DAS28(3)CRP is a reliable measure of rheumatoid arthritis disease activity in pregnancy

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Ethics and consent

Ethical approval was obtained from North of Scotland Research Ethics Committee reference: 18/ND/0077. Patients received oral and written information on the objectives of the study and gave signed informed consent to participate and consent to publish before entering the study.

Short running title: Validation of DAS28(3)CRP in RA pregnancy

Abstract

Objective

The disease activity of rheumatoid arthritis (RA) in pregnancy is most commonly assessed with the modified Disease Activity Score (DAS)-28, the DAS28(3)CRP. However, the performance of the DAS28(3)CRP in pregnancy has not been compared to musculoskeletal ultrasound (MSK-US) as a gold standard. We performed a prospective pilot study to test the hypothesis that pregnancy-related factors limit the reliability of the DAS28(3)CRP.

Methods

Pregnant women with RA were recruited from an Obstetric Rheumatology clinic and assessed during pregnancy and postpartum with DAS28(3)CRP and MSK-US scores, with quantification of Power Doppler (PD) signal in small joints (hands and feet). Age-matched non-pregnant women with RA underwent equivalent assessments. PD scores were calculated as mean scores of all joints scanned.

Results

We recruited 27 pregnant and 20 non-pregnant women with RA. DAS28(3)CRP was sensitive and specific for active RA in pregnancy and postpartum as defined by positive PD signal, but not in non-pregnancy. There were significant correlations between DAS28(3)CRP and PD scores throughout pregnancy (T2, $r = 0.82$ (95% CI [0.42, 0.95], $p < 0.01$); T3, $r = 0.68$ (95% CI [0.38, 0.86], $p < 0.01$)) and postpartum, $r = 0.84$ (95% CI [0.60, 0.94], $p < 0.01$), while this correlation in non-pregnancy was weaker ($r = 0.47$ (95% CI [0, 0.77], $p < 0.05$).

Conclusion

This pilot study found that DAS28(3)CRP is a reliable measure of disease activity in pregnant women with RA. Based on these data, pregnancy does not appear to confound clinical evaluation of the tender and/or swollen joint counts.

Key Indexing Terms

Rheumatoid arthritis, Pregnancy, Ultrasonography

Introduction

Modern 'treat to target' regimens achieve low disease activity or remission in the third trimester in 90% of pregnant women with rheumatoid arthritis (RA) (1). Treatment decisions in RA rely on disease activity assessment with standardised scores (2), of which the most frequently used is the Disease Activity Score (DAS)-28. This measure is a composite of the tender (TJC) and swollen (SJC) joint counts of a 28-joint assessment, a patient-derived global health (GH) score, and either erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) (3). Criticisms of this score include subjectivity of the joint assessment, poor specificity of GH, and lack of measurement of foot involvement (4).

Studies of RA in pregnancy have used many different disease activity scores and definitions of remission/flare, none of which were devised for use in pregnancy. The modified DAS28(3)CRP, which omits the GH as it may be confounded by pregnancy, has been proposed as the most reliable scoring tool (5). However, this score has not been validated in pregnancy by comparison against a gold standard such as musculoskeletal ultrasound (MSK-US), which may detect active joint inflammation in DAS28 remission (6). In a cohort of non-pregnant women with RA, we previously found that DAS28 correlated poorly with hand and foot joint inflammation measured on MSK-US with Power Doppler (PD) signal (7). We hypothesised that non-inflammatory musculoskeletal pain and/or peripheral oedema in pregnancy may confound the assessment of tender and/or swollen joints relative to non-pregnancy, thereby reducing the reliability of DAS28(3)CRP. Therefore, we conducted this exploratory pilot study to compare DAS28(3)CRP scores with MSK-US quantification of joint synovitis in pregnant and non-pregnant women with RA.

Methods

Recruitment and data collection

Written informed consent to participate and for study publication was obtained from all subjects (Research Ethics Committee reference: 18/ND/0077). Given the pilot nature of this study no formal sample size estimate was made (8).

