

# Diagnostic and Prognostic Value of Plasma Amyloidopathy, Tauopathy, and Neurodegeneration Biomarkers in a Real-World MCI Cohort

**Guido Maria Giuffrè, Davide Quaranta, Maria Gabriella Vita, Alessandro Scalese, Domenico Fusco, Giorgia Fari, Cinzia Carrozza, Paolo Calabresi, Camillo Marra**

*Affiliations: Memory Clinic, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy; Department of Neuroscience, Catholic University of the Sacred Heart, Rome, Italy; Department of Psychology, Catholic University of the Sacred Heart, Milan, Italy; UOC of Chemistry, Biochemistry and Clinical Molecular Biology, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy.*

**Introduction** The recent regulatory approvals of new amyloid targeting therapies for Alzheimer’s disease (AD), highlights the urgent need for diagnostic strategies that are more accessible, cost-effective, and less invasive to address the growing diagnostic demands. In this context, blood-based biomarkers are increasingly recognized as promising tools for early AD.

The present study had the aim of providing evidence on the potential of plasma biomarkers to support clinical decision-making in the prodromal stages of AD in real-world clinical practice. The main objectives of the study were to: assess the diagnostic performance of plasma biomarkers in detecting AD pathology using both single-cut-off and two-cut-off strategies; examine their prognostic utility in predicting clinical progression to dementia over a two-year follow-up.

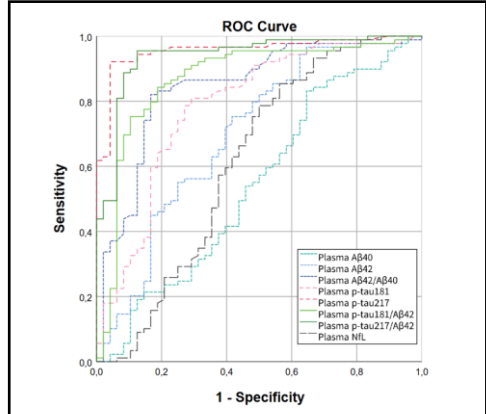
**Materials & Methods:** CSF and plasma samples were collected from 137 mild cognitive impairment (MCI) subjects, classified as AD or non-AD (NAD) based on their CSF biomarkers profile. CSF Aβ40, Aβ42, p-tau181 and t-tau and plasma Aβ40, Aβ42, p-tau181, p-tau217 and NFL quantification were conducted using the Lumipulse G assays (Fujirebio). The same neuropsychological battery was administered at baseline and at both one-year and two-year follow-up to assess clinical progression. Comparison among groups, correlation analyses, ROC curves and binomial regression models were performed.

**Results:** All CSF and plasma biomarkers showed significant inter-correlations, except plasma NFL, which was not significantly associated with amyloid markers in either CSF or plasma. AD and NAD MCI subgroups did not differ significantly in age, education, MMSE baseline scores, or plasma NFL levels. As expected, significant between-group differences were observed in plasma amyloidopathy and tauopathy biomarkers. Plasma p-tau217 and the p-tau217/Aβ42 ratio demonstrated the highest diagnostic accuracy (AUC>0.90) in distinguishing AD from NAD MCI (Figure 1).

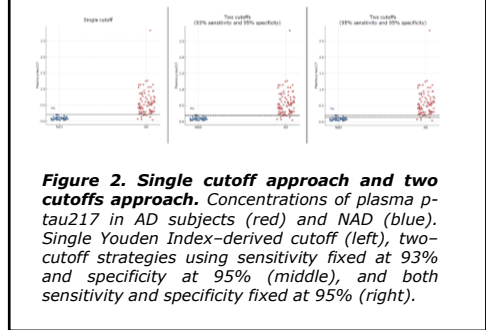
Applying increasingly stringent dual cut-off strategies (sensitivity and specificity ≥93%, and ≥95%) for plasma p-tau217 led to a progressive improvement of the accuracy with only a limited number (<10%) of intermediate results falling in the “grey zone” that would require further testing (Figure 2).

Longitudinal analyses revealed that plasma tauopathy and neurodegeneration markers—especially p-tau217—were significantly associated with cognitive decline. In multivariable logistic regression models adjusted for age, sex, education, and baseline MMSE, p-tau217 emerged as the strongest independent predictor of progression, both in the overall cohort and among MCI due to AD subjects.

**Discussion & Conclusions:** Plasma p-tau217 and the p-tau217/Aβ42 ratio exhibit excellent diagnostic performance and robust prognostic value in a real-world MCI cohort. These findings support their clinical utility as minimally invasive biomarkers for early disease stratification and individualized risk assessment. As blood-based biomarkers become more widely available, their integration into clinical practice will represent a transformative step toward precision medicine in AD.



**Figure 1. ROC curves.** Performance of plasma biomarkers (Aβ40, Aβ42, Aβ42/40, p-tau181, p-tau217, p-tau181/Aβ42, p-tau217/Aβ42, and NFL) in distinguishing AD from NAD.



**Figure 2. Single cutoff approach and two cutoffs approach.** Concentrations of plasma p-tau217 in AD subjects (red) and NAD (blue). Single Youden Index-derived cutoff (left), two-cut-off strategies using sensitivity fixed at 93% and specificity at 95% (middle), and both sensitivity and specificity fixed at 95% (right).

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