

PLASMA EXTRACELLULAR VESICLE PROTEINS DETECT CORTICAL MEAN DIFFUSIVITY IN ALZHEIMER'S DISEASE

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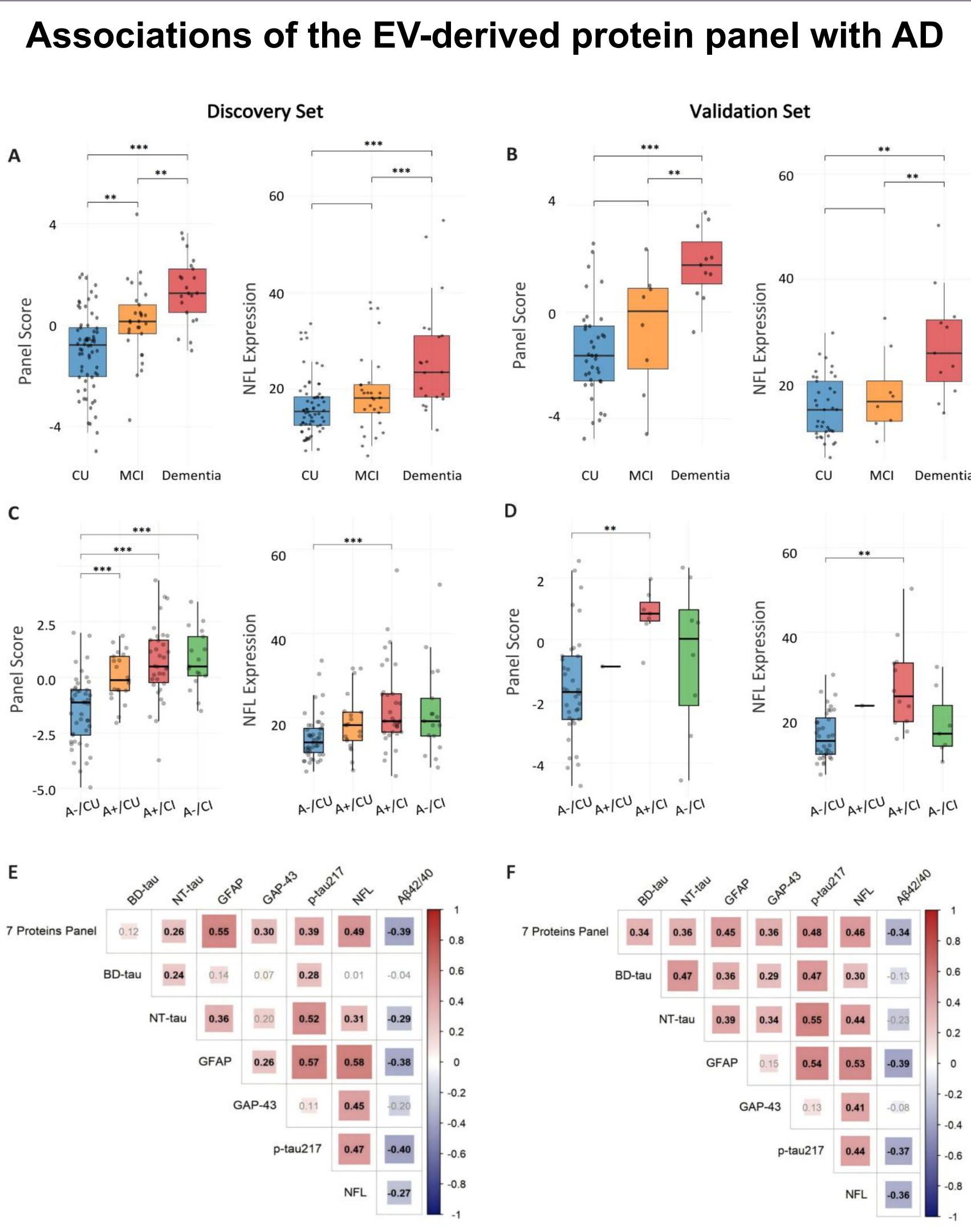
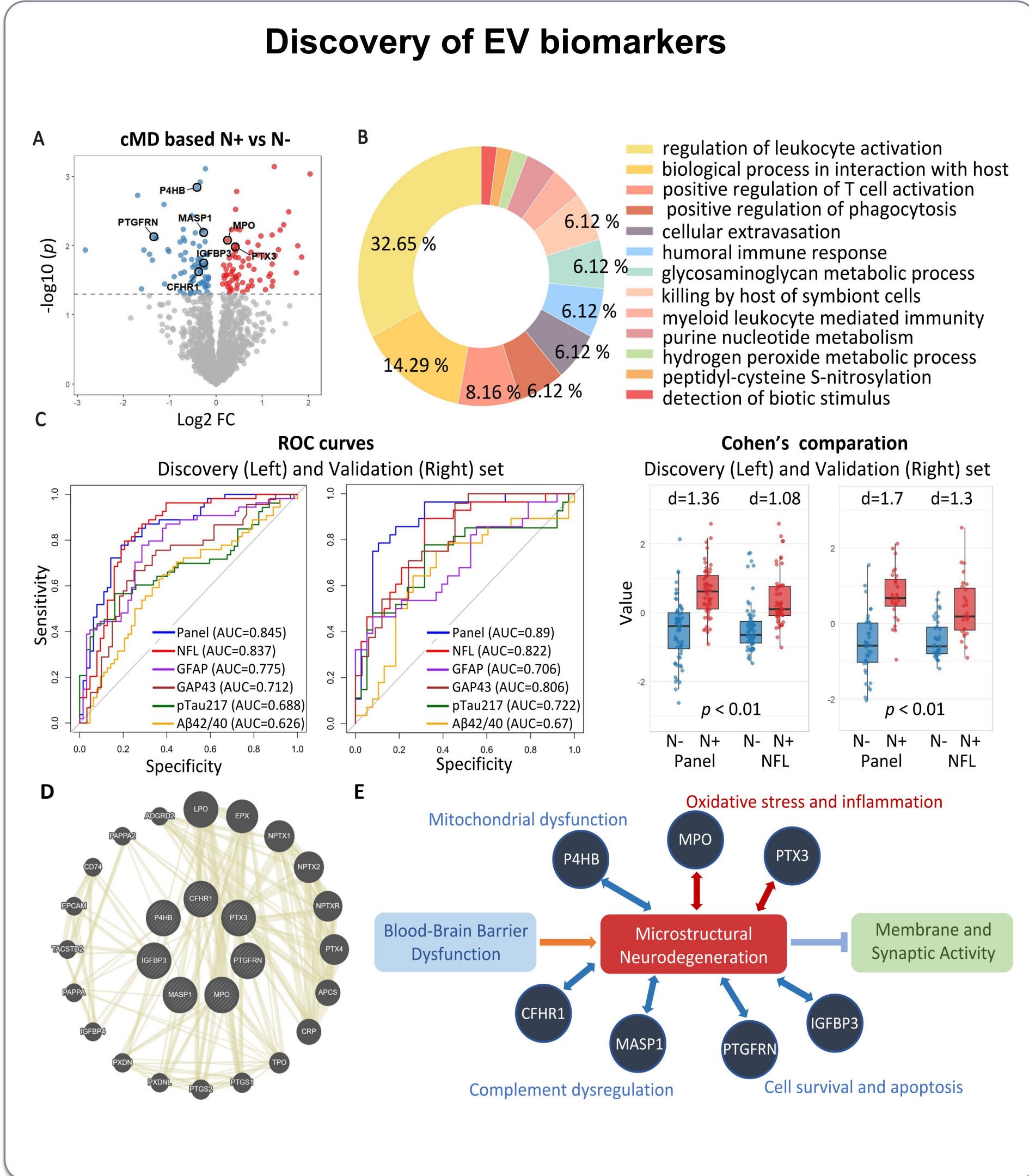
BACKGROUND

