

Prognostic Value Of Plasma p-Tau217 And Amyloid PET For Predicting Clinical Progression

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Introduction

- Amyloid- β (A β) positron emission tomography (PET) often fails to predict near-term cognitive decline, limiting its prognostic value in Alzheimer's disease (AD).
- In line with AD's proposed pathophysiological cascade of an A β -triggered tau phosphorylation response, plasma p-tau217 is more closely linked to subsequent cognitive decline than A β burden.
- Incorporating this cascade into disease progression models, rather than treating p-tau217 as an interchangeable proxy for A β , may therefore improve AD risk stratification.

Methods

- Multicohort longitudinal study: n = 2,902; 5 cohorts (ADNI, A4, HABS-HD, BICWALZS, and WRAP).
- 822 cognitively impaired and 2,080 cognitively unimpaired individuals at baseline.
- Baseline: A β PET Centiloid scale, plasma p-tau217 and clinical dementia rating scale (CDR).
- Impairment defined as CDR sum of boxes (CDR-SB) > 0 and no impairment as CDR-SB = 0.
- Follow-up (up to 6 years): progression defined as any increase in CDR-SB or worsening diagnosis.
- Sensitivity analysis for Mild Cognitive Impairment (MCI) conversion to dementia, using Global CDR of 0.5 converting to 1.0.
- Cox proportional hazards models and Kaplan-Meier analyses of progression-free survival.
- Biomarker positivity thresholds: A β PET Centiloid $\geq$ 20; p-tau217 z-score $\geq$ 1.

Results

Groupings	(n)	HR (95% CI)	P value	AR (95% CI)
Impaired				
A β - p-tau217- (351)		Ref.	Ref.	26.5% (22.0 - 31.4)
A β + p-tau217- (115)		1.06 (0.71 - 1.58)	1.00	29.6% (21.4 - 38.8)
A β - p-tau217+ (57)		1.53 (0.96 - 2.45)	0.4395	40.4% (27.6 - 54.2)
A β + p-tau217+ (299)		3.57 (2.76 - 4.62)	<0.0001	70.6% (65.0 - 75.7)
MCI to dementia				
A β - p-tau217- (282)		Ref.	Ref.	4.3% (2.2 - 7.3)
A β + p-tau217- (76)		0.97 (0.31 - 3.02)	1.00	5.3% (1.5 - 12.9)
A β - p-tau217+ (40)		2.63 (0.83 - 8.34)	0.6039	10.0% (2.8 - 23.7)
A β + p-tau217+ (168)		8.02 (4.17 - 15.43)	<0.0001	33.9% (26.8 - 41.6)
Unimpaired				
A β - p-tau217- (796)		Ref.	Ref.	13.1% (10.8 - 15.6)
A β + p-tau217- (420)		1.21 (0.89 - 1.64)	1.00	18.8% (15.2 - 22.9)
A β - p-tau217+ (132)		2.56 (1.73 - 3.77)	<0.0001	27.3% (19.9 - 35.7)
A β + p-tau217+ (732)		3.09 (2.42 - 3.95)	<0.0001	41.8% (38.2 - 45.5)

Table 1. Hazard ratios and progression risk across all four biomarker profiles. Hazard ratios (HRs) with 95% confidence intervals (CIs) are shown across biomarker profiles, with arrows indicating values beyond the axis limits. P values are derived from Wald tests of model coefficients and Bonferroni-corrected within each group-specific Cox model across all reported coefficients. Models were adjusted for age, sex, and education, and stratified by study cohort. Absolute risk (AR) is also reported with 95% CIs. The double-positive profile was associated with a significantly higher risk of progression, whereas the profile positive for A β PET and negative for p-tau217 was not associated with increased risk and comprised a substantial proportion of A β PET-positive individuals (27.8% of impaired and 36.5% of unimpaired participants).

Δ C-index

- We compared two nested Cox proportional hazards models (adjusted for age, sex, and education, and stratified by study cohort): a base model using continuous Centiloid values and an augmented model that added plasma p-tau217 values.
- p-tau217 significantly improved discrimination: Δ C-index was 0.0206 (95% CI, 0.0078–0.0333; P = 0.0015) in the cognitively impaired group, 0.0480 (95% CI, 0.0253–0.0707; P < 0.0001) in the MCI-to-dementia sub-analysis, and 0.0259 (95% CI, 0.0147–0.0370; P < 0.0001) in the cognitively unimpaired group.

