

Blood-based Biomarkers As Predictors Of Longitudinal Cognitive Decline And Hippocampal Atrophy

The Vallecas Study

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Introduction

Alzheimer's disease (AD) is the predominant driver of the global dementia crisis, accounting for up to 70% of the current cases¹. AD leads to the ultimate loss of cognitive and functional independence, representing a critical public health priority that demands urgent innovation in scalable, early-stage diagnostic tools ^{1,2}. Blood-Based Biomarkers (BBMs) have emerged as a transformative alternative for large-scale clinical use³.

Aim

To perform a head-to-head comparison of the Amyloid Probability Score 2 (APS2), %p-tau217, and the Aβ42/40 ratio quantified by mass spectrometry, alongside p-tau217 measured by immunoassay (Lumipulse), within the Vallecas Project (VP) cohort.

Methods

Study Participants:

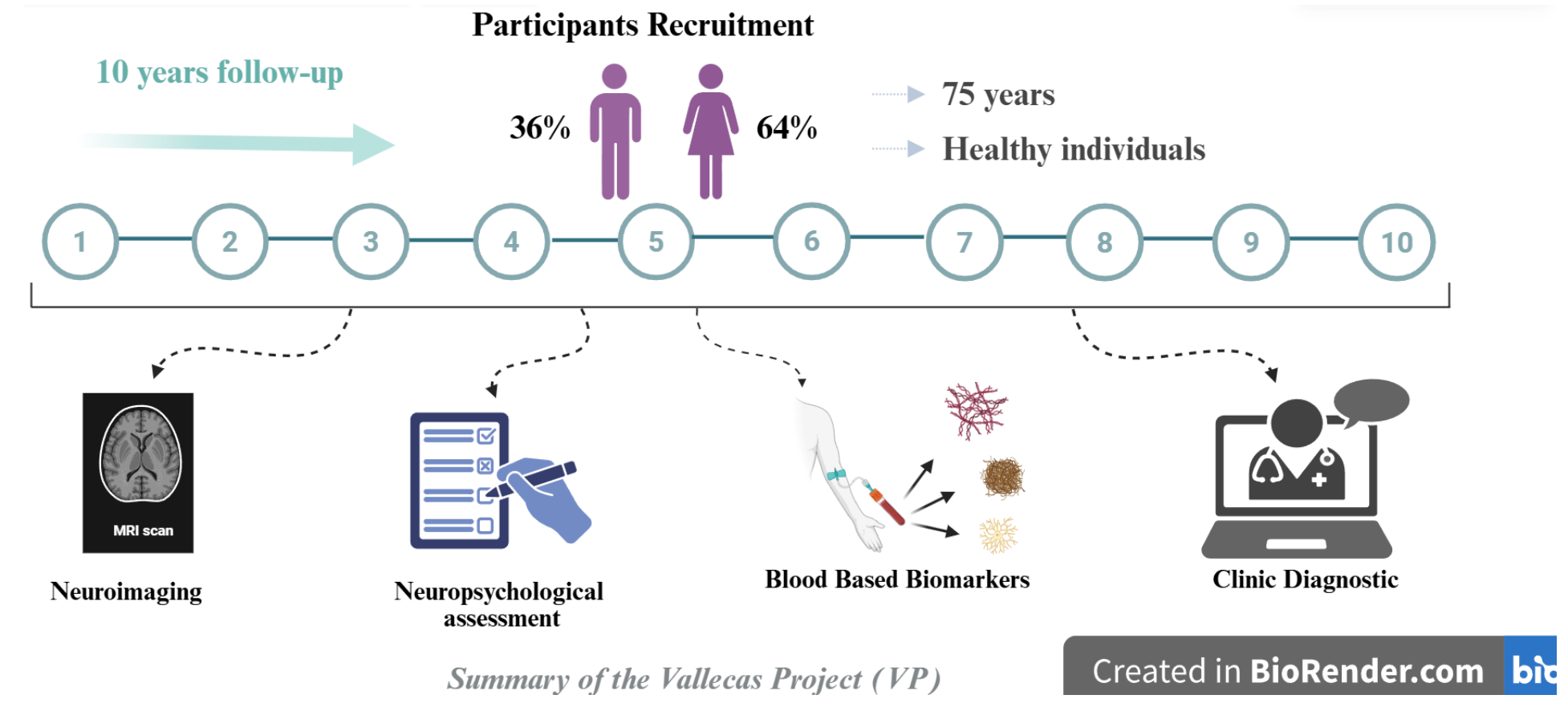
The Vallecas Project (VP) is a longitudinal, single-center, community-based study in Madrid. 1173 elderly individuals physically and cognitively healthy were enrolled.

