

**Table 1:** Baseline Characteristics of rheumatoid arthritis patients.

Age (mean ± DS), years	52±10
Sexe ratio	0.13
Disease duration (mean ± DS), months	116 ± 80
SJC (mean ± DS)	5.62 ± 3.95
DAS 28 (mean ± DS)	4.66 ± 1.54
DAS 28 < 2.6 (%)	10.1
2,6 ≤ DAS 28 < 3.2 (%)	10.1
3,2 ≤ DAS 28 < 5.1 (%)	34.8
DAS 28 ≥ 5.1 (%)	44.9
HAQ (mean ± DS)	1.22 ± 0.73
ESR (mean ± DS, mm H1)	40 ± 24
Naredo Score (mean ± DS)	16 ± 15.4
Backhaus Score (mean ± DS)	17 ± 7

RA: Rheumatoid arthritis; SJC: Swollen Joint Count ; DAS28: Disease Activity Score (28 joints); HAQ: Health Assessment Questionnaire; ESR: Erythrocyte sedimentation rate.

**Table 2:** Evolution of rheumatoid arthritis disease activity parameters

	D7	Difference D0 - D7 (p)	D30	Difference D7-D30 (p)
<b>DAS 28</b> (mean ± DS)	4.5 ± 1.42	<10 <sup>-3</sup>	4.31 ± 1.26	<10 <sup>-3</sup>
<b>HAQ</b> (mean ± DS)	0.95 ± 0.61	0.04	0.81 ± 0.59	NS
<b>NS</b> (mean ± DS)	15.89 ± 14.45	<10 <sup>-3</sup>	12.25 ± 10.6	NS
<b>BS</b> (mean ± DS)	16,65 ± 7.03	<10 <sup>-3</sup>	14.9 ± 5.7	0.001

SJC: Swollen Joint Count ; DAS28: Disease Activity Score ; HAQ: Health Assessment Questionnaire ; NS: Naredo Score; BS: Backhaus Score.



**Table 3:** Utility of ultrasound in detecting synovitis in the short-term follow-up

Synovitis	D0			D7			D30		
	P Ex	US	<i>p</i>	P Ex	US	<i>p</i>	P Ex	US	<i>p</i>
Right wrist	29	29	<b>0.56</b>	20	29	<b>0.04</b>	15	22	<b>0.06</b>
Left wrist	22	24	<b>0.07</b>	13	23	<b>0.03</b>	12	18	<b>0.05</b>
Right MCP 2	25	36	<b>0.04</b>	2	25	<b>&lt;10<sup>-3</sup></b>	3	17	<b>&lt;10<sup>-3</sup></b>
Left MCP 2	13	25	<b>0.01</b>	2	24	<b>&lt;10<sup>-3</sup></b>	2	11	<b>0.01</b>
Right MCP 3	9	24	<b>&lt;10<sup>-3</sup></b>	0	24	<b>&lt;10<sup>-3</sup></b>	0	10	<b>&lt;10<sup>-3</sup></b>
Left MCP 3	7	25	<b>&lt;10<sup>-3</sup></b>	0	24	<b>&lt;10<sup>-3</sup></b>	0	12	<b>&lt;10<sup>-3</sup></b>
Right elbow	8	9	<b>0.17</b>	4	9	<b>0.07</b>	2	8	<b>0.002</b>
Left elbow	1	11	<b>0.05</b>	0	11	<b>&lt;10<sup>-3</sup></b>	1	6	<b>&lt;10<sup>-3</sup></b>
Right knee	11	21	<b>0.001</b>	5	20	<b>&lt;10<sup>-3</sup></b>	3	16	<b>0.001</b>
Left knee	9	16	<b>&lt;10<sup>-3</sup></b>	3	16	<b>&lt;10<sup>-3</sup></b>	4	13	<b>&lt;10<sup>-3</sup></b>
Right PIP 2	2	15	<b>&lt;10<sup>-3</sup></b>	1	15	<b>&lt;10<sup>-3</sup></b>	1	8	<b>0.001</b>
Right PIP 3	5	20	<b>&lt;10<sup>-3</sup></b>	1	20	<b>&lt;10<sup>-3</sup></b>	1	12	<b>&lt;10<sup>-3</sup></b>

PEx: Physical examination; US: Ultrasound Examination; MCP: Metacarpophalangeal; PIP: Proximal Interphalangeal

