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CHAPTER 4.

A multi-biomarker based disease activity (MBDA) score system compared to a conventional disease activity score (DAS) system in the BeSt rheumatoid arthritis (RA) study

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ABSTRACT

Objective: To evaluate a multi-biomarker disease activity (MBDA) score, a novel index based on 12 serum proteins, as a tool to guide management of rheumatoid arthritis (RA) patients.

Methods: A total of 125 RA patients from the BeSt study were studied. Clinical data and serum samples were available from 179 visits, 91 at baseline (BL) and 88 at year 1. In each serum sample, 12 biomarkers were measured by quantitative multiplex immunoassays, and the concentrations were used as input to a pre-specified algorithm to calculate MBDA scores. MBDA scores were compared to clinical disease measures including DAS28, CDAI, SDAI and HAQ.

Results: MBDA scores had a significant correlation with DAS28 (Spearman's $\rho = 0.66$, $p < 0.0001$). Changes in MBDA between BL and year 1 were also correlated to changes in DAS28 ($\rho = 0.55$, $p < 0.0001$). Groups stratified by EULAR disease activity (DAS28 ≤ 3.2, 3.2 to 5.1, and > 5.1) had significantly different MBDA scores ($p < 0.0001$) and the MBDA score could discriminate ACR/EULAR Boolean remission with area under ROC curve of 0.83 ($p < 0.0001$). MBDA scores had a significant correlation with HAQ-DI ($\rho = 0.50$, $p < 0.0001$). Changes in MBDA between BL and year 1 were also correlated to changes in HAQ-DI ($\rho = 0.45$, $p = 0.0006$).

Conclusions: The MBDA score reflects current clinical disease activity and can track changes in disease activity over time. In addition, the MBDA score is associated with HAQ in early RA patients.

INTRODUCTION

The management of patients with rheumatoid arthritis (RA) has been improved considerably in recent decades (1). This is partly due to intensive therapeutic strategies such as the combination of methotrexate (MTX) and anti-TNF biologic agents (2) and partly due to the introduction of therapeutic strategies in which composite measures are used to assess patients' disease activity and guide treatment decisions. In recent guidelines for management of RA, it was recommended to evaluate disease activity by composite measures at regular intervals and adapt treatment decisions based on the results (3).

In particular, the disease activity score (DAS) has been widely accepted as one of the standard methods to evaluate disease activity in RA patients and, along with variants such as the DAS28 and DAS-CRP, has been extensively explored as a guide for treatment decisions in clinical practice. For example, the TICORA study revealed that DAS-guided intensive maintenance could bring a better outcome than a non-DAS based strategy (4); Tanaka E. et al. reported that DAS-guided efficient management could reduce long-term functional disability (5); Goekoop-Ruiterman et al. showed that DAS-driven therapy resulted in reduced radiographic progression (6); and Hallert et al. reported that DAS28 levels were predictive of future healthcare utilization costs (7). Other composite disease activity measures have also been found valuable in management of RA(8-11).

Optimal management of RA requires the care of a specialist rheumatologist. However, it is difficult for some RA patients to have frequent assessments by rheumatologists because of the insufficient number of rheumatologists, long journeys to access a rheumatology clinic or lack of time due to working or parental care. Thus, alternative procedures for regular assessment of RA disease activity could aid in optimal management.

Biomarkers are promising for assessing disease status of patients with various chronic conditions. To date, several biomarkers have been proposed to reflect the activity of RA (12), but no one biomarker has been able to adequately assess RA disease activity. Therefore, a combination of multiple biomarkers may provide richer information, and be more robust than any single marker, yielding a composite index similar to the DAS.

The Vectra™ Disease Activity (Vectra™ DA) test is a novel blood test using measurements of 12 serum proteins to calculate a multi-biomarker disease activity (MBDA) score (13). The algorithm of the test was developed using DAS28-CRP as a reference standard, and is designed to produce a score ranging from 1 to 100. The algorithm was derived from statistical analysis of clinical data from three cohorts, the OKC (Oklahoma City Community) cohort,

BRASS (Brigham & Women's RA Sequential Study), and InFoRM (Index For Rheumatoid Arthritis Measurement) (14). Briefly, 396 candidate biomarkers were considered upon the basis of literature review, screening experiments and bioinformatics databases. A series of studies was used to evaluate 130 of these as biomarkers of disease activity and to select the subset with greatest utility. The final algorithm training process selected the combination of 12 biomarkers that gives the best assessment of current disease activity.

