Characterizing MSDA Score and MSDA Panel Biomarker Associations with Disease Activity and Progression Measures in the Graz MS Study

Gargi Datta[1], Maria Martinez-Serrat[2, 3], Cansu Tafrali[2, 3], Rina Demjaha[2, 3], Daniela Pinter[2, 4], Bettina Heschl[2], Anna Damulina[2, 3], Edith Hofer[5], Stefan Ropele[2], Christian Enzinger[2], Shannon McCurdy[1], Luong Ruiz[1], Elisa Sheng[1], Alexander Hari[1], Srushti Tiwari[1], Wayne Hu[1], David Brazel[1], Ferhan Qureshi*[1], Michael Khalil[2, 3]
[1]Octave Bioscience, Menlo Park, United States, [2]Department of Neurology, Medical University of Graz, Graz, Austria, [3]Neurology Biomarker Research Unit, Medical University of Graz, Graz, Austria, [4]Research Unit for Neuronal Plasticity and Repair, Medical University of Graz, Graz, Austria, [5]Institute for Medical Informatics, Statistics and Documentation, Medical University of Graz, Graz, Austria

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Introduction

The Graz MS study investigated clinical, morphological, and biochemical dimensions of multiple sclerosis (MS), with the goal of uncovering mechanisms driving disease activity and progression. The Multiple Sclerosis Disease Activity (MSDA) test is a validated multi-protein assay that quantifies the concentration of 18 protein biomarkers, corrects for age and sex, and generates a Disease Activity (DA) score (1 to 10 in 0.5 increments). The MSDA test has been validated against MRI and clinical assessments of disease activity.[1]

Objectives

Determine the association of the DA score and the 18 protein biomarkers with MS disease activity and progression measures in the Graz MS study.

Methods

Retrospective longitudinal analytical and clinical data from 102 participants (up to 15 timepoints over 16.4 years; 785 serum samples) were used to calculate a DA score for each sample.

The following analyses were performed to evaluate the relationship between the DA score and individual biomarkers in the MSDA panel, and clinical endpoints for disease activity and progression:

- *Area Under the Curve (AUC)* of DA score probabilities assessed classification accuracy for each sample for
  - **Gadolinium-enhancing (Gd+) lesions**
  - **No Evidence for Disease Activity-3 (NEDA-3) status**
  - **Expanded Disability Status Scale (EDSS) worsening**
- *Linear mixed-effects models* (adjusted for age and sex, with participant-level variability) evaluated associations between DA score (or log-transformed biomarker concentrations) and either
  - **Relapse proximity** (within ±30 days vs. >±30 days of relapse). Relapse analyses included participants with at least one sample within ±30 days of relapse (N=31; 252 samples).
  - **EDSS** at each timepoint
  - **Change in EDSS** across consecutive timepoints and biomarkers at the earlier timepoint

Total samples	785
Total patients	102
Sex	
Female	61.8%
Male	38.2%
Age at baseline, mean±SD (range)	31.7±7.7 years (18.8-50.1)
Total follow-up time, mean±SD (range)	10.4±3.4 years (3.8-16.4)
Relapse Proxmity (31 pts, 252 samples)	
0	85.3%
1	14.7%
Gd + status	
0	79.9%
>=1	8.9%
NA	11.2%
NEDA-3 status per patient	
NEDA	80.4%
EDA	19.6%
EDSS worsening per patient	
Worse	62.7%
Not Worse	37.3%
EDSS, mean±SD (range)	1.5±1.4 (0-7)

Table 1: Cohort description

Results

DA score and protein biomarkers were associated with clinical outcomes, relapse proximity, and EDSS. All p-values are Bonferroni-corrected.

