Does the multi-biomarker disease activity score have diagnostic value in early rheumatoid arthritis and unclassified arthritis?

The 2010 American College of Rheumatology (ACR) / European League Against Rheumatism (EULAR) updated classification criteria for rheumatoid arthritis (RA) focus on identifying patients at early disease stage.[1] They facilitate early implementation of RA disease-modifying therapy, which has been associated with improved clinical and structural outcomes.[2] [3] Some patients with inflammatory oligoarthritis or polyarthritis initially not meeting RA classification criteria and classified with undifferentiated arthritis (UA) based on clinical and laboratory assessments, might later fulfil those criteria.[4] Diagnosing these patients earlier would enable better therapeutic intervention and suppression of RA disease activity.[5–7]

The multi-biomarker disease activity (MBDA) score, calculated from the concentrations of 12 serum biomarkers, is an objective validated disease activity measure for patients with RA. It has been shown to track disease activity in patients with early and established RA, treatment-naïve or not, and to associate with risk of radiographic progression.[8] Here we investigated whether the MBDA score might inform RA diagnosis in patients with UA.

We evaluated 126 patients from the prospective Synoviomics cohort[9]; 81 fulfilled ACR/EULAR 2010 criteria for RA and 45 for UA.[1] [4] At study entry, all patients had ≥1 swollen joint, <1 year of clinical symptoms, and were naïve to disease-modifying antirheumatic drugs and corticosteroids. Following baseline clinical assessment and serum collection, patients were treated according to EULAR guidelines. Patients were grouped as UA-UA (n=29), UA-RA (n=16) or RA-RA (n=81) based on their fulfilment of ACR/EULAR 2010 classification criteria for RA at baseline and after 2 years.

Baseline MBDA score, DAS28, joint counts, acute phase protein concentrations and autoantibody status differed significantly between patient with UA and RA (p<0.005) (table 1). Significant correlations (p<0.001) were observed between baseline MBDA score and DAS28 (r=0.62), erythrocyte sedimentation rate (ESR) (r=0.67), and C reactive protein (CRP) (r=0.84) in the overall population and separately in the RA (r=0.57; 0.59; 0.83) and UA (r=0.63; 0.70; 0.82) groups.

To test whether baseline MBDA score or other disease activity measures were associated with fulfilment of RA classification criteria after 2 years, trends across the three groups (RA-RA, UA-RA and UA-UA) were evaluated using Jonckheere-Terpstra test. Statistically significant (p<0.05) decreasing trends were observed for all measurements tested (figure 1). Pairwise comparisons by Wilcoxon's rank-sum test showed that baseline disease activity score based on 28 joints, ESR, CRP, swollen joint count based on 66 joints, tender joint count based on 68 joints (TJC68) and MBDA score were significantly greater in patients with RA-RA versus UA-RA (p<0.01). MBDA score was not significantly different between UA-RA versus UA-UA (p=0.132). Only baseline TJC68 was significantly greater in UA-RA versus UA-UA (median (IQR): 5 (1–7.25) versus 1 (1–3), p=0.010); this difference remained statistically significant after adjustment for multiple testing (p=0.019).[10] Female gender was also associated with UA-RA (14/16) versus UA-UA (13/29) (p=0.005).

In summary, baseline MBDA score did not inform fulfilment of RA classification criteria in patients with UA. However, consistent with MBDA score measuring active disease in patients with RA, baseline MBDA scores were higher in patients with an initial RA diagnosis compared with UA. Limitations to be considered include the relatively small number of patients with UA-RA and possible treatment effect on disease course in patients with UA.

Table 1 Baseline demographic and clinical characteristics by diagnosis group*

Variables	Overall (N=126)	RA (N=81)	UA (N=45)	p Value
Female, n (%)	88 (70%)	61 (75%)	27 (60%)	0.07
Age (years), median (IQR)	51 (40–58)	51 (39–57)	51 (43–59)	0.457
Disease duration (months), median (IQR)†	4 (2–7.5)	4 (2–8)	3 (2–6)	0.28
IgM-RF positive, n (%)	56 (44%)	49 (60%)	7 (16%)	<0.001
Anti-CCP positive, n (%)	51 (40%)	49 (60%)	2 (4%)	<0.001
IgM-RF and anti-CCP positive, n (%)	43 (34%)	41 (51%)	2 (4%)	<0.001
IgM-RF and anti-CCP negative, n (%)	62 (49%)	24 (30%)	38 (84%)	<0.001
ESR (mm/h), median (IQR)†	20 (9–35)	25 (11–37)	12 (5–25)	0.003
CRP (mg/L), median (IQR)‡	6.2 (3–22.7)	8 (3.7–28.3)	3 (1.9–12.5)	0.003
TJC68, median (IQR)	7.5 (2–17)	14 (5–23)	2 (1–4)	<0.001
SJC66, median (IQR)	5 (1–9)	7 (4–12)	2 (1–3)	<0.001
DAS28, median (IQR)§	4.5 (3.1–5.7)	5.1 (4.3–6.1)	3.3 (2.7–3.9)	<0.001
MBDA score, median (IQR)	42 (32–59)	46 (34–61)	35 (18–44)	0.001
HAQ score, median (IQR)¶	1.1 (0.5–1.6)	1.3 (0.8–1.8)	0.6 (0.3–1.3)	0.001

*Parameters were summarised as number (n (%)) or median (IQR) as appropriate. p Values were calculated using the χ^2 test for categorical variables and Wilcoxon's rank-sum test for continuous variables.
†Values missing for 1 patient with RA and 1 patient with UA.
‡Values missing for 1 patient with RA.
§Values missing for 2 patients with RA and 1 patient with UA.
¶Values missing for 4 patients with RA.
Anti-CCP, anticyclic citrullinated peptide; CRP, C reactive protein; DAS28, disease activity score based on 28 joints (based on ESR); ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; IgM-RF, immunoglobulin M rheumatoid factor; MBDA, multi-biomarker disease activity; RA, rheumatoid arthritis; SJC66, swollen joint count based on 66 joints; TJC68, tender joint count based on 68 joints; UA, unclassified arthritis.

