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Plasma p-tau217 Identifies Alzheimer's Pathology 15+ Years Before Death Regardless of Co-pathologies, Age, or Disease Stage

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BACKGROUND

The Alzheimer's Association practice guidance now supports validated blood biomarkers in the diagnostic workup of suspected AD, and blood-based biomarkers are being positioned as core diagnostic tools for sporadic Alzheimer's disease, yet their validation has largely relied on clinical diagnosis or proximal antemortem sampling.

Autopsy remains the definitive reference for AD. How early plasma reflects eventual pathology, and whether performance holds across demographic and pathologic heterogeneity, remain poorly defined. Here, we linked antemortem plasma p-tau217, p-tau181, GFAP and NfL to standardized neuropathology in 473 autopsied participants, the largest and longest-followed cohort to date for sporadic AD.

METHODS

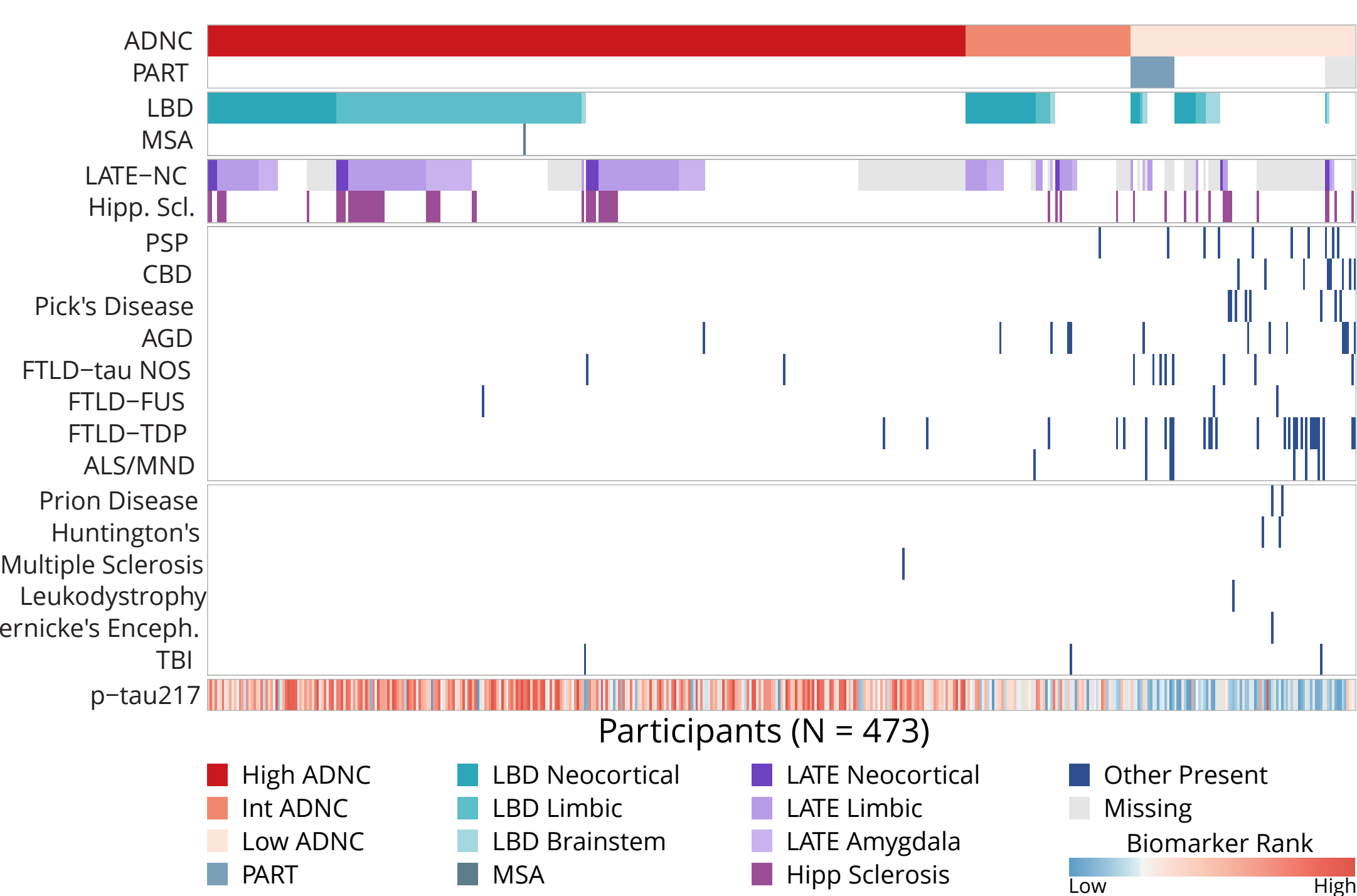
- 473 autopsied participants with sporadic disease from the Pitt ADRC: 93 Low, 68 Intermediate, 312 High ADNC
- Plasma p-tau217, p-tau181, GFAP and NfL measured on Simoa platform at the visit closest to death. All longitudinal samples retained for trajectory models.
- Primary outcome: discrimination of Intermediate/High vs Low ADNC, with autopsy as the reference standard.
- Statistical Analysis: ROC / AUC (DeLong), mixed-effects trajectories vs time-to-death, prespecified subgroup AUCs, and Cox models for dementia conversion.