- Classification AUCs using DA score probabilities were (Figure 3)
  - **0.79** *(95% CI [0.73, 0.84])* for **Gd+ lesions**
  - **0.77** *(95% CI [0.66, 0.86])* for **NEDA-3**
  - *0.55 (95% CI [0.43,0.66])* for **EDSS worsening**
- Relapse proximity significantly predicted **DA score**, with samples within ±30 days of relapse showing a mean score **1.43 units higher** than timepoints >±30 days, adjusted for age and sex ($p=3e^{-6}$; Figure 2).
  - **NfL** *(β=0.14, p<0.01)*, **IL-12B** *(β=-0.15,p=<0.001)*, **SERPINA9** *(β=-0.12, p=0.02)*, and **OPN** *(β=0.05, p=0.048)* were significantly different by relapse proximity category (Figure 4).
- **GFAP** was a significant predictor of EDSS score *(β=0.02, p=0.02)*.
- For change in EDSS between consecutive timepoints, **CXCL13** at the earlier timepoint was significant *(β=-0.38, p=0.01)*.

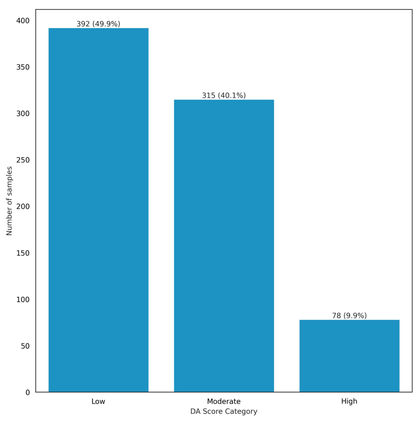

Figure 1: Number of samples by DA score category

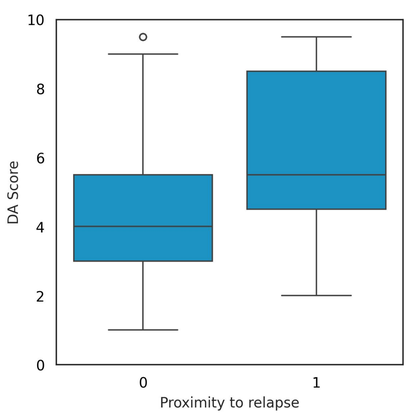

Figure 2: DA score by proximity to relapse

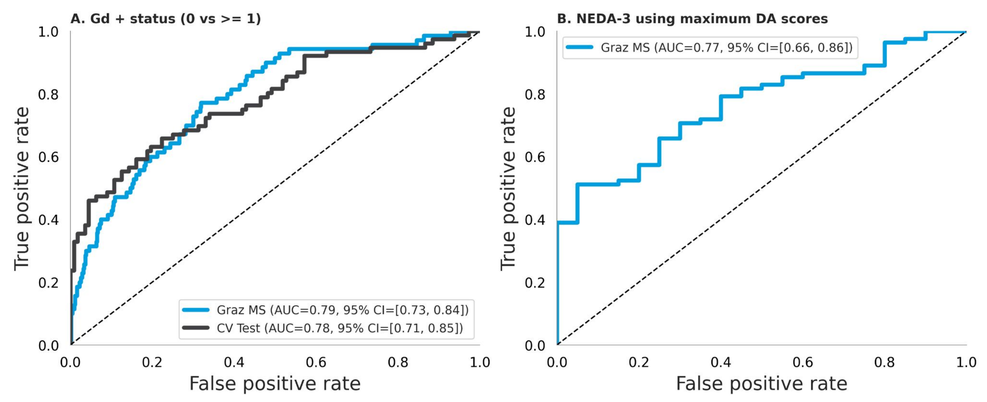

Figure 3: AUC of DA score probabilities for Gd+ lesions and NEDA-3

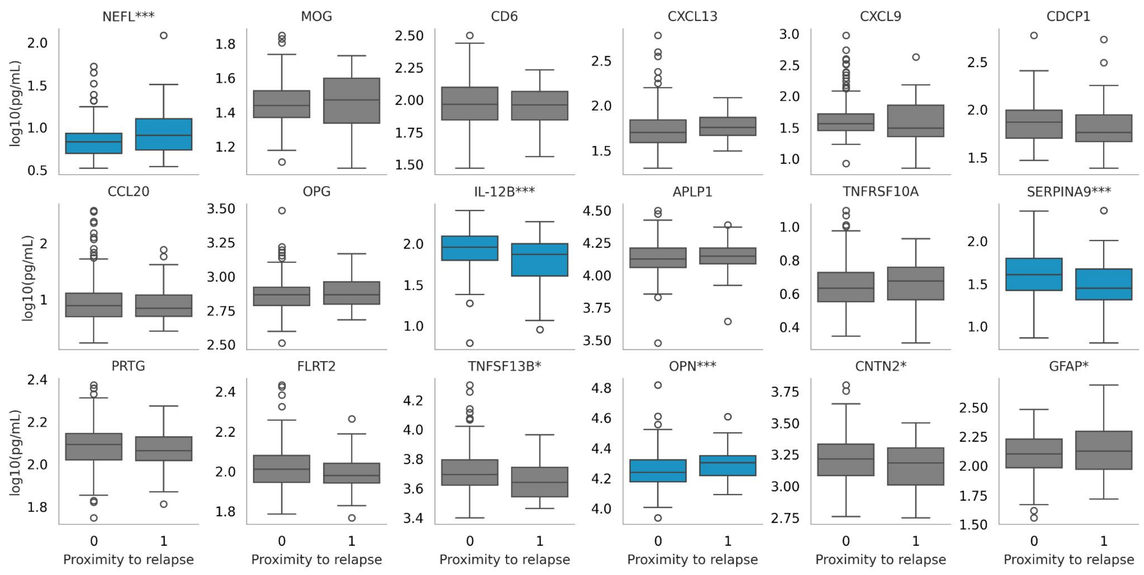

Figure 4: Log biomarker concentrations by relapse proximity; blue indicates Bonferroni-significance

Conclusions

- The performance of the DA score for predicting Gd+ lesions in this cohort corroborates the MSDA clinical validation evidence.[1]
- The strong association between the DA score and NEDA-3 status, proximity to relapse (±30 days vs. >±30 days), and Brain Atrophy tertiles are novel findings.
- Biomarkers in the MSDA panel were significant predictors of EDSS.

Together, these results further support the MSDA test as a quantitative tool for assessing disease activity in MS. Further research is needed to explore the utility of biomarkers in predicting long-term MS progression.