Using independent samples to confirm the relationship between MBDA scores and conventional DAS28 is an important step to validate the MBDA algorithm. In this study, we examined the validity of the MBDA score system as a novel index for evaluating disease activity and physical ability in the RA patients who participated in the Behandel Strategieën (BeSt) study (2).

PATIENTS AND METHODS

Patients and sample collection

A total of 125 patients with arthritis symptoms < 2 years who fulfilled the 1987 ACR revised criteria for RA (15) and participated in the BeSt study (2) were analyzed. Patients provided informed consent before peripheral blood was collected and the serum was separated with centrifugation, dispensed, and stored at -70 ºC. Clinical data (including DAS28 and HAQ-DI) and serum samples were available at 179 visits (91 at baseline (BL), 88 at year 1). Clinical data and samples at both baseline (BL) and year 1 were available in 54 patients (108 visits). The characteristics of the 125 patients at the enrollment of the BeSt study are summarized in Table 1.

Conventional disease activity and physical disability assessment

In the single blind BeSt study, specially trained nurses evaluated the tender joint count (TJC) and the swollen joint count (SJC) of participants at regular intervals including the baseline visit and after one year of follow up. The participant registered general health assessment (GH) on a visual analogue scale (VAS). Erythrocyte sedimentation rate (ESR) was also measured. Based on the TJC, SJC, GH, and ESR, the DAS28 was calculated. Further, physical disability was measured with the Health Assessment Questionnaire – Disability Index (HAQ-DI).

Multiple biomarker-based disease activity assessment

The biomarker platform, assays and algorithm were the same as those used in the Vectra™ DA test (Crescendo Bioscience, CA, USA). The concentrations of 12 serum proteins, SAA1, IL6, TNFRSF1A, VEGFA, MMP1, YKL40 (cartilage glycoprotein 39), MMP3, EGF, VCAM1, leptin, resistin, and CRP, were measured by customized immunoassays and quantified on a Sector Imager 6000 (Meso Scale Discovery, Gaithersburg, Maryland, USA). The MBDA algorithm uses different subsets of biomarkers to estimate TJC, SJC and GH, and then combines the estimates of these components into an overall score as follows:

$$\text{PTJC} = \text{Prediction of Tender Joint Count} = -26.72 + 3.243 * [\text{YKL-40}]^{1/10} - 11.97 * [\text{EGF}]^{1/10} + 15.72 * [\text{IL-6}]^{1/10} + 0.4594 * [\text{Leptin}]^{1/10} + 3.881 * [\text{SAA}]^{1/10} + 0.7388 * [\text{TNF-RI}]^{1/10} - 0.2557 * [\text{VCAM-1}]^{1/10} + 0.7003 * [\text{VEGF-A}]^{1/10}$$

$$\text{PSJC} = \text{Prediction of Swollen Joint Count} = -26.63 + 3.232 * [\text{YKL-40}]^{1/10} - 11.93 * [\text{EGF}]^{1/10} + 15.67 * [\text{IL-6}]^{1/10} + 0.4578 * [\text{Leptin}]^{1/10} + 3.868 * [\text{SAA}]^{1/10} + 0.7363 * [\text{TNF-RI}]^{1/10} - 0.2548 * [\text{VCAM-1}]^{1/10} + 0.6979 * [\text{VEGF-A}]^{1/10}$$

