OCTAVE

Serum Proteomics Identifies Candidate Biomarkers of PIRA and Disability Worsening in a Pilot Multiple Sclerosis Cohort

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Introduction

Large-scale proteomic platforms enable high-dimensional biomarker discovery beyond conventional targeted approaches. The Alamar CNS 120 and Inflammation (INF) panels and the Olink Reveal panel measure 131, 249, and 1,034 biomarkers in relative quantification, respectively.[1,2,3]

Objectives

Identify serum proteomic biomarkers associated with MS disability progression in a small, well-characterized pilot cohort.

Methods

Retrospective data from 32 ocrelizumab-treated patients (matched groups representing a spectrum of MS disease activity and progression profiles) were collected up to 4 years (~5 annual timepoints, 135 serum samples) and analyzed across Alamar NULISAseq (CNS 120 + INF combined; 380 biomarkers) and Olink Reveal (1,034 biomarkers) panels to generate log2 relative quantifications.

Progression Independent of Relapse Activity (PIRA) was defined per Müller et al. (2025) with annual confirmation (8 events / 8 patients). [4]

Number of samples		135
Number of patients		32
Patient groups		PIRA: 36 samples / 8 patients Active: 34 samples / 8 patients NEDA: 33 samples / 8 patients RAW: 32 samples / 8 patients
Age at baseline	Mean ± sd (range)	40 ± 9.6 (23-55)
Sex (%)	Female	21 (66%)
	Male	11 (34%)
EDSS	Median (range)	3.25 (0-7.5)
Had a PIRA event	Y	8 (25%)
	N	24 (75%)
Time to first PIRA (years)	Median (range)	3 (2-4)

Table 1: Patient Demographics

Three sets of models were applied. All models were adjusted for age, sex, and patient-level variability as appropriate. False Discovery Rate (FDR) correction was applied for multiple testing (pFDR<0.1).

- **Time-to-event analyses |** Per-biomarker Cox Proportional Hazard (PH) models of time to first PIRA event on log2 biomarker concentration.
- **Differential abundance |** Within PIRA patients, per-biomarker linear mixed-effects models (LMEs) for differential abundance between samples with PIRA events and samples without PIRA events.
- **EDSS worsening |** Per-biomarker LMEs of follow-up Expanded Disability Status Scale (EDSS) with log2 biomarker quantification at the prior visit, restricted to visit pairs meeting established EDSS progression thresholds, adjusted for prior EDSS and follow-up time.

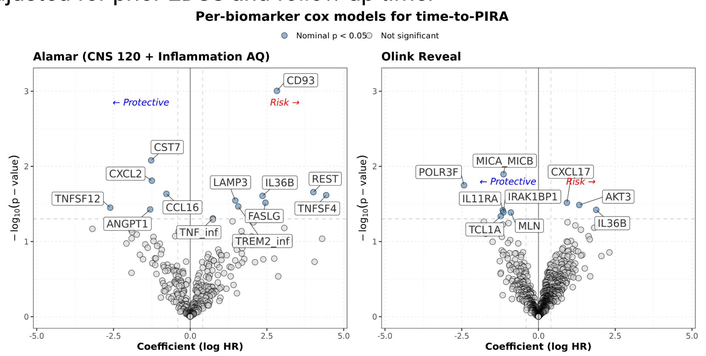


Figure 1: Per-biomarker Cox PH regression, shown as volcano plots of log hazard ratio with $-\log_{10}(p)$.

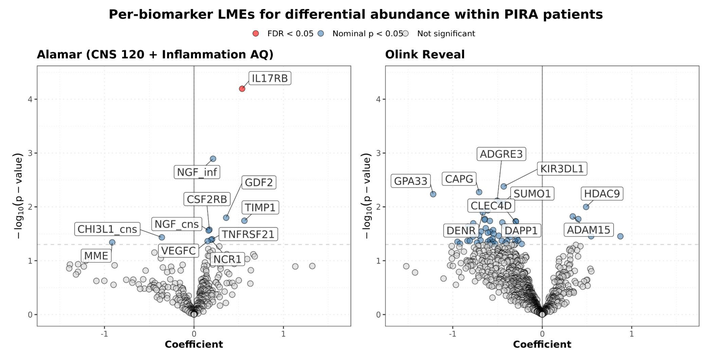


Figure 2: Per-biomarker LME for differential abundance, shown as volcano plots of coefficient with $-\log_{10}(p)$.

Results

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

- **Time-to-event analyses |** Per-biomarker Cox PH models identified 13 and 9 nominally significant biomarkers in Alamar and Olink respectively, though none were significant after FDR correction (Figure 1).
- **Differential abundance |** Within PIRA patients, IL17RB (β=0.54 [0.32,0.76], FDR=0.02) was significantly differentially abundant in PIRA samples for the Alamar dataset; no biomarkers were significant in Olink after FDR correction (Figure 2).
- **EDSS worsening |** No biomarkers were significant in Alamar. In Olink, higher TNFAIP8 (β=−0.96 [−1.19,−0.73], FDR<0.001) at the prior timepoint was associated with decreased follow up EDSS. TNF (β=−0.88 [−1.22,−0.55], FDR=0.08) was also identified as a potential candidate for future evaluation (Figure 3).

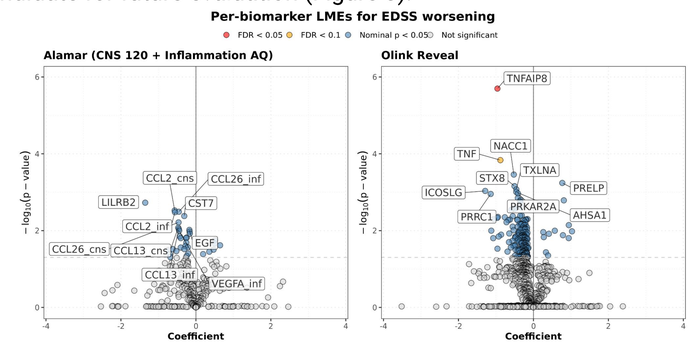


Figure 3: Per-biomarker LME for EDSS worsening, shown as volcano plots of coefficient with $-\log_{10}(p)$.

Conclusions

In this small pilot cohort, serum proteomic profiling identified IL17RB as a candidate biomarkers of PIRA, and TNFAIP8 and TNF for EDSS worsening respectively. NfL and GFAP did not reach significance, possibly reflecting limited sample size. These findings should be interpreted as hypothesis-generating and will require replication in larger, independent cohorts for confirmation.

References: [1] Ma XJ, et al. Development of NULISA™ CNS Disease Panel 120 for comprehensive proteomic profiling of neurodegenerative diseases. Alzheimers Dement. 2025 Jan 9;20(Suppl 2):e089847.
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