Disclosure: G. Datta, S. McCurdy, L. Ruiz, E. Sheng, A. Hari, S. Tiwari, W. Hu, D. Brazel and F. Qureshi are employees of Octave Bioscience. M. Martinez-Serrat, B. Heschl, E. Hofer and S. Ropele have nothing to disclose. C. Tafrali has received travel funding and speaker honoraria from Merck. R. Demjaha has received travel funding from Janssen, Novartis and Sanofi. D. Pinter is a member of the advisory board for "Cognition and MS" for Novartis and has received speaking honoraria from Biogen, Novartis, MedAhead and Bristol-Myers Squibb. A. Damulina has participated in meetings sponsored by, received speaker honoraria or travel funding from Sanofi-Aventis, Novartis and Janssen. C. Enzinger has received funding for traveling and speaker honoraria from Biogen Idec, Bayer Schering Pharma, Merck Serono, Novartis, Genzyme and Teva Pharmaceutical Industries Ltd./Sanofi-Aventis, Shire; received research support from Merck Serono, Biogen Idec, and Teva Pharmaceutical Industries Ltd./Sanofi-Aventis; and serves on scientific advisory boards for Bayer Schering Pharma, Biogen Idec, Merck Serono, Novartis, Genzyme, Roche, and Teva Pharmaceutical Industries Ltd./Sanofi- Aventis. M. Khalil has received travel funding and speaker honoraria from Bayer, Biogen, Novartis, Merck, Sanofi and Teva and serves on scientific advisory boards for Biogen, Bristol-Myers Squibb, Gilead, Merck, Novartis, Alexion, Amgen and Roche. He received research grants from Biogen, Novartis and Teva.

References: 1 **Chitnis T et al.** Clinical validation of a multi-protein, serum-based assay for disease activity assessments in multiple sclerosis. *Clin Immunol 2023; Aug:253:109688.*

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