Characterizing MSDA Score and Biomarker Associations with Disease Activity, Progression, and PIRA in a Pilot MS Study of Four Well-Defined Patient Groups at AUMC

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Introduction

The Octave® Multiple Sclerosis Disease Activity (MSDA) Test is a validated serum assay measuring 18 biomarkers, adjusted for age and sex, to generate a disease activity (DA) score (1–10, 0.5 increments)[1]. The MSDA score was trained and clinically validated against active MRI lesions, but its relation to MS progression and ability to assess Progression Independent of Relapse Activity (PIRA) is unclear.

Objectives

Using data from a Multiple Sclerosis (MS) pilot cohort, we evaluated the MSDA Test across the MS spectrum, examining associations of DA score and individual biomarkers with disease activity and progression, focusing on PIRA versus other subgroups.

Methods

Retrospective data from 32 participants on ocrelizumab were collected over up to 4 years (5 timepoints, 135 serum samples). Participants were categorized into four groups during follow-up (8 patients per group):

- **PIRA** (EDSS increase without disease activity)
- **Active** (MRI activity without progression - no EDSS increase)
- **NEDA** (no evidence of disease activity: MRI, relapses, or EDSS)
- **RAW** (Relapse-associated Worsening; clinical relapse/MRI activity followed by EDSS increase).

Group	# Samples	Age at baseline	Sex		EDSS at baseline	Gd+ Lesion status across timepoints		N/E T2 Lesion status across timepoints	
	Total=135	Mean (sd)	F	M	Mean (sd)	0 (n=18)	≥1 (n=15)	0 (n=100)	≥1 (n=35)
PIRA	36 samples from 8 participants	49.2 (6.0) *Range: [38.5-54.5]*	5 (62.5%)	3 (37.5%)	3.4 (1.1) *Range: [1.5-5]*	7 (19.4%)	1 (2.8%)	33 (91.7%)	3 (8.3%)
Active	34 samples from 8 participants	33.7 (8.1) *Range: [23.3-42.8]*	5 (62.5%)	3 (37.5%)	2.4 (0.8) *Range: [1.5-4]*	4 (11.8%)	4 (11.8%)	21 (61.8%)	13 (38.2%)
NEDA	33 samples from 8 participants	40.3 (8.3) *Range: [31.7-55.2]*	6 (75%)	2 (25%)	3.9 (1.6) *Range: [2-6]*	3 (9.1%)	3 (9.1%)	29 (87.9%)	4 (12.1%)
RAW	32 samples from 8 participants	37.8 (9.5) *Range: [24.3-47.9]*	5 (62.5%)	3 (37.5%)	2.8 (2.1) *Range: [0-7]*	4 (12.5%)	7 (21.9%)	17 (53.1%)	15 (46.9%)

Table 1: Baseline demographics and dataset characteristics

- **AUC analyses** | Area Under the Curve (**AUC**) of MSDA score probabilities was used to assess classification accuracy for **Gadolinium-enhancing (Gd⁺)** and **New/Enlarging (N/E) T2** lesions, and compared with the clinical validation dataset (Figure 1).[1]
- **PIRA vs other subgroups** | Maximum MSDA scores and corresponding $\log_{10}$-transformed biomarker concentrations were compared between PIRA and other groups using age- and sex-adjusted OLS models.
- **EDSS** | Age- and sex-adjusted Linear mixed-effects(LME) models assessed associations between MSDA scores or biomarkers and EDSS, accounting for participant-level variability. All p-vaues were Bonferroni-corrected (n=18 for biomarkers and n=1 for MSDA score).