$$\text{PGH} = \text{Prediction of Patient Global Health} = -13.489 + 5.474 * [\text{IL6}]^{1/10} + 0.486 * [\text{SAA1}]^{1/10} + 2.246 * [\text{MMP1}]^{1/10} + 1.684 * [\text{leptin}]^{1/10} + 4.14 * [\text{TNFRSF1A}]^{1/10} + 2.292 * [\text{VEGFA}]^{1/10} - 1.898 * [\text{EGF}]^{1/10} + 0.028 * [\text{MMP3}]^{1/10} - 2.892 * [\text{VCAM1}]^{1/10} - .506 * [\text{resistin}]^{1/10}$$

$$\text{MBDA Score} = \text{round}(\max(\min((0.56 * \sqrt{\text{PTJC}} + 0.28 * \sqrt{\text{PSJC}} + 0.14 * \text{PGH} + 0.36 * \log(\text{CRP}/10^6 + 1)) * 10.53 + 1, 100), 1))$$

To calculate the final MBDA score, the predicted TJC, SJC and GH are combined with CRP in a formula analogous to that of the DAS28-CRP. The results are scaled and rounded to be integers on a scale of 1-100 such that a MBDA score of 1 would be equivalent to a DAS28-CRP value of 0, and a MBDA score of 100 would be equivalent to a DAS28-CRP value of 9.4. This mathematical relationship between MBDA and DAS28-CRP defines MBDA score thresholds to distinguish patients with remission, low, moderate and high disease activity.

According to the DAS28-CRP thresholds of Inoue et al. (16), MBDA scores ≤ 25 would indicate remission, scores 26-29 would indicate low disease activity, scores 30-44 would indicate moderate disease activity and scores > 44 would indicate high disease activity. These thresholds were established in the development of the MBDA algorithm.

Statistics

Spearman's rank correlation coefficients (Spearman's ρ) were calculated to evaluate the association between MBDA and DAS28, between ΔMBDA score and ΔDAS28, between MBDA and HAQ-DI, and between ΔMBDA and ΔHAQ-DI. The values of MBDA stratified by EULAR disease activity (Low, Moderate, or High Disease Activity) were compared by one-way analysis of variance (ANOVA) with Tukey's multiple comparison procedure. Statistical analyses were performed using JMP software version 9.0.2 (SAS Institute, Cary, North Carolina, US). All reported p-values are two sided and p-values < 0.05 were considered significant.

RESULTS

Baseline clinical characteristics

Representative clinical baseline characteristics of the 125 patients are summarized in Table 1. Since the BeSt study included patients with early active rheumatoid arthritis, median symptom duration of the disease was less than six months at baseline, disease activity was high (median DAS 4.19, interquartile range (IQR) 3.67 – 4.91), median HAQ was 1.38 (IQR 1.0 – 1.88) and there was little joint destruction evident on radiographs (median total Sharp-van der Heijde Score (SHS) 3, IQR 1 – 7).

The MBDA score reflects clinical disease activity

The relationship between MBDA score and DAS28 is shown in Figure 1. The MBDA score was significantly correlated to DAS28, with a Spearman's rank correlation coefficient (ρ) of 0.66 (p < 0.0001, Figure1A). Similar results were obtained for correlation between MBDA score and SDAI (ρ = 0.67, p < 0.0001) and between MBDA score and CDAI (ρ = 0.56, p < 0.0001).

A key requirement for a disease activity index is the ability to evaluate patients' changes in disease activity over time. The correlation between the change in DAS28 (ΔDAS28) and the change in MBDA (ΔMBDA) between BL and year 1 was assessed in 54 patients (108 visits). As shown in Figure 1B, ΔDAS28 and ΔMBDA had a strongly significant correlation ($\rho = 0.55$, $p < 0.0001$), which indicates that MBDA can track changes in disease activity over time. Next, we stratified the disease activity score into three groups according to EULAR disease activity criteria, low disease activity (DAS28 $\leq$ 3.2), moderate disease activity (3.2 to 5.1) and high disease activity (DAS28 > 5.1). Cumulative probability curves are shown in figure 2. The groups defined by DAS28 had different MBDA scores ($p < 0.0001$), with the highest MBDA scores in the high DAS28 group and lowest MBDA scores in the low DAS28 group. When patients were assigned into low, moderate or high disease activity categories based on the MBDA score, 58% were placed in the same category by the MBDA score as by the DAS28 (Table 2). 9% of patients were placed in high disease activity by one measure and low disease activity by the other.

