# Development of an Adjusted Multi-Biomarker Disease Activity (MBDA) Score for Rheumatoid Arthritis (RA) That Accounts for Age, Sex and Adiposity, with Subsequent Evaluation of Ability to Predict Risk for Radiographic Damage

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## BACKGROUND

- The multi-biomarker disease activity (MBDA) score is validated for assessing disease activity of rheumatoid arthritis (RA).
- Age, gender, and adiposity may influence biomarkers comprising this score.
- We developed and validated an adjusted MBDA score that accounts for these confounders.

## METHODS

### MBDA SCORE

- De-identified serum specimens were tested centrally at a CLIA-certified laboratory (Crescendo Bioscience, Inc.).
- A multiplexed, sandwich immunoassay (Mesoscale Discovery) was used to measure concentrations of the 12 MBDA protein biomarkers: VCAM-1, EGF, VEGF-A, IL-6, TNFRI, MMP-1, MMP-3, YKL-40, leptin, resistin, serum amyloid A, and CRP.
- Concentration values were combined using a previously validated algorithm to generate an integer score from 1-100.[1]

### ADJUSTED MBDA SCORE

- The MBDA score was adjusted to account for age, gender, and adiposity, using serum leptin and body mass index (BMI) as proxies for adiposity.
- *Commercial cohort:* Data from RA patients undergoing MBDA testing as part of routine care (N=325,781) were used to generate the leptin-adjusted MBDA score and to estimate age and gender effects in the BMI-adjusted MBDA score.
- *Clinical study/registry cohort:* BMI data from patients in BRASS[2], CERTAIN[3], InFoRM[4], OPERA[5] and RACER[6] (n=1411) were used to generate the BMI-adjusted MBDA score.

### VALIDATION OF ADJUSTED MBDA SCORES

- Adjusted MBDA scores and other variables were evaluated for their ability to predict radiographic progression (RP) in patients with available radiographic data (OPERA[5] and BRASS[2]) using univariate and multivariate linear regression analyses.
- Rate of RP was assessed as change in modified total Sharp score (ΔmTSS) per year after MBDA testing.
- Prediction of RP was compared among original and adjusted MBDA scores and conventional measures.

## DEVELOPMENT OF ADJUSTED MBDA SCORES

- The commercial cohort and clinical study/registry cohort are described in Table 1.
- MBDA score increased with age, BMI, and leptin concentration and was greater in females than males (Figures 1 and 2).
- The relationship between MBDA score and leptin was non-linear and was best expressed exponentially; the exponent of leptin that maximized leptin's ability to predict the MBDA score was 0.58.
- The interactions between age and gender, gender and serum leptin concentration, and serum leptin concentration and age were all statistically significant predictors of MBDA score (Table 2).
- MBDA scores were adjusted for direct interactions between MBDA score, age, gender, and leptin concentration (leptin-adjusted MBDA score) or BMI (BMI-adjusted MBDA score).

***Table 1. Demographic characteristics and MBDA scores***

| Variable | Commercial Cohort | Clinical Study/ Registry Cohort |
|---|---|---|
| Total | 325,781 | 1,411 |
| Age, Mean | 57.6 years | 57.3 years |
| Female, N (%) | 256,470 (78.7%) | 1,098 (77.8%) |
| Disease Duration, Mean | N/A | 12.3 years |
| BMI, Mean (SD) | N/A | 27.6 kg/m$^2$ (6.2) |
| MBDA Score, Mean (SD) | 40.9 (15.3) | 43.8 (16.8) |

***Table 2. Magnitude and direction of variable effects on MBDA score in commercial cohort (N=325,781)***

| Variable | Coefficient (95% CI) | p-value |
|---|---|---|
| Age | 0.437 (0.429, 0.444) | — |
| Gender (female as reference) | 3.31 (2.74, 3.88) | — |
| Leptin concentration (to the 0.58th power) | 0.0502 (0.0492, 0.0513) | — |
| Age × Gender | -0.0247 (-0.0338, -0.0155) | $1.3\times10^{-7}$ |
| Gender × Leptin | 0.00254 (0.00174, 0.00334) | $4.1\times10^{-10}$ |
| Leptin × Age | -0.000483 (-0.000500, -0.000465) | $<2.2\times10^{-16}$ |