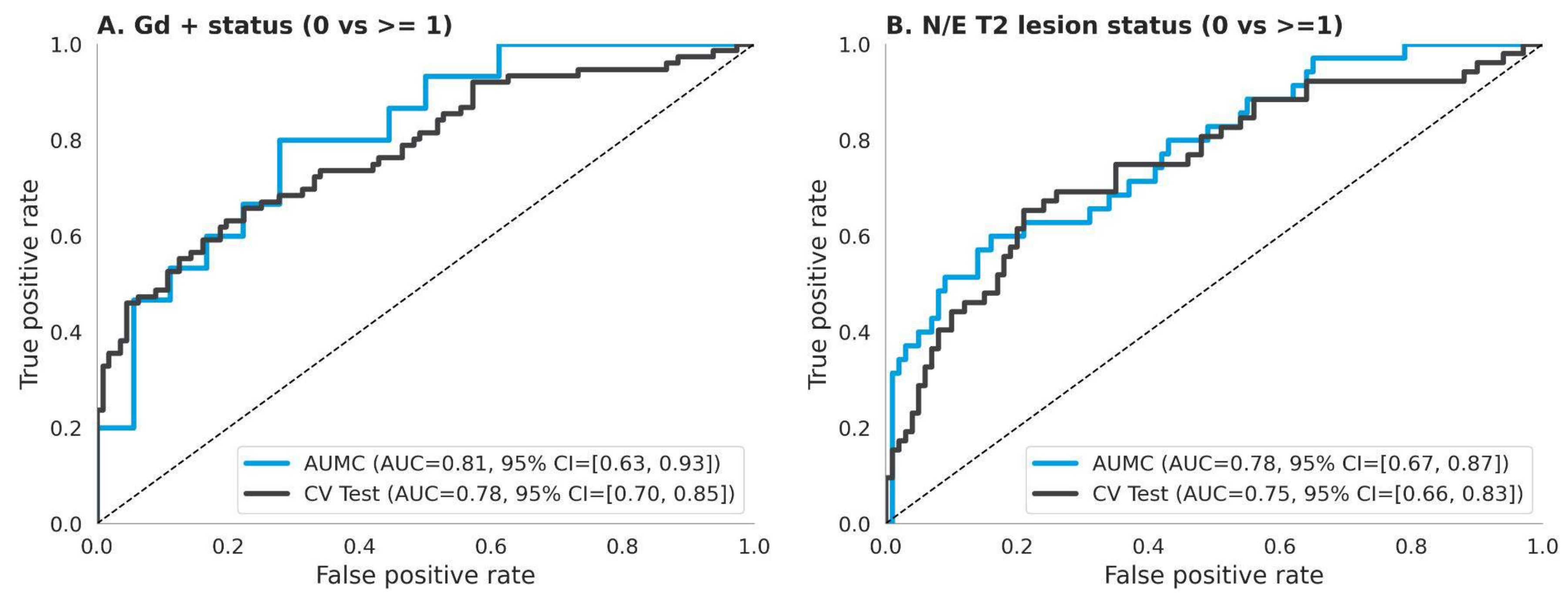

Figure 1: AUC of MSDA score probabilities for Gd+ lesions and N/E T2 Lesions, for AUMC pilot and clincal validation test set.