We also tested whether the MBDA score would distinguish patients in remission based on the ACR/EULAR criteria (17). Low MBDA scores were associated with ACR/EULAR Boolean remission (TJC28 $\leq$ 1, SJC28 $\leq$ 1, VAS-GH $\leq$ 1, CRP $\leq$ 1mg/dL), with area under the ROC curve of 0.83 ($p < 0.0001$).

The MBDA score reflects HAQ-DI in early RA

In addition to being correlated to a clinical composite index of disease activity such as the DAS28, a valid biomarker-based disease activity score should also reflect patient-reported disease measures such as the HAQ-DI. The relationship between MBDA score and HAQ-DI is shown in figure 3. There was a strongly significant correlation between MBDA and HAQ-DI (Figure 3A) with a Spearman's ρ of 0.50 ($p < 0.0001$).

In rheumatology, it is important to evaluate patients' changes in physical ability over time. The correlation between the change in HAQ-DI (ΔHAQ-DI) and the change in MBDA (ΔMBDA) between BL and year 1 was assessed in 54 patients (108 visits). As shown in figure 3B, ΔHAQ-DI and ΔMBDA had a significant correlation (ρ 0.45, $p = 0.0006$), reinforcing the relationship between underlying biomarker levels and changes in physical ability over time.

DISCUSSION

The outcome of RA patients is best when care is guided by regular measurements of a disease activity score. Several clinical disease activity indices are appropriate for this purpose, and the most widely used in clinical studies is the DAS. However, in some circumstances measurement of composite indices is not carried out, due to limited resources or lack of access to a rheumatologist or limited resources. A biomarker-based disease activity score could complement clinical assessment and provide information to guide patient care when a composite clinical disease activity score is unavailable. A care system in which an objective, precise measurement could provide information about disease activity would help rheumatologists and would be easier for the patient.

We found that the MBDA score is strongly associated with the conventional clinical disease activity indices and can track changes in disease activity over time. The value of MBDA, designed to have a range of 1 to 100, corresponded approximately to ten times the value of DAS28, which has a range of 0 to about nine. Our results demonstrate that the MBDA score reflects RA disease activity, and in the majority of patients it gives a similar result to the DAS28. However, there are some cases in which the DAS28 is high and the MBDA score is low, or vice versa. There are several potential explanations for these cases of discordance. For example, the MBDA biomarkers could be affected by conditions such as vaccination or acute infection. Further studies are needed to investigate this possibility. On the other hand, since the DAS28 includes two subjective components, tender joint count (TJC) and patients' general health (GH), it can overestimate disease activity especially in patients with severely deformed joints, with extreme sensitivity to pain, or with pain of other causes (e.g. fibromyalgia) (18, 19). In cases where the MBDA score and clinical assessment are discordant, it is unclear which is the more correct reflection of true RA disease activity. Independent outcomes such as imaging of synovitis or progressive joint damage may be used to evaluate which disease activity measures provide the best information to support clinical decision-making. Ultimately, since biomarkers and clinical examination are indicative of different aspects of disease activity, they may complement one another and provide the best information when used together.

In this study, we focused on distinguishing patients across the range of disease activity. Identifying patients in remission is another challenge of great clinical importance. Patients with quiescent biomarkers may represent a state of "molecular remission", in which the inflammatory pathways involved in RA have been rendered inactive by effective therapy or

the natural waning of disease. Such "molecular remission" might have different characteristics from the state of clinical remission, for example if one state precedes the other in the course of a patient's disease. Additional studies with large numbers of patients in remission will determine whether and how biomarkers can help identify and characterize the remission state.