- It is critical to monitor Early AD neurodegeneration using scalable blood biomarkers. [1,2]
- Cortical mean diffusivity (cMD) from diffusion MRI captures microstructural damage before overt atrophy, but MRI is costly and impractical for large-scale follow-up. [3–5]
- Plasma neurofilament light (NFL) reflects neuroaxonal injury yet may miss the earliest gray-matter microstructural change and provides limited biological specificity. [1,2]
- Extracellular vesicles (EVs) carry disease-relevant proteins and may offer a more informative blood-accessible window into early AD neurodegeneration. [6–8]
- Objective:** to identify a plasma EV protein signature anchored to cMD-defined neurodegeneration and test whether it outperforms conventional plasma biomarkers.

METHODS

- 183 older adults from the GHABS cohort underwent plasma collection, clinical assessment, structural MRI, diffusion MRI, and amyloid PET.
- Participants were classified as N– or N+ using a predefined cMD cutoff of 1.199 and split into discovery (n=117) and validation (n=66) cohorts.
- Plasma EVs were isolated by ultracentrifugation and profiled by DIA-MS, yielding 3,989 EV proteins in the discovery cohort.
- Candidates were prioritized through differential expression, EV-database overlap, neurodegeneration-related filtering, and machine-learning feature selection.
- The final EV panel was validated by ROC analysis and tested against clinical stage, established plasma biomarkers, cMD, cortical thickness, and longitudinal progression.

RESULTS



CONCLUSIONS

- Imaging-anchored plasma EV proteomics can generate a scalable blood signature for early AD neurodegeneration.
- The 7-protein EV panel provides biologically interpretable information beyond a single injury marker.
- Compared with plasma NFL, the EV panel shows similar or better cross-sectional discrimination and stronger prediction of longitudinal progression.
- Potential applications include early screening, risk stratification, and longitudinal monitoring in observational cohorts or therapeutic trials.
- Limitations: single-study framework, modest longitudinal sample size, and the need for targeted assay development plus external multicenter validation.

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KEY FINDINGS

- Final 7-protein panel: PTX3, MPO, MASP1, P4HB, PTGFRN, IGFBP3, CFHR1.
- Diagnostic performance for cMD-defined neurodegeneration: AUC 0.845 in discovery and 0.890 in validation.
- The panel numerically exceeded NFL and outperformed GFAP, GAP-43, p-tau217, and Aβ42/Aβ40.
- Panel score increased stepwise across CU → MCI → dementia.
- Higher panel levels were associated with higher cMD and lower cortical thickness.

TAKE-HOME MESSAGE

A plasma EV 7-protein panel tracks early ad neurodegeneration and predicts future MRI progression better than NFL.

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