Plasma Biomarkers:

- Mass Spectrometry (C2N diagnostics): %p-tau217 , p-tau217, Aβ42/40 ratio and APS2 Score (PrecivityAD2).
- Immunoassay (Lumipulse, Fundación CIEN): p-tau217.

Statistical Analysis:

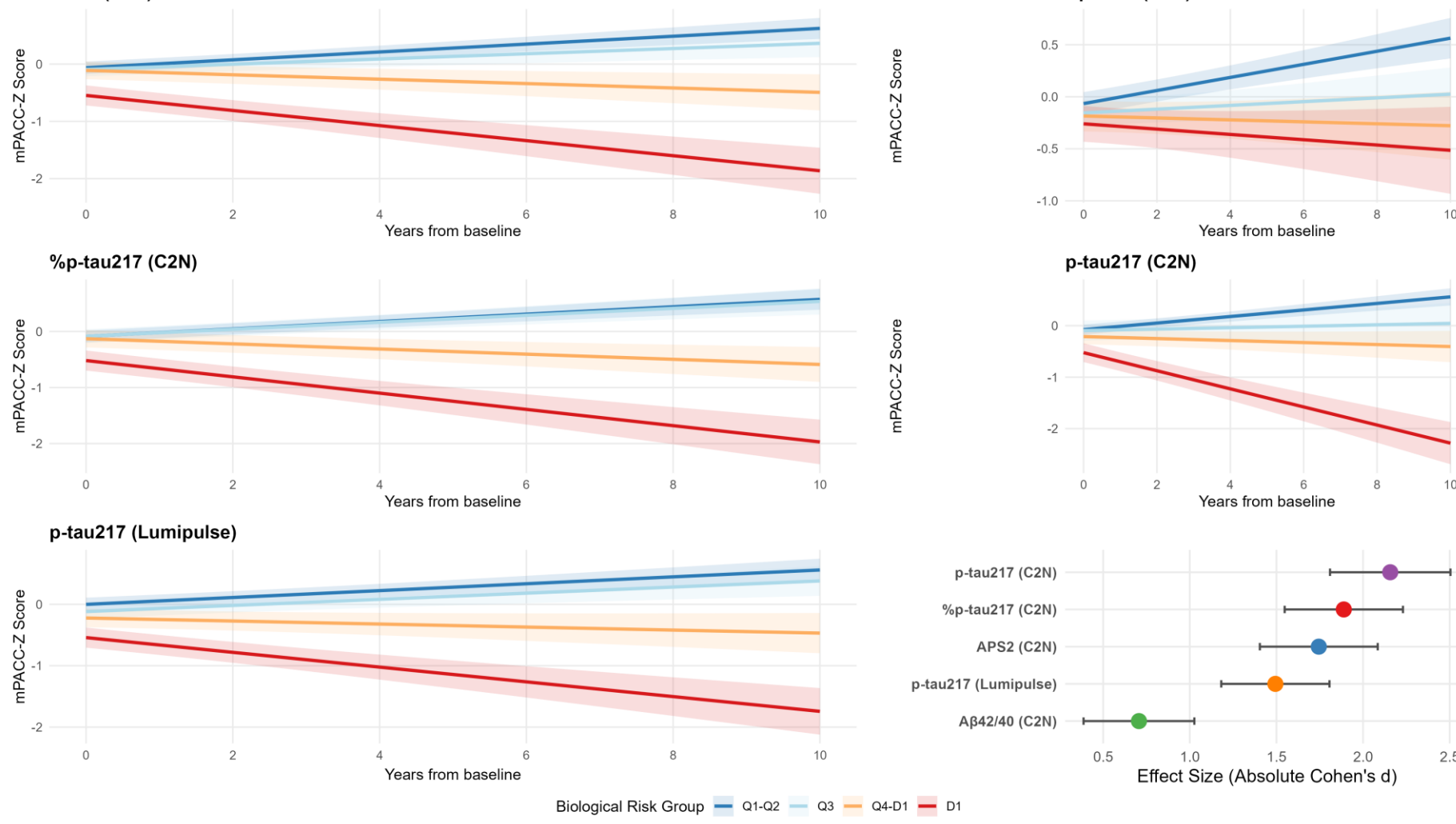
- Linear Mixed models (LMM): Cognitive decline and hippocampal atrophy.
- Cox proportional Hazard Models: clinical conversion to AD.
- Time-dependent ROC and predictive values (PPV/NPV) at 5 and 10 years.