Since we analyzed only patients who participated in the BeSt study, with a relatively short duration of RA, further investigation is necessary to elucidate how helpful MBDA is for RA patients with long-term disease duration. This is particularly relevant for analysis of the HAQ-DI, which can be considered to reflect both current disease activity (ACT-HAQ) and accumulated damage (DAM-HAQ (20)). Since the majority of the BeSt study population had short disease duration and low Sharp-van der Heijde scores (2), the component of DAM-HAQ might be minimal, which means that the majority of the HAQ in this study population would be explained by the ACT-HAQ, which is thought to be closely related to disease activity (20). This is consistent with the strong association observed between HAQ-DI and the MBDA score in this study. Since the MBDA score is not intended to reflect accumulated damage, it might be less associated with the HAQ-DI in patients with longer disease duration, in whom damage makes a larger contribution to the overall HAQ-DI.

Of course any biomarker assay is an aid, which can never substitute careful clinical judgment. However, our current analysis suggests that a biomarker-based disease activity test could provide complementary information. For example, the TICORA study (4) and the CAMERA study (21) showed that monthly assessment of disease activity and subsequent adaptation of therapy yielded improved outcomes. The MBDA test could be used to enable monthly monitoring of disease activity while allowing clinical assessment to take place less frequently, for example every 3 months. This would provide additional information about patient status and might allow more efficient use of precious health care resources.

CONCLUSION

The 12-biomarker based MBDA score is a novel blood-based index for disease activity in early RA.

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Table 1. Characteristics of the 125 patients with rheumatoid arthritis.

Variables	Mean ± SD	Min., Max.	Median [IQR]
Age, years	52.9 ± 13.6	21, 82	54 [45 – 63]
Symptom duration, weeks	43.8 ± 61.7	3, 584	24.5 [13 – 57]
DAS	4.29 ± 0.87	1.90, 7.10	4.19 [3.67 – 4.91]
HAQ-DI	1.42 ± 0.71	0, 3	1.38 [1.0 – 1.88]
TJC28	11.1 ± 6.4	0, 28	10 [6 – 15]
SJC28	5.44 ± 8.16	0, 24	9 [7 – 13]
DAS28	5.80 ± 1.04	1.43, 8.57	5.85 [5.20 – 6.45]
CRP, mg/L	55.7 ± 63.8	0.3, 240.5	23.9 [9.4 – 83.9]
ESR, mm/hr	39.4 ± 25.3	4, 126	37 [19– 51]
DAS28-CRP	5.45 ± 0.94	2.35, 8.31	5.49 [4.90 – 6.02]
Patient Global (VAS) mm	53.3 ± 22.0	0, 100	53 [37 – 71]
SHS	5.5 ± 8.2	0, 49	3 [1 – 7]

| Categorical Variables	Percentage
Treatment Arms *	
Sequential monotherapy	17.6
Step-up combination	24.0
Initial combination with prednisone	30.4
Initial combination with infliximab	28.0
Gender (female)	74.4
Presence of erosion at Baseline	67.2
ACPA positivity	56.5
RF positivity	62.4

Min: minimum, Max: maximum, IQR: interquartile range, DAS: Disease Activity Score. HAQ-DI: Health Assessment Questionnaire-Disability Index. TJC: tender joint count, SJC: swollen joint count, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, VAS: visual analog scale, SHS: Sharp - van der Heijde Score. ACPA: anti-citrullinated peptide antibody. RF: rheumatoid factor. *Treatment arms in the BeSt study are described in detail in the original article (2).

Table 2. Agreement of disease activity classification between MBDA score and DAS28.

| | | DAS28 | | | |
		LDA (≤ 3.2)	MDA (3.2 - 5.1)	HDA (> 5.1)	Total
MBDA score	LDA (≤ 29)	26	8	6	40
	MDA (29 - 44)	19	15	8	42
	HDA (> 44)	11	24	62	97
	Total	56	47	76	179