All RA patients fulfilled classification criteria (9). Pregnant women with RA (RA-P) were recruited from the obstetric rheumatology clinic at University College London Hospital between September 2018 and October 2021. Study assessments were at 13 – 27 weeks (second trimester, T2), > 28 weeks (third trimester, T3), and within 6 months postpartum. Data collection comprised: demographics; disease features; drug history; obstetric history; tender joint count (TJC); swollen joint count (SJC) (both from 28-joint count); DAS28(3)CRP; and MSK-US. DAS28 scores within the 6 months prior to pregnancy were obtained from patient records. Age-matched (+/- 5 years) non-pregnant female RA patients (RA-NP) were recruited from general rheumatology clinics with equivalent assessments at a single time-point for the purpose of cross-sectional comparison with T3 of RA-P. Modified DAS28CRP thresholds for remission, low (LDA), moderate (MDA) and high (HDA) disease activity were used (10) (which were developed for DAS28(4)CRP but were used for feasibility reasons as equivalent thresholds for DAS28(3)CRP have yet to be established), Table 1. Healthy age-matched (+/- 5 years), pregnant women (HC-P) were recruited from routine antenatal clinics upon exclusion criteria of autoimmune disease, small joint pain, or use of immunosuppressive therapy.

MSK-US examination

All MSK-US examinations were performed by a single operator blinded to DAS28(3)CRP evaluations. MSK-US was undertaken using a Logiq S8 US machine equipped with a multi-

frequency linear matrix array transducer (8-22 MHz). B-mode and PD machine settings were optimised for all examinations. The protocol comprised 22-joint assessment of hands (dorsal longitudinal and transverse views of wrists, metacarpophalangeal and proximal interphalangeal joints); additionally, bilateral metatarsophalangeal (MTP) joints were scanned with longitudinal views depending on the presence of foot symptoms. The presence of active joint inflammation was defined as PD signal within a region of grey scale (GS) synovitis, graded 1-3, as per the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) US definitions developed for RA (11). Any PD signal within the MTP1 bursa was discounted from the overall PD score. RA activity measured by MSK-US was defined by 'PD score', calculated as the mean of the PD scores of individual joints (22 hand joints and 10 feet joints).

Statistical analysis

Statistical analysis was performed in SPSS version 27 (SPSS, Chicago, IL). Demographic data were analysed using the unpaired t-test, Mann-Whitney or Fisher's exact tests as appropriate. Longitudinal comparison of PD and DAS28(3)CRP scores were analysed using repeated measures ANOVA; sensitivity/specificity analyses by receiver operating characteristic (ROC) curves; correlations of DAS28(3)CRP and components versus PD score were performed with Spearman's rank as data were non-parametric; comparison of correlational coefficients was with Fisher r-to-z transformation. P values < 0.05 were considered statistically significant. Figures were produced with GraphPad Prism version 9.0.

Patient and public involvement

Previously, we conducted an online survey of women with RA regarding pregnancy-related issues. Respondents expressed enthusiasm for research into RA and pregnancy and 93 % would consent to MSK-US during pregnancy (12).

Results

Patient recruitment and demographics

We recruited 27 RA-P and 20 RA-NP subjects, Table 2. MSK-US was additionally performed on four healthy pregnant women. The only significant difference between groups was use of methotrexate in RA-NP. In the RA-P group, three women received >10 mg prednisolone, for two of whom the dose was increased from T2 to T3, while the other woman was on a stable dose throughout pregnancy. No DMARD or biologic therapy was initiated during pregnancy.