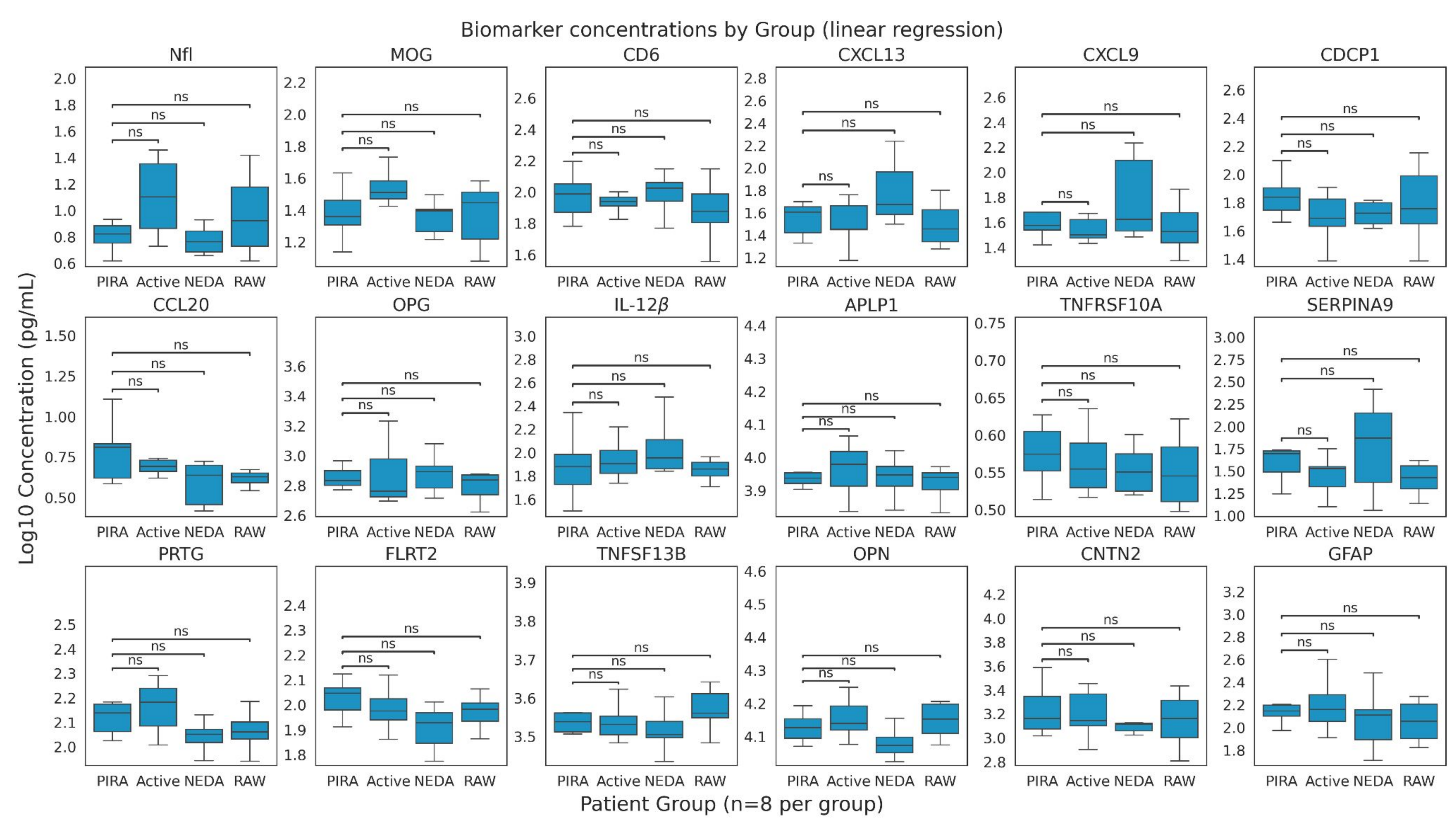

Figure 2: Biomarker concentrations at sample with maximum MSDA score per participant. Significance assessed by linear regression.

Results

Participants had a mean age of 40 years at baseline and were 66% female *(Table 1)*. All p-values were Bonferroni-corrected.

- **AUC analyses** | Classification AUCs using MSDA score probabilities were *(Figure 1)*
  - **0.81 (95% CI [0.63,0.93])** for Gd+ lesions and
  - **0.78 (95% CI [0.67,0.87])** for N/E T2 lesions.

  Figure 1 compares AUCs to the independent test set used for clinical validation.
- **PIRA vs other subgroups** | MSDA scores and biomarkers did not differ significantly between PIRA and other groups at each patient's maximum MSDA timepoint (Figures 2 and 3).
  - Although PIRA patients had lower MSDA scores than Active patients, this difference was not significant after Bonferroni correction using age- and sex-adjusted OLS (p=0.3) or a Mann–Whitney U test (p=0.12).
  - The lack of significance may reflect limited power due to small sample size.
- **EDSS** | Mean baseline EDSS was 3.4 for PIRA, 2.4 for Active, 2.8 for RAW, and 3.9 for NEDA (medians 3.8, 2.0, 3.5, and 2.5; Table 1).
  - MSDA scores and individual biomarkers were not significantly associated with EDSS after adjusting for age, sex, and participant-level variability (Figure 4).

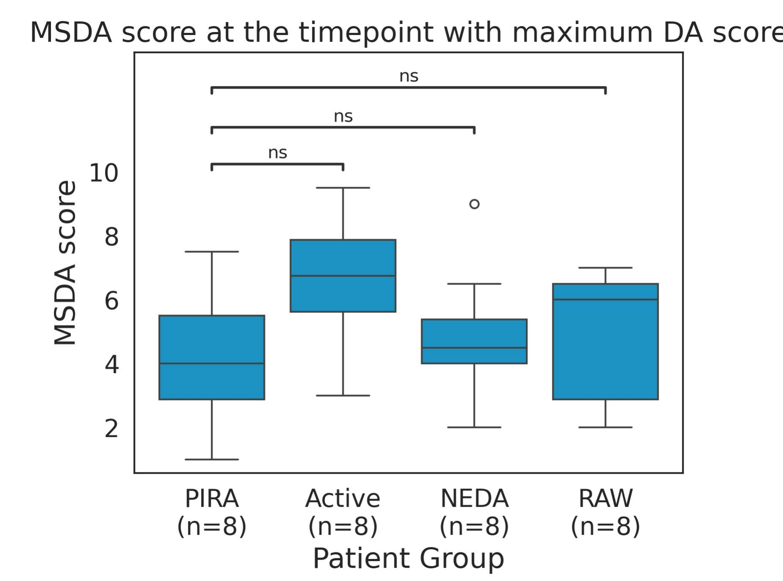

Figure 3: MSDA score at sample with maximum MSDA score per participant. Significance from linear regression.