Figure 1 Comparison of baseline disease activity measures across the diagnosis groups. Disease activity measures are shown for patients grouped according to their diagnosis at baseline and at 2 years. Thick horizontal line: median; box: IQR; whiskers: most extreme points within 1.5× IQR. p Values were derived by Wilcoxon's test. p values in the upper left corners represent the significance of the trends across the three groups by Jonckheere-Terpstra test. CRP, C reactive protein; DAS28, disease activity score based on 28 joints (based on ESR); ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; MBDA, multi-biomarker disease activity; RA, rheumatoid arthritis; SJC66, 66 swollen joint count; TJC68, 68 tender joint count; UA, unclassified arthritis.
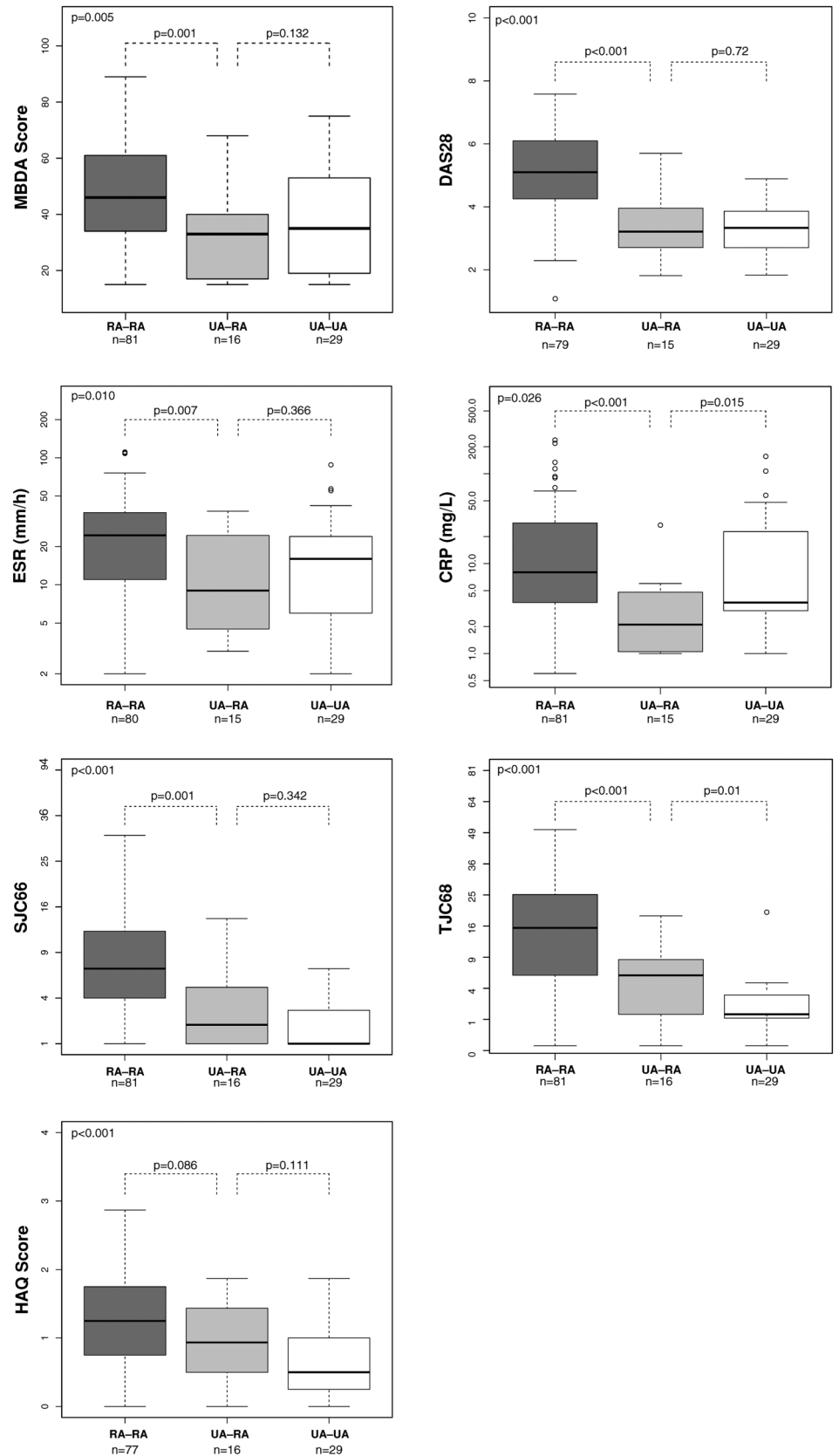
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