DAS28(3)CRP and MSK-US assessment of disease activity of RA in pregnancy

RA disease activity measured by DAS28(3)CRP and MSK-US in pregnant and non-pregnant groups is shown in Figure 1 and Table 2. Over half of patients were in DAS28(3)CRP remission in RA-NP and each timepoint of pregnancy/postpartum, but the following proportion of patients had at least moderate disease activity: in RA-NP, 26.3 %; T2, 29.4 %; in T3, 29.2 %; in postpartum, 35.0 % (Figure 1A). In the RA-P cohort, median DAS28(3)CRP scores were as follows: in T2, 1.92 (95% CI [1.70, 3.03]); in T3, 2.01 (95% CI [1.79, 3.17]); in postpartum, 1.94 (95% CI [1.59, 3.64]). In RA-NP, median DAS28(3)CRP was 2.37 (95% CI [1.42, 2.96]). The proportion of patients with detectable PD signal on MSK-US examination was 36.4 % in T2, 30.4 % in T3, 36.8 % in postpartum, and 36.8 % in RA-NP (Figure 1B). There were no significant differences in DAS28(3)CRP or PD scores on comparison of T3 RA-P and RA-NP groups. Longitudinal analysis of DAS28(3)CRP or PD scores also showed no statistical differences on comparison of T2 and T3 and T3 and postpartum. Similarly, no differences were found in the proportions of patients with detectable PD signal at each DAS28(3)CRP-defined disease activity category in RA-P and RA-NP (Figure 1C).

Sensitivity and specificity of DAS28(3)CRP for Power Doppler signal on MSK-US examination in pregnant women with RA

ROC curve analysis of the ability of DAS28(3)CRP to discriminate between patients with positive and negative PD signal on MSK-US (PD >0 vs PD = 0) in RA-P and RA-NP is shown in Figure 2. DAS28(3)CRP was highly sensitive and specific for positive PD signal in pregnancy (T2, AUC = 0.96 (95% CI [0.86, 1], p = 0.01); T3, AUC = 0.93 (95% CI [0.82, 1], p < 0.01) and post-partum (AUC = 1 (95% CI [1, 1], p < 0.01), but not in non-pregnancy (AUC = 0.76 (95 % CI [0.51, 1], p = 0.07). DAS28(3)CRP cut-off values for the absence of PD signal in pregnancy were as follows: in T2, < 2.07 (sensitivity 100%, specificity 85.7%); in T3, < 2.15 (sensitivity 100%, specificity 81.3%); in postpartum, < 2.46 (sensitivity 100%, specificity 100%); in RA-NP, < 2.47 (sensitivity 71.4%, specificity 83.3%).

Correlation between DAS28(3)CRP and MSK-US

DAS28(3)CRP and its components were correlated with PD scores in RA-P and RA-NP (Table 3). Significant positive correlations between DAS28(3)CRP and PD score were found at T2 (r = 0.82 (95% CI [0.42, 0.95], p < 0.01)), T3 (r = 0.68 (95% CI [0.38, 0.86], p < 0.01)) and postpartum (r = 0.84 (95% CI [0.60, 0.94], p < 0.01)). Each correlation was of greater magnitude than the equivalent comparison in RA-NP (r = 0.51 (95% CI [0.06, 0.79], p < 0.05). There were significant positive correlations between TJC and PD score in each trimester of pregnancy and postpartum (T2, r = 0.86 (95% CI [0.52, 0.96], p < 0.001); T3, r = 0.77 (95% CI [0.51, 0.90], p < 0.001); postpartum, r = 0.90 (95% CI [0.75, 0.97], p < 0.001)), while this correlation in RA-NP was weaker (r = 0.47 (95% CI [0, 0.77], p < 0.05)). There was significant correlation of SJC with PD score at each stage of pregnancy/postpartum and in RA-NP. At each time-point of RA-P, there was no difference between the strength of correlation of TJC

or SJC with PD score, whereas in RA-NP, SJC correlated significantly more strongly with PD score than TJC ($z = 2.35$, $p < 0.05$).

MSK-US of healthy pregnant women

To exclude non-specific effects of pregnancy on MSK-US assessment, we assessed four age-matched healthy pregnant women in T3. Subcutaneous oedema in the feet was noted in each, while two women had grade 1 synovial hypertrophy of MCP1, but no PD signal was detected in any joint.

Discussion

We present the first prospective pilot study to validate the use of DAS28(3)CRP in pregnant women with RA by comparison with MSK-US as a gold standard. DAS28(3)CRP is the most widely used disease activity score in pregnant women with RA, having been described as the "best clinimetric index to evaluate disease activity in pregnant RA patients" (13). However, in this context it has not yet been compared to an imaging tool such as MSK-US for the objective detection of active synovitis.