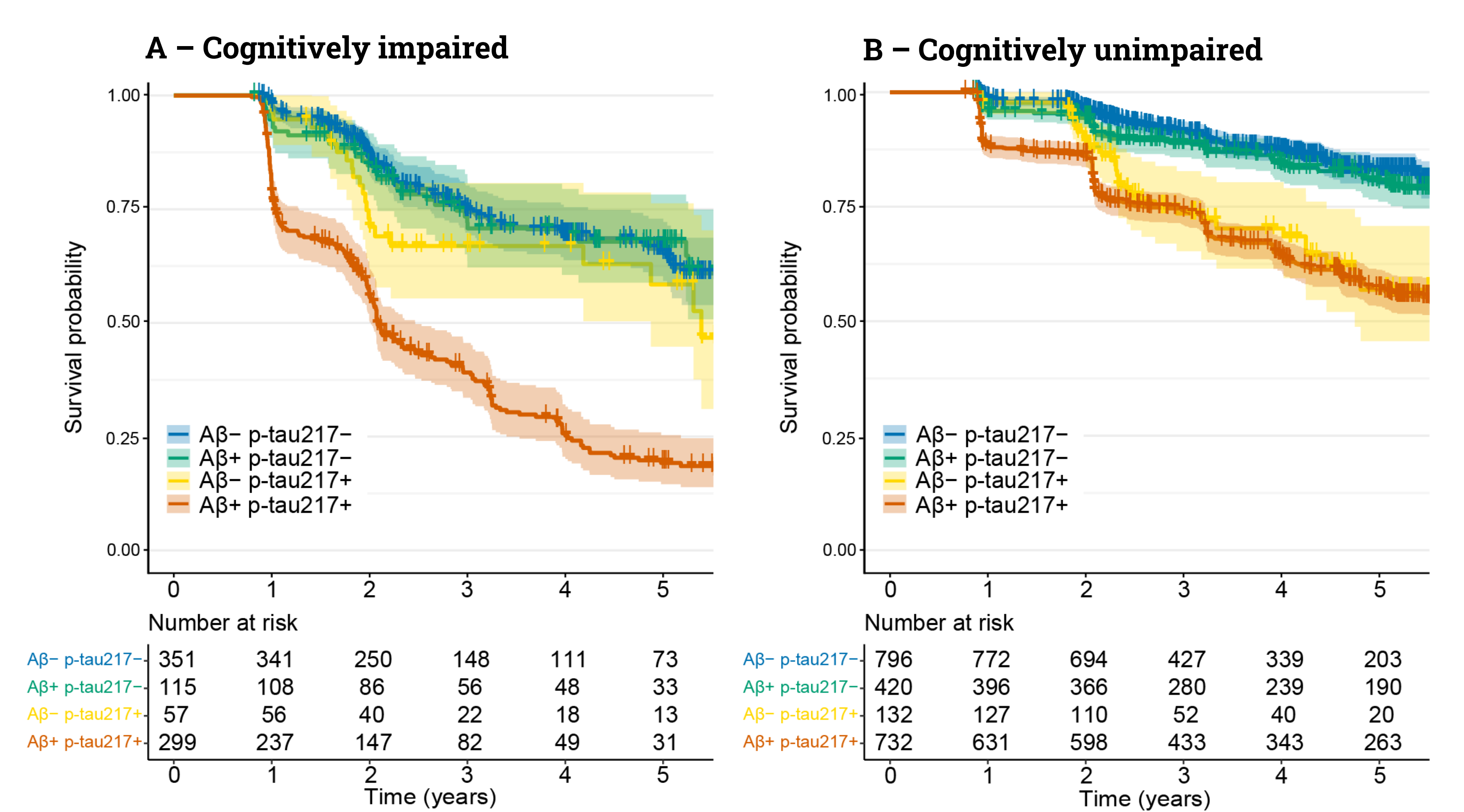
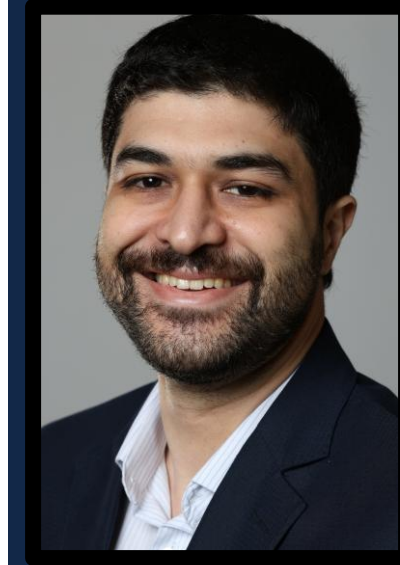


Figure 1. Progression-free survival curves across all four biomarker profiles. Kaplan–Meier estimates of progression-free survival across biomarker profiles defined by A β PET and plasma p-tau217 status in participants classified at baseline as (a) cognitively impaired and (b) cognitively unimpaired. Double-positive individuals (A β PET+/p-tau217+) show the shortest progression-free survival, whereas A β PET+/p-tau217- individuals show survival comparable to that of the double-negative group.

Conclusion

Plasma p-tau217 refines prognostic stratification beyond establishing A β positivity, even when amyloid burden is modeled continuously. Our results support a complementary, dual-biomarker framework in which A β PET confirms amyloid status and plasma p-tau217 adds clinically relevant prognostic information to support risk stratification and participant selection in clinical trials.

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Get to know our lab

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