

Longitudinal plasma ATN biomarker trajectories in individuals with Subjective Cognitive Complaints in Latin America

P1-9117

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Distinct longitudinal plasma biomarker trajectories exist among older adults, highlighting heterogeneous biological progression driven mainly by changes in p-tau217, GFAP, and NfL

INTRODUCTION

Subjective cognitive complaints (SCC) represent an early, potentially preclinical stage within the Alzheimer’s disease (AD) continuum, often coexisting with subtle objective cognitive impairment in community-based settings. Plasma ATN biomarkers provide a minimally invasive tool to characterize early AD-related changes and distinguish biological trajectories across cognitive stages. However, most longitudinal ATN biomarker evidence derives from high-income countries, with scarce data from Latin America (LA).

METHODS

1 Plasma biomarker measurements
Baseline (T1) and follow-up (T3)

T1 (Baseline) → T3 (Follow-up)

- Aβ42/40 ratio
- p-tau217
- GFAP
- NfL

2 Calculate longitudinal changes (Δ)

Biomarker level

Δ = T3 – T1

Compute Δ for each biomarker

3 Data standardization

Z-score normalization applied to all Δ values (across all participants)

$z = \frac{x - \mu}{\sigma}$

4 Unsupervised clustering

Clustering performed on standardized Δ values

Optimal solution: k = 3 clusters

RESULTS

The **Δ-space analysis** effectively segregates patients into three distinct biological trajectories, identifying a subset of 'Rapid Progressors' (Cluster 2) that may require more intensive clinical monitoring.

A. PCA displaying cluster separation in Δ space (T3–T1) regarding plasma differences of Aβ ratio, p-tau217, NfL and GFAP

B. Co-clustering Matrix: Heatmap showing the frequency at which pairs of subjects were assigned to the same cluster across 200 bootstrap iterations. High intensity (dark red) indicates a stable grouping.

C. Longitudinal changes in plasma ATN biomarkers across identified clusters

Cluster 0 (Green - Stable/Mildly progressive): Moderate increases in neurodegeneration markers (↑↑ NfL and ↑↑ GFAP) while p-tau217 and Aβ ratio remain stable (→).

Cluster 1 (Purple - Improving/Low-risk): Significant decrease in neurodegeneration markers (↓↓ NfL and ↓↓ GFAP) and a mild, stabilizing increase in p-tau217 (↑).

Cluster 2 (Orange - Rapidly progressive): Aggressive profile with very high increases across almost all markers, particularly ↑↑ GFAP, ↑↑ NfL, and ↑↑ p-tau217

CONCLUSION

Longitudinal plasma biomarker changes (Aβ42/40, p-tau217, GFAP, NfL)

Three stable clusters identified over time (validated by bootstrap clustering)

Cluster 0 (n=77): Lower p-tau217 progression. Relatively stable GFAP and NfL.

Cluster 1 (n=88): Selective increase in p-tau217. Modest changes in GFAP and NfL.

Cluster 2 (n=27): Greater increases in p-tau217. Increased GFAP and NfL.

Cluster separation driven primarily by p-tau217, GFAP and NfL (PCA results)

Distinct longitudinal biomarker trajectories reveal heterogeneous patterns of tau pathology, astroglial activation and neurodegeneration over time.

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