In non-pregnancy, the TJC and GH are most prone to confounding by non-inflammatory factors. Even though the GH is excluded from the DAS28(3)CRP score, we postulated that pregnancy might confound evaluation of the TJC and SJC. Non-inflammatory musculoskeletal pain is common in pregnancy (14, 15), while peripheral oedema of the hands and feet, particularly in later pregnancy, could conceivably complicate clinical assessment of the SJC.

Contrary to this hypothesis, these data show that DAS28(3)CRP performed with higher sensitivity and specificity in pregnancy and postpartum compared to non-pregnant women with

RA when assessed against MSK-US as a gold standard. There were significant positive correlations between TJC, SJC and DAS28(3)CRP and PD score throughout pregnancy and postpartum. Correlations between SJC and PD score were similar in pregnant and non-pregnant patients, suggesting that peripheral oedema did not confound clinical assessment of the SJC. Interestingly, both TJC and SJC scores correlated well with PD score in RA-P at all time points. In RA-NP, SJC correlated significantly better with PD score than TJC. The finding that the TJC may be a more reliable indicator of MSK-US-confirmed synovitis in pregnancy than in non-pregnancy in women with RA is unexplained and requires validation in a larger study, but could possibly relate to complex hormonal and psychological factors influencing patient-reported joint pain and clinical examination. For example, the production of various hormones such as beta-endorphins may influence pain perception during pregnancy (16).

Limitations

This study is limited by recruitment from a single centre and use of a single ultrasound operator. It requires replication with a larger sample size. The number and type of joints assessed by DAS28(3)CRP and MSK-US were not identical, as the MSK-US examination included the feet, which are not a component of the DAS28(3)CRP, while excluding the larger joints assessed by the DAS28(3)CRP score.

Conclusion

In conclusion, this prospective pilot study found that the DAS28(3)CRP score was a reliable indicator of disease activity of RA in pregnancy. In fact, DAS28(3)CRP was a more sensitive and specific indicator of the presence of PD signal on MSK-US in pregnant compared to non-pregnant women with RA, which is a novel finding. It appears that pregnancy does not

confound assessment of the DAS28(3)CRP. These findings require validation in a larger prospective cohort study.

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DAS28(3)CRP	Disease activity definition
< 2.4	Remission
≥ 2.4 – ≤ 2.9	Low disease activity
> 2.9 – ≤ 4.6	Moderate disease activity
> 4.6	High disease activity

Table 1. Modified DAS28CRP threshold values, from (10).

	RA pregnant		RA non-pregnant	P value
N	27		20	
Age; mean +- SD (range)	33.85 +- 3.58 (27 – 41)		32.00 +- 4.94 (24 – 41)	0.50
Ethnicity (%)				
White	21 (77.8)		11 (55)	0.12
Asian	4 (14.8)		7 (35)	0.16
Black	0 (0)		1 (5)	0.43
Other	2 (7.41)		1 (5)	> 0.99
Disease features				
Median disease duration; months	60		41	0.34
RF+; n (%)	20 (74.1)		15 (75)	>0.99
ACPA+; n (%)	18 (66.7)		16 (80)	0.35
Disease activity				
TJC; median (range)	T2	0 (0 – 8)	0 (0 – 14)	0.19
	T3	0 (0 – 5)		
	PP	0.5 (0 – 17)		
SJC; median (range)	T2	0 (0 – 7)	0 (0 – 11)	0.40
	T3	0 (0 – 4)		
	PP	0.5 (0 – 16)		
CRP (mg/L); median (range)	T2	4.2 (0.6 – 33.5)	1.4 (0.6 – 23.7)	0.07
	T3	4.6 (0.6 – 15.6)		
	PP	2.35 (0.6 – 32.0)		
DAS28(3)CRP; median (range)	T2	1.92 (1.46 – 4.88)	2.37 (1.15 – 5.41)	0.78
	T3	2.01 (1.15 – 3.98)		
	PP	1.94 (1.15 – 5.53)		
PD score; median (range)	T2	0 (0 – 0.625)	0 (0 – 0.82)	0.65
	T3	0 (0 – 0.45)		
	PP	0 (0 – 0.68)		
Treatment (%)				
None	7 (25.9)		3 (15)	0.48
Prednisolone > 10 mg	3 (11.1)		0 (0)	0.25
MTX	0 (0)		7 (35)	**<0.01**
HCQ	14 (51.9)		12 (60)	0.77
SSZ	13 (48.2)		5 (25)	0.14
Anti-TNF	7 (25.9)		3 (15)	0.48
Anti-IL-6	1 (3.7)		1 (5)	>0.999
Anti-CD20 (< 6/12)	1 (3.7)		1 (5)	>0.999
CTLA-4 fusion protein	1 (3.7)		0 (0)	>0.999