Results

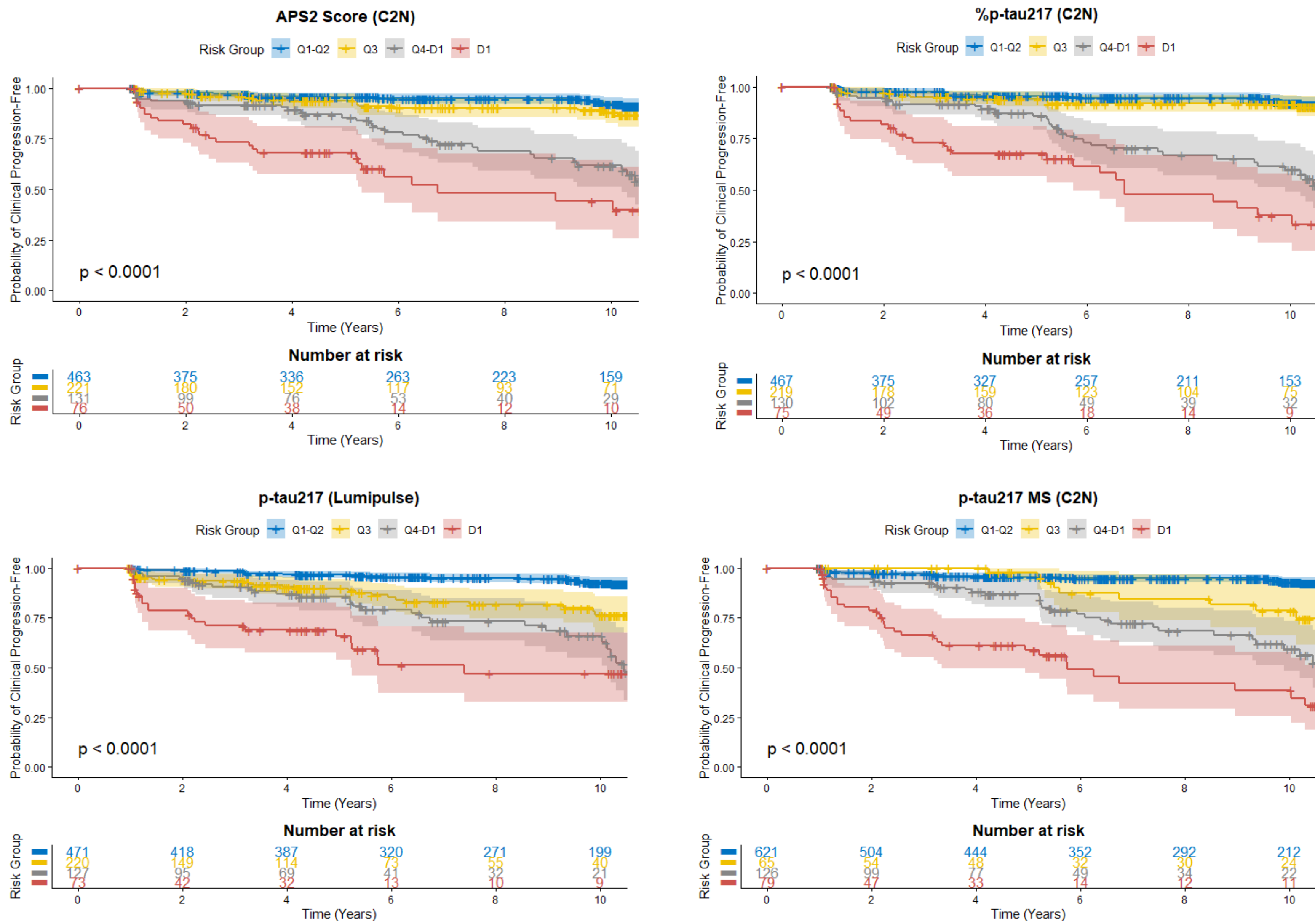
Longitudinal Cognitive Decline (mPACC)