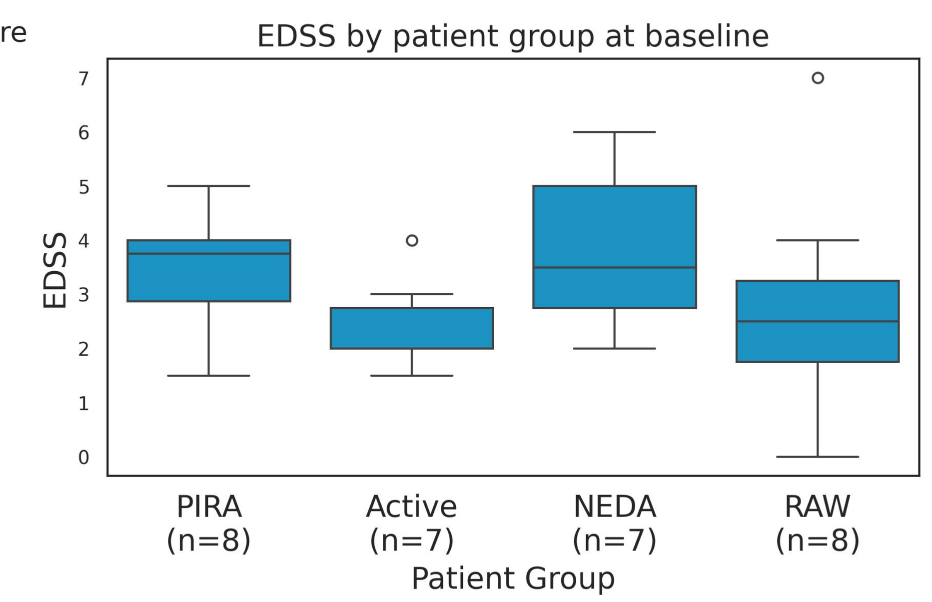

Figure 4: EDSS at the baseline timepoint for each patient group

Conclusions

- The performance of the DA score for predicting Gd+ and N/E T2 lesions in this cohort corroborates the MSDA clinical validation evidence.[1]
- However, no significant association with progression measures was observed, likely due this study's small sample size and the focus on disease activity endpoints during training of the MSDA score model.
- Future studies will expand to larger biomarker panels to identify novel biomarkers associated with MS disease progression.

Disclosure: G. Datta, S. McCurdy, L.Ruiz, W. Hu, S. Tiwari, A. Hari, D. Brazel, F. Qureshi are employees of and hold equity in Octave Bioscience. M. Wessels reports no disclosures. A.M. Schumacher received compensations as an advisor to Dehaze, Biogen, Mymee Inc, all not related to this work. His research is being supported by the Walter und Getrud Siegenthaler Foundation, University of Zurich and the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) – 568249057". C. Teunissen has research contracts with Acumen, ADx Neurosciences, AC-Immune, Alamar, Aribio, Axon Neurosciences, Beckman-Coulter, BioConnect, Bioorchestra, Brainstorm Therapeutics, C2N diagnostics, Celgene, Cognition Therapeutics, EIP Pharma, Eisai, Eli Lilly, Fujirebio, Instant Nano Biosensors, Merck, Muna, Nitrase Therapeutics, Novo Nordisk, Olink, PeopleBio, Quanterix, Roche, Sysmex, Toyama, Vaccinex, Vivoryon. She is editor in chief of Alzheimer Research and Therapy, and serves on editorial boards of Molecular Neurodegeneration, Alzheimer's & Dementia, Neurology: Neuroimmunology & Neuroinflammation, Medidact Neurologie/Springer, and is committee member to define guidelines for Cognitive disturbances, and one for acute Neurology in the Netherlands. She has consultancy/speaker contracts for Aribio, Biogen, Beckman-Coulter, Cognition Therapeutics, Danaher, Eisai, Eli Lilly, Janssen, Merck, Neurogen Biomarking, Nordic Biosciences, Novo Nordisk, Novartis, Olink, Quanterix, Roche, Sanofi and Veravas.

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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