Table 2. Demographic and clinical characteristics of study subjects

RF, rheumatoid factor; ACPA, anti-citrullinated protein antibody; TJC, tender joint count; SJC, swollen joint count; CRP, C-reactive protein; PD, power doppler; MTX, methotrexate; HCQ, hydroxychloroquine; SSZ, sulfasalazine; TNF, tumour necrosis factor; IL-6, interleukin-6. Statistics with unpaired t, Mann-Whitney or Fisher's exact test. Comparison of disease activity individual and composite scores performed between third trimester of pregnant RA and non-pregnant RA.

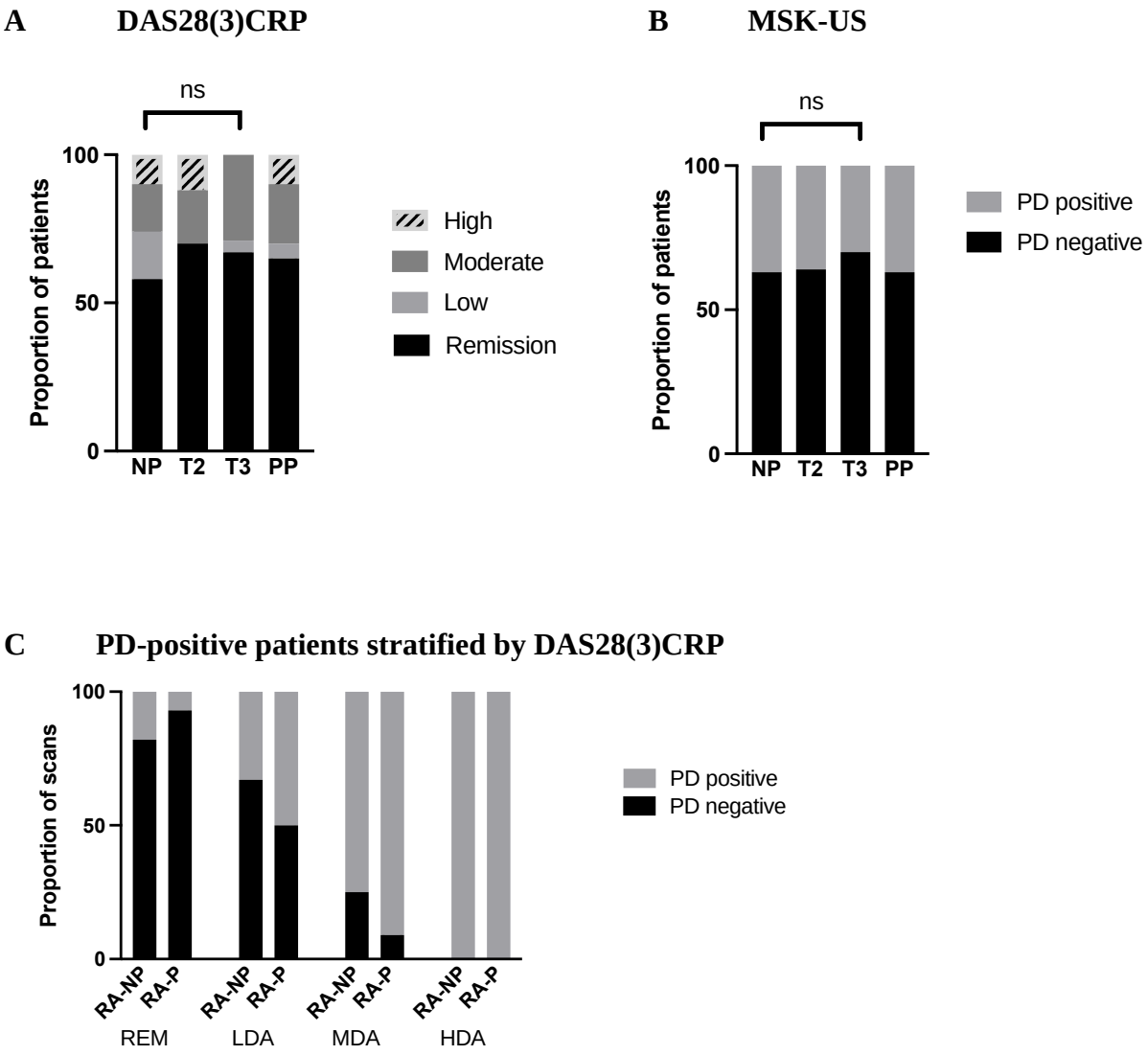

Figure 1. Disease activity of RA in pregnancy measured by DAS28(3)CRP and MSK-US (**A**) Proportion of RA patients in DAS28(3)CRP remission; low disease activity; moderate disease activity; and high disease activity in non-pregnancy and second trimester to postpartum. (**B**) Proportion of RA patients with MSK-US examinations positive for PD signal in non-pregnancy and second trimester to postpartum. (**C**) Proportions of MSK-US examinations of non-pregnant and pregnant RA patients with positive PD signal in each DAS28(3)CRP category. RA-P, pregnant women with RA; RA-NP, non-pregnant women with RA; T2, second trimester; T3, third trimester; PP, postpartum; PD, Power Doppler; MSK-US, musculoskeletal ultrasound; REM, remission; LDA, low disease activity; MDA, moderate disease activity; HDA, high disease activity