## Discussion

To our knowledge, this is the first study comparing two US scores to DAS28 in the assessment of RA in real life and in Tunisian patients. Our study confirms the feasibility of NS and BS in daily practice and their added value in evaluating RA activity. Nearly 80% of our patients had active RA. This fact is explained by RA severity (deforming, destructive, old, significant functional disability) making patients consult a tertiary Teaching Hospital. The therapeutic adaptation interested 79% of these patients with a good clinical outcome in 56% of the cases. This therapeutic adaptation deserves an adequate evaluation by means of simple clinical indices but also more objective and reliable indices, mainly ultrasonographic ones. Especially since the articular US offers multiple advantages such as accessibility, low cost, absence of irradiation, good tolerance, dynamic character and multiplicity of the sites studied during a single examination, possible evaluation of inflammatory activity and structural damage at the same time and sensitivity to change over time [24]. The validity of US assessment during RA has been well demonstrated [5,15-20]. Reproducibility is as good as or better than the reproducibility of clinical examination for the detection of synovitis [18]. Our study showed more synovitis detected on US compared to the physical assessment. DAS28 may not reflect the reality of inflammatory activity and US scores are thus more appropriate. Clinical improvement is correlated with US improvement and the sensitivity to the change of US has been well demonstrated under treatment [25]. However, the synovitis count at D7 and D30 remains higher by US compared to the clinical examination and may indicate that anatomical synovitis takes time to disappear under treatment. In addition, it was shown that synovitis may persist in patients achieving RA remission and detected by US [26]. In our study, also, asymptomatic synovitis were better detected in patients in remission or with low activity, often without doppler activity and mainly at the level of large joints. The Doppler signal is crucial here to indicate

the risk of structural progression [25], relapse [27] and probably to encourage local treatment of these "rebel" synovitis. US evaluate predictive factors to relapse and radiographic progression (persistent synovitis despite the favorable clinical course) and thus contribute to better patient management [27].

The persistence of some subclinical synovitis detected on US may explain the decrease in the correlation between the 3 disease activity scores over time. On the other hand, the NS did not change significantly between D7 and D30. This shows that patients who did not respond to treatment on D7 had the same state of disease activity on D30 and thus probably required therapeutic adaptation earlier than one month. This score evaluates more joints than the BS, thus testifying that the joints not explored by the BS require special attention. There is a significant correlation between US scores and DAS28 initially and over time under treatment. Responsiveness and variation in US score changes indicate that NS is better able to follow DAS28. In the Zufferey study [28], the DAS28 and SONAR ultrasound score also showed a similar reactivity according to the standardized mean response and confirms that the RA evaluation by an echographic score previously taught to rheumatologists can be used in daily practice. However, other prospective and longitudinal studies will help to better understand how the US score could improve clinical practice. In the Zufferey study [28], the US evaluation was performed by different rheumatologists with different machines, which is an important limitation for a reliable interpretation of the results. In our study, only one sonographer provided assessment of patients under the same technical conditions, however, he was aware of clinical evaluation and biological data.

Standardization of scores and machines especially for Doppler evaluation is required. After the initial US examination, and according to the data of the literature, there is no consensus on

the rhythm of the US or on the target joints [29].

Discrepancies at the individual level between US scores and DAS28 reflect real differences and US could provide additional information. For example a high score in B mode with a low DAS28 could mean a non-active old fibrotic synovitis. A high DAS28 and a low US score might reflect a biological inflammatory state not related to synovitis. If the DAS28 is elevated without swelling or synovitis, fibromyalgia is possible [28].

Our cohort of RA was unselected consisting of old active and severe RA patients, with clear and conclusive change in disease activity scores assessment under treatment adaptation, but the same sonographer was not blinded to clinical data.

### Conclusion

Joint US improve the assessment of inflammatory activity and structural impairment during RA compared to standard data. It allows a direct evaluation of the inflammatory activity and the morphological damage at the same time and brings complementary information to the clinical, biological and radiological data. It is sensitive to change under treatment in real life and in RA Tunisian patients with a high disease activity. NS and BS are significantly associated with RA disease activity. The NS better tracks the change in the DAS28 and the BS better assesses the structural damage. The NS and BS are feasible in real life; they are easy, little time-consuming and could be interesting during RA follow-up. Further, larger, longitudinal studies will demonstrate their impact in therapeutic management and in improving RA patient outcome.

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