

Clinical utility of a quantitative neurodegeneration proteomic panel for clinical and biomarker outcomes in a memory-clinic cohort

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Key takeaway: To evaluate the clinical utility of a novel plasma proteomic neurodegenerative panel for clinical diagnoses and prognosis in a real-world memory clinic setting.

INTRODUCTION	METHODS	RESULTS	RESULTS	CONCLUSIONS
Multiplex proteomic immunoassays are promising tools for clinical risk stratification in the presence of concomitant neuro-pathologies. We evaluated the clinical utility of a novel, quantitative, targeted neurological proteomic panel for discrimination of 1) cross-sectional clinical phenotypes, 2) biomarker status, and 3) prognostication of outcomes in a memory-clinic cohort. Figure 1: Overview of 41 baseline plasma proteins profiled (Olink Target48 Neurodegeneration panel)	A prospective cohort of Singaporean memory-clinic participants was followed-up for 4 years. Annual neurocognitive assessments were performed alongside brain MRI scans. Clinical cognitive diagnoses were assigned to each participant at baseline: no cognitive impairment (NCI), cognitive impairment no dementia (CIND), or dementia. Brain amyloid status (Amyloid positive: A+ (N=82); Amyloid negative: A- (N=99)) was determined using brain amyloid PET scans (N=114) or plasma pTau-217 levels measured using the SIMOA platform where PET was unavailable (N=67). The presence of concomitant CeVD (CeVD+) was determined on brain MRI scans at baseline. Incident cognitive decline was defined as a Clinical Dementia Rating Scale Sum-of-Boxes ≥ 3 increment from baseline. Baseline plasma samples underwent targeted quantitative profiling of 41 neurological proteins using the Olink Target48 Neurodegeneration panel (Figure 1). Protein associations with cognitive and biomarker outcomes were evaluated using multivariable regression models.	181 participants were included (mean age 72 ± 7.9 years, 41% male), with 59% CeVD, 22.2% NCI, 49.1% CIND and 28.7% dementia. The most significant proteins distinguishing NCI from CIND included NPTXR (fdr-p<0.05, Figure 2), and for dementia: pTau-217 (fdr-p<0.05, Figure 2). A+ participants displayed most significant elevations in pTau-217 and GFAP (adjusted p-value<0.05). Amongst A+ participants, elevated MOG most significantly associated with the presence of concomitant CeVD+ (fdr-p<0.05, Figure 2). Figure 2: Top 2 significant proteins for cross-sectional biomarker and clinical diagnoses	31.5% of participants developed incident cognitive decline, with pTau-217 being the most predictive protein (adjusted hazards ratio 1.97, 95% C.I. 1.56-2.49, fdr-p<0.05, C-index 0.81). Strong inter-platform agreement was observed between paired pTau-217 levels measured using the Olink Target48 and SIMOA platforms (R=0.92, p<0.001, Figure 3). Figure 3: Strong inter-platform correlation of pTau-217 levels measured on Olink Target 48 and SIMOA platforms	We demonstrate clinical utility of novel quantitative neurodegeneration proteomics panel for discriminating cross-sectional and longitudinal outcomes in a memory-clinic setting. Future studies should elucidate the applicability of curated neurological biomarker panels, for improved patient stratification in clinical settings CONTACT Correspondence: mingann.sim@gmail.com; ming_ann_sim@Nuhs.edu.sg. ALZHEIMER'S ASSOCIATION AAIC 26