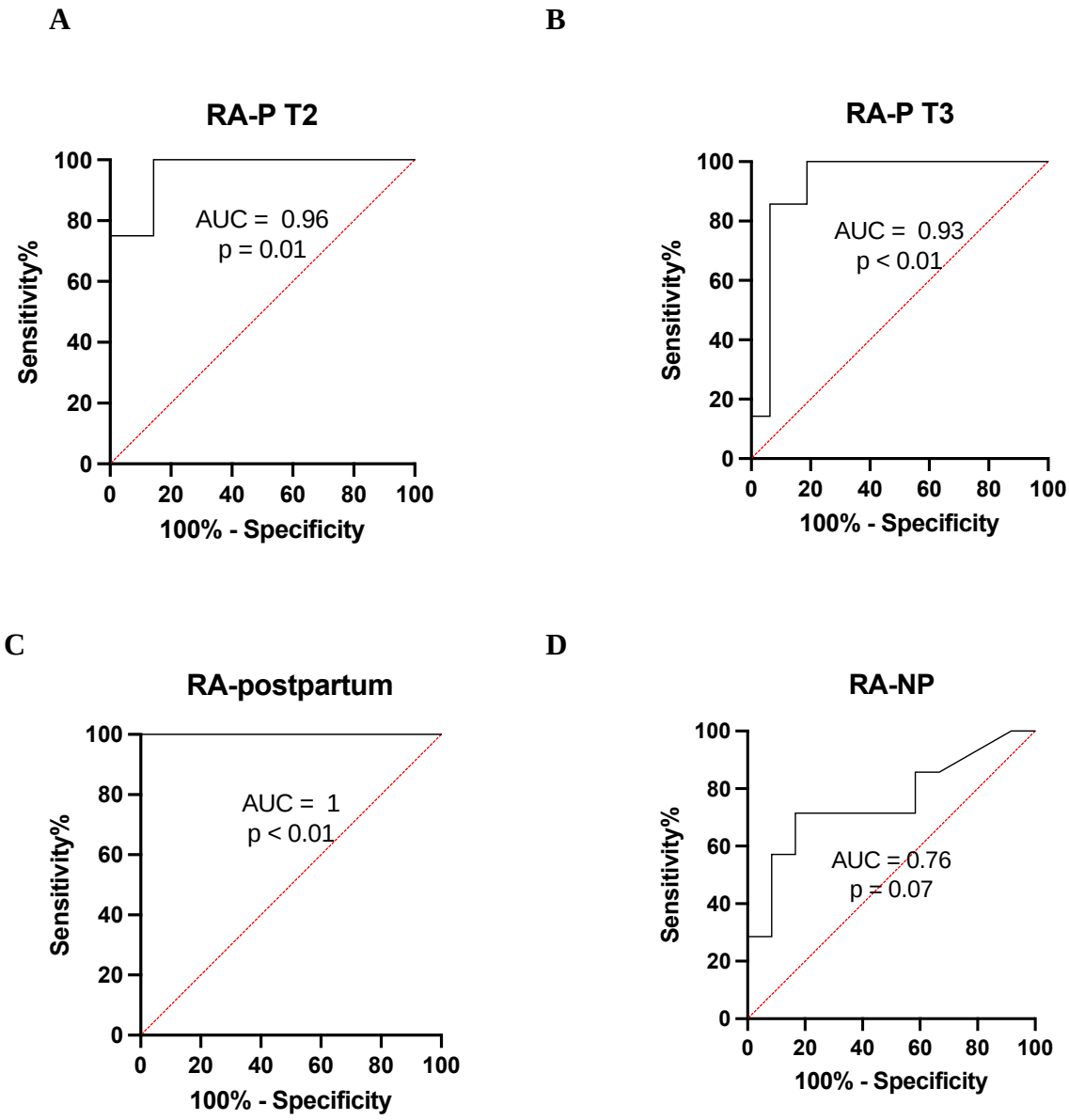

Figure 2. ROC curve analysis of the ability of DAS28(3)CRP score to detect Power Doppler signal in pregnant, postpartum and non-pregnant women with RA
(A) RA-P T2; **(B)** RA-P T3; **(C)** RA-postpartum; **(D)** RA-NP. Area under the curve (AUC) displayed. ROC, receiver operating characteristic; RA-P, pregnant women with RA; T2, second trimester; T3, third trimester; RA-NP, non-pregnant women with RA.

A

RA-P T2	SJC	CRP	DAS28(3)CRP	PD score
TJC	.689**	.395	.875**	.858**
SJC	1	.329	.612**	.921**
CRP		1	.671**	.507
DAS28(3)CRP			1	**.820****

B

RA-P T3	SJC	CRP	DAS28(3)CRP	PD score
TJC	.607**	.450*	.850**	.767**
SJC	1	.360	.683**	.744**
CRP		1	.773**	.295
DAS28(3)CRP			1	**.684****

C

RA-postpartum	SJC	CRP	DAS28(3)CRP	PD score
TJC	.823**	.388	.875**	.904**
SJC	1	.343	.846*	.914**
CRP		1	.579**	.540*
DAS28(3)CRP			1	**.835****

D

RA-NP	SJC	CRP	DAS28(3)CRP	PD score
TJC	.632**	.024	.927**	.465*
SJC	1	.267	.715**	.870**
CRP		1	.235	.161
DAS28(3)CRP			1	**.510***

Table 3. Correlation matrices of DAS28(3)CRP components versus PD score.

Components of the DAS28(3)CRP were correlated in RA-P patients in (**A**) T2; (**B**) T3; (**C**) postpartum and (**D**) in RA-NP. *$p < 0.05$ **$p < 0.01$; Spearman's rank coefficient. RA-P, pregnant women with RA; RA-NP, non-pregnant women with RA; T2, second trimester; T3, third trimester; TJC, tender joint count; SJC, swollen joint count; CRP, C-reactive protein; PD, Power Doppler.