***Figure 1. Relationship between MBDA score and serum leptin levels in commercial cohort (N=325,781)***

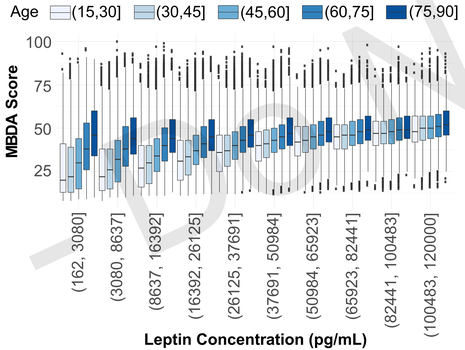
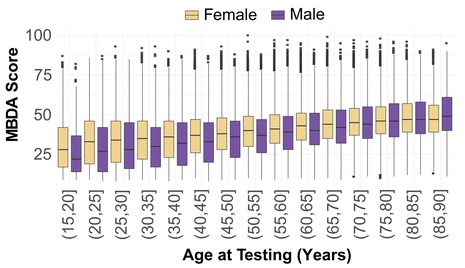


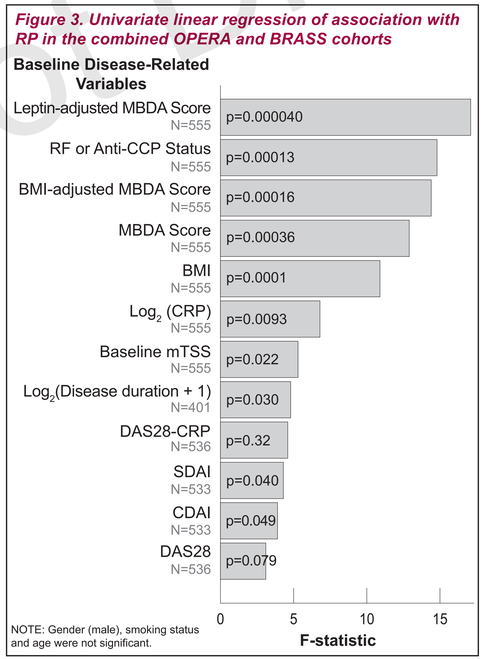

***Figure 2. Distribution of MBDA scores by age category and gender in the commercial cohort (N=325,781).***




## VALIDATION OF ADJUSTED MBDA SCORES

- In univariate analysis of 13 baseline disease-related variables, leptin-adjusted MBDA score was the most highly associated with RP (Figure 1).

***Figure 3. Univariate linear regression of association with RP in the combined OPERA and BRASS cohorts***




NOTE: Gender (male), smoking status and age were not significant.

- In bivariate analysis evaluating association with RP:
  - BMI-adjusted (p=0.0027) and leptin-adjusted (0.00063) MBDA scores were significant predictors of RP after adjusting for DAS28-CRP, but not vice versa (p=0.87 and 0.74, respectively).
  - Leptin-adjusted MBDA score was a significant predictor of RP after adjusting for the original MBDA score (p=0.024) or BMI-adjusted MBDA score (p=0.020) but not vice versa (p=0.32 and 0.094, respectively).
- In the commercial cohort, use of leptin-adjusted MBDA score resulted in the reclassification of 21.8% of patients relative to the original MBDA score results (Table 3).

***Table 3. Risk of RP in the commercial cohort (N=325,781)***

| Original MBDA Score | Leptin-Adjusted MBDA Score | | |
|---|---|---|---|
| | Low | Moderate | High |
| Low | 55,701 (76%) | 17,148 (23%) | 182 (0.2%) |
| Moderate | 11,390 (9%) | 97,461 (79%) | 14,189 (12%) |
| High | 0 (0%) | 27,915 (22%) | 101,795 (78%) |

## CONCLUSION

- Leptin-adjusted MBDA score significantly outperformed DAS28-CRP and the original MBDA score in predicting RP, suggesting that it may offer improved clinical utility for personalized management of RA.

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