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Longitudinal Plasma Phosphorylated Tau-217 and Neurofilament Light Chain as Predictors of Cognitive Decline in Preclinical Alzheimer's Disease

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ABSTRACT

Background: Early identification of preclinical Alzheimer's disease pathology remains essential for disease-modifying therapies. In this prospective 5-year multicenter study of 1,420 cognitively unimpaired elderly individuals, baseline plasma p-tau217 demonstrated exceptional diagnostic accuracy (AUC 0.94) for identifying brain amyloid-beta burden.

KEYWORDS: Alzheimer's Disease, Plasma p-tau217, Neurofilament Light, Amyloid PET, Preclinical Biomarkers

1. INTRODUCTION & THEORETICAL CONTEXT

Alzheimer's disease (AD) is defined pathologically by the progressive accumulation of extracellular amyloid-beta ($A\beta$) plaques and intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein, culminating in neurodegeneration and cognitive collapse. Historically, definitive diagnosis in living subjects required either invasive cerebrospinal fluid (CSF) lumbar puncture or expensive positron emission tomography (PET) neuroimaging with radiotracers. Because the biological onset of AD pathology precedes clinically overt cognitive impairment by 15 to 25 years, the preclinical window represents the optimal therapeutic target for newly approved monoclonal antibody immunotherapies. Recent breakthroughs in ultra-sensitive immunoassays and mass spectrometry have enabled the detection of picogram-per-milliliter concentrations of brain-derived proteins in peripheral blood. Among these candidates, tau phosphorylated at threonine-217 (p-tau217) and neurofilament light chain (NfL) have emerged as front-runners reflecting cerebral tau tangle deposition and unspecific axonal destruction, respectively. Nevertheless, prospective validation across diverse community cohorts assessing whether longitudinal blood biomarker trajectories can forecast annual cognitive degradation in preclinical stages has remained an unfulfilled necessity.

2. MATERIALS & EXPERIMENTAL METHODOLOGY

We conducted an international multicenter prospective cohort study involving 1,420 cognitively unimpaired elderly participants (aged 60–85 years) enrolled across three memory research centers in Sweden, the United States, and France between 2018 and 2023. At baseline, all participants completed high-resolution 3T MRI, 11C-PiB or 18F-florbetapir Amyloid-PET imaging, and baseline neurocognitive testing including the Preclinical Alzheimer Cognitive Composite (PACC-5) and Clinical Dementia Rating sum of boxes (CDR-SB). Peripheral blood was drawn in EDTA tubes, centrifuged under standardized protocols within 60 minutes, and stored at -80°C . Plasma concentrations of p-tau217 were quantified using the ALZpath high-sensitivity immunoassay platform, and plasma NfL was determined via Single Molecule Array (Simoa NF-light) assays. Annual cognitive assessments and biennial blood collection were carried out over a 5-year follow-up period. Linear mixed-effects regression models adjusted for age, sex, educational attainment, and APOE $\epsilon 4$ allele status evaluated the association between baseline and longitudinal biomarker rates and cognitive slope deterioration.

3. RESULTS & EMPIRICAL ANALYSIS

At baseline, 342 of the 1,420 participants (24.1%) were classified as amyloid-PET positive (Centiloid > 25). Baseline plasma p-tau217 demonstrated superior discriminatory accuracy in differentiating amyloid-PET positive from amyloid-PET negative individuals, yielding an area under the receiver operating characteristic curve (AUC) of 0.94 (95% CI 0.92–0.96). This significantly outperformed other plasma biomarkers, including p-tau181 (AUC 0.82) and the $A\beta 42/A\beta 40$ ratio (AUC 0.79; $p < 0.001$). Over the 5-year longitudinal follow-up, participants in the highest quartile of baseline plasma p-tau217 exhibited an accelerated decline in PACC-5 scores compared to those in the lowest quartile (annual slope difference: -0.42 standard deviation units/year; 95% CI -0.51 to -0.33 ; $p < 0.0001$). Furthermore, longitudinal increases in plasma NfL correlated directly with structural neurodegeneration on MRI, exhibiting significant hippocampal volume shrinkage ($\beta = -0.38$, $p < 0.001$) and whole-brain cortical thinning. In multivariate survival models, individuals possessing both elevated p-tau217 (> 90 th percentile) and accelerated NfL elevation faced an eleven-fold higher risk of converting to mild cognitive impairment (MCI) or clinical dementia over 5 years (HR 11.4; 95% CI 7.2–18.1; $p < 0.001$).

4. DISCUSSION, MECHANISTIC INSIGHTS & LIMITATIONS

These clinical data confirm that plasma p-tau217 acts as a highly sensitive surrogate marker for early cortical amyloidosis and spreading tauopathy, while plasma NfL serves as an independent marker of downstream axonal injury and active neurodegenerative speed. The combination of both biomarkers provides a robust, dual-axis biological assessment: p-tau217 confirms disease-specific Alzheimer pathology, whereas NfL benchmarks the immediate tempo of neuronal loss. The implementation of plasma-based biomarkers will dramatically democratize clinical trial screening and clinical diagnostic pathways, avoiding the prohibitive expense and logistical complexity of amyloid PET scans. Several limitations warrant consideration: plasma p-tau217 levels can be modestly elevated in patients with severe chronic renal impairment ($\text{eGFR} < 30 \text{ mL/min/1.73 m}^2$), necessitating renal-adjusted cutoff thresholds. Furthermore, while the cohort represented multiple geographic centers, ethnic diversity was predominantly Caucasian, underscoring the need for continued validation across more demographically representative global cohorts.

5. CONCLUSION & FUTURE TRAJECTORIES

Plasma p-tau217 combined with longitudinal NfL dynamics accurately predicts amyloid status and cognitive deterioration in preclinical Alzheimer's disease. Incorporating plasma p-tau217 into routine secondary healthcare and trial recruitment workflows can slash trial screening costs by up to 70% while accelerating the enrollment of candidates most likely to benefit from anti-amyloid and anti-tau therapeutics. Future efforts should standardize assay calibrators worldwide to establish universal clinical diagnostic cutoffs.

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Data Availability: Analytical datasets and computational models are archived under open repositories under DOI: 10.5923/researchium.2024.jmhr.0103-data.

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