Trapoaxes by risk group (Left) & Effect Size D1 vs Ref (Right) N=541



Clinical progression-free survival according to baseline biomarker risk groups. Kaplan-Meier curves shows the probability of remaining cognitively unimpaired over 10 years.

P-values indicate the log-rank test for differences between strata. Risk groups were defined by quantiles (Q1-Q2: <50%; Q3:50-75%; Q4-D1:75-90%;D1>90%).



For Aβ42/40 ratio, groups were defined by inverted values, such that D1 represents the highest pathological risk as in the rest of the biomarkers.

Table 1. Multivariable Cox proportional hazards models predicting clinical progression.

Basic Model adjusted by age, sex, education and A4 carriers (n participants= 891; n events= 115). Fully Adjusted models: includes NFL, GFAP, MRI, mPACC covariates (n participants= 344; n events= 67).

Biomarker	HR Basic Model (95% CI)	HR Fully adjusted Model (95%CI)
p-tau217 (MS)	1.87(1.67-2.10)	1.64(1.37-1.95)
%p-tau217	1.83(1.63-2.06)	1.65(1.40-1.94)
APS2 score	1.88(1.65-2.16)	1.70(1.41-2.05)
Aβ42/40 ratio	1.25(1.04-1.50)	1.24(0.96-1.60)
p-tau217 (Lumipulse)	1.08(0.95-1.22)	2.21(1.25-3.91)

Table 2. Clinical utility for High-Risk stratification. Prognostic Accuracy in the Top decile (D1).

N participants= 797, n events= 114.

Biomarker	NPV at 5 years (%)	PPV at 10 years (%)
p-tau217 (MS)	94.6 (92.9-96.4)	57.6 (41.5-73.7)
%p-tau217	94.3 (92.5-96.1)	66 (49.5-82.5)
APS2 score	94 (92.2-95.9)	56.4 (40-72.8)
Aβ42/40 ratio	91.4 (89.2-93.5)	24.4 (11.7-37.1)
p-tau217 (Lumipulse)	94 (92.2-95.9)	57.5 (40.6-74.4)

Table 3. Incremental predictive value (Time-dependent AUC) at 5 years.

N participants= 797, n events= 114.

Biomarker	tAUC at 5 years (CI 95%)
p-tau217 (MS)	0.820 (0.754-0.880)
%p-tau217	0.803 (0.735-0.866)
APS2 score	0.788 (0.715-0.852)
Aβ42/40 ratio	0.723 (0.649-0.791)
p-tau217 (Lumipulse)	0.724 (0.653-0.797)

Conclusions

The survival analysis indicates that APS2 prognostic power in the Vallecas Project cohort is primarily driven by the p-tau217 component. Although, APS2 demonstrated strong associations with cognitive decline and clinical conversion, it was statistically indistinguishable from p-tau217 measured by mass spectrometry and %p-tau217 across all metrics.

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