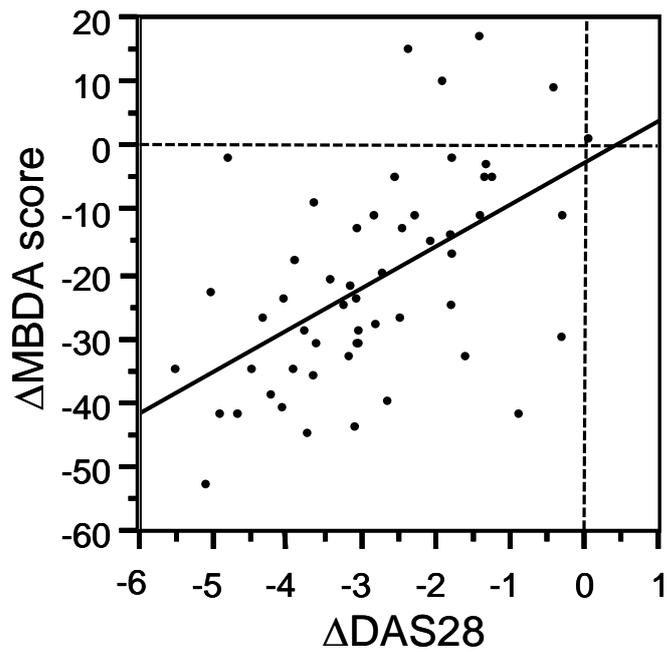MBDA: Multi-biomarker disease activity, LDA: low disease activity, MDA: moderate disease activity, HDA: high disease activity.

A.
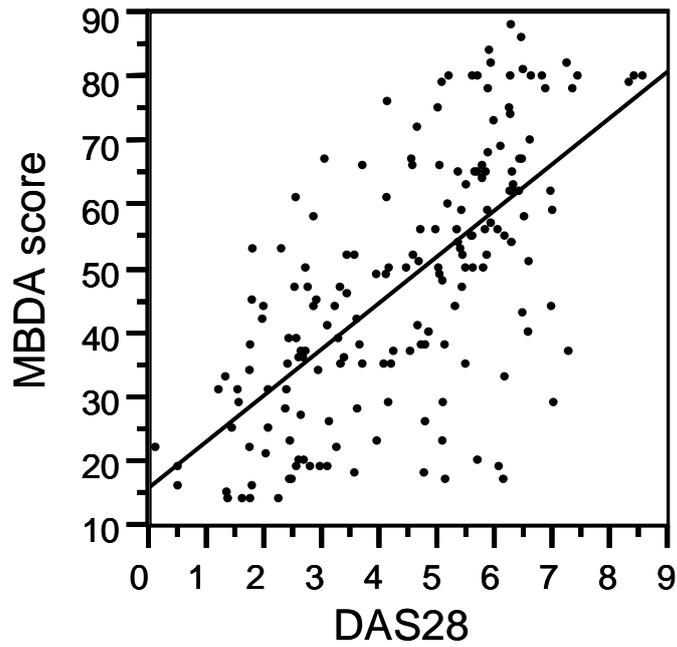
B.

Figure 1. (A) Correlation and linear regression of MBDA score with DAS28. Spearman's rank correlation coefficient was 0.66 ($p < 0.0001$). (B) Correlation and linear regression of ΔMBDA score with ΔDAS28. Spearman's rank correlation coefficient was 0.55 ($p < 0.0001$).
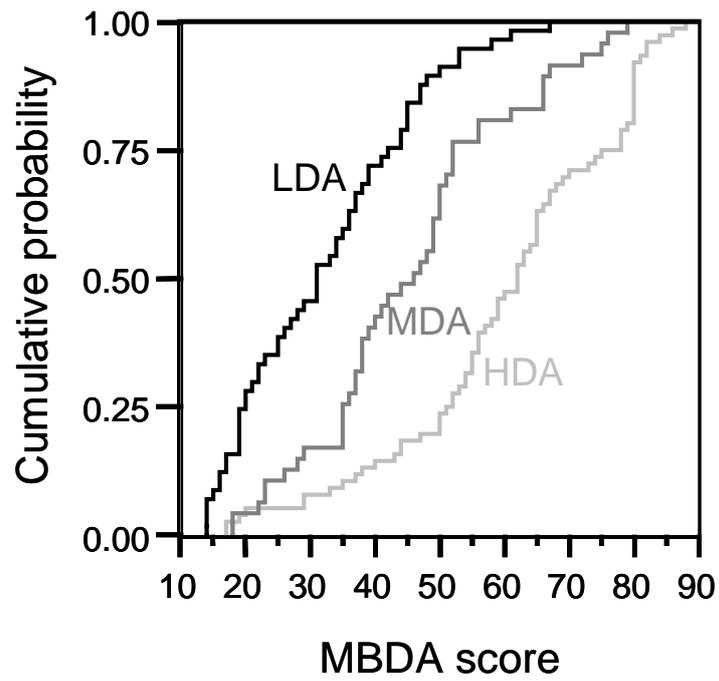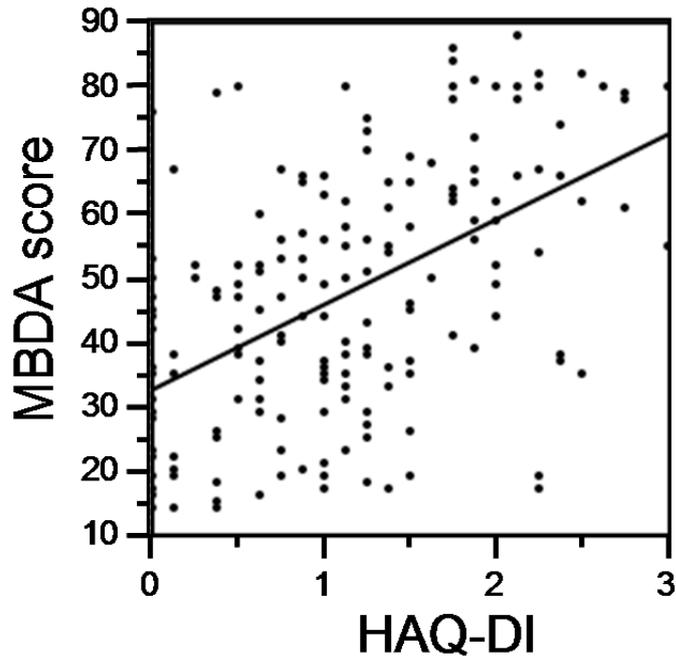
Figure 2. Cumulative probability plot of MBDA scores within DAS28 categories. High disease activity (DAS28 >5.1), Moderate disease activity (3.2 to 5.1), and Low disease activity (DAS28 ≤ 3.2).
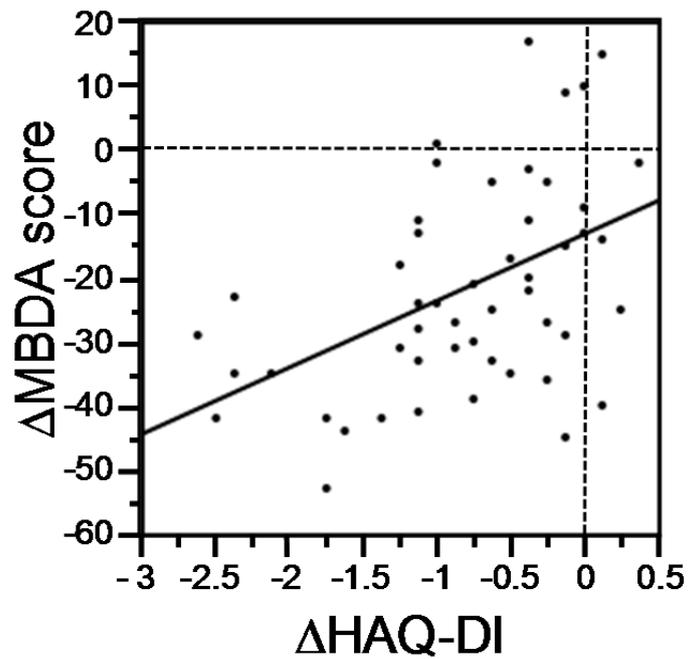
A.

B.

Figure 3. (A) Correlation and linear regression of MBDA score with HAQ-DI. Spearman's rank correlation coefficient was 0.50 ($p < 0.0001$). (B) Correlation and linear regression of ΔMBDA score with ΔHAQ-DI. Spearman's rank correlation coefficient was 0.45 ($p = 0.0006$).