COHORT DEMOGRAPHICS

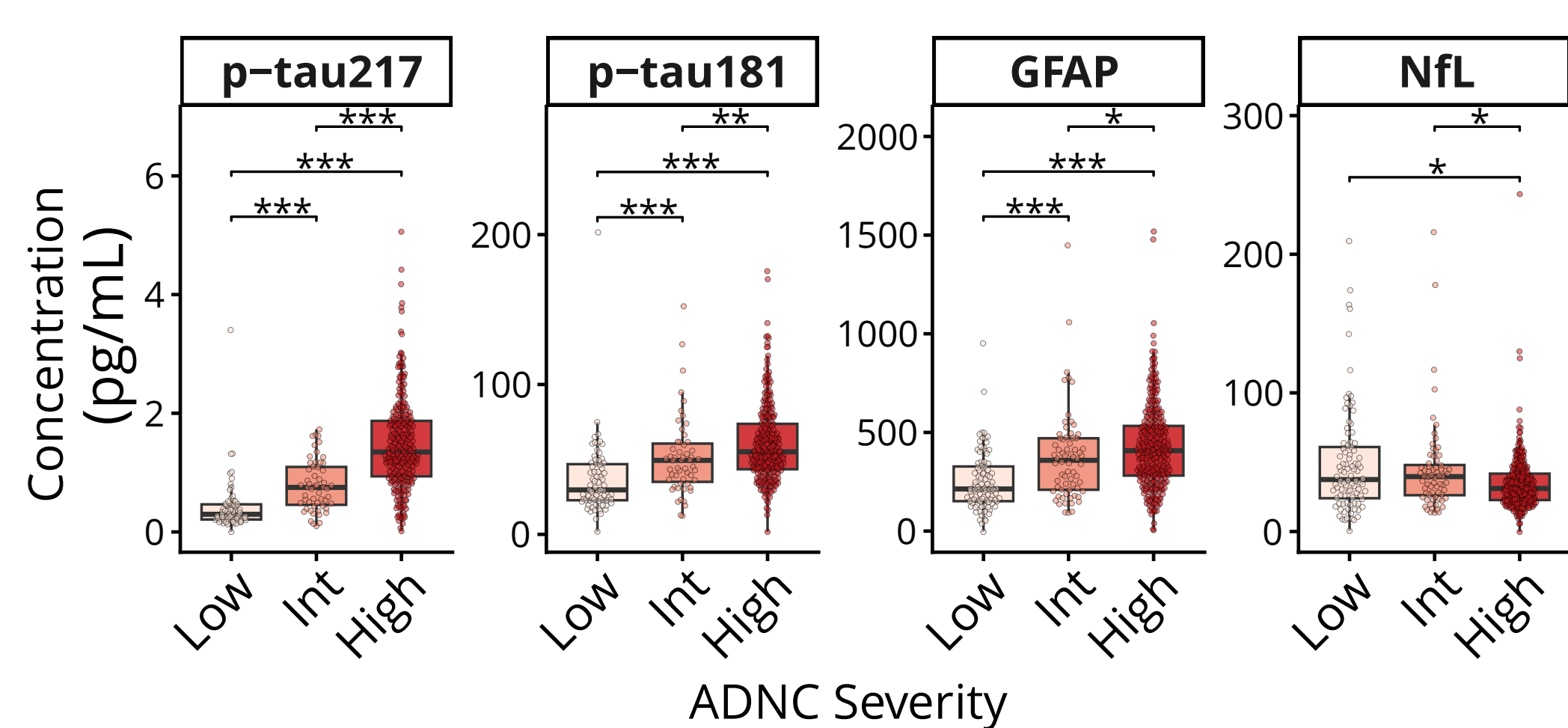
	Low ADNC	Int ADNC	High ADNC	p
N	93	68	312	
Age at death, y	74.6 (11.7)	83.9 (7.7)	77.5 (10.6)	<0.001
Blood-to-autopsy, y	5.9 (4.5)	5.1 (3.6)	6.2 (3.5)	0.021
MMSE	21.8 (6.1)	21.7 (5.8)	18.6 (6.2)	<0.001
Education, y	14.5 (3.3)	14.8 (3.8)	14.6 (3.2)	0.874
Female Sex	34 (36.6%)	29 (42.6%)	171 (54.8%)	0.004
APOE ε4 carrier	26 (28.3%)	35 (51.5%)	203 (65.1%)	<0.001

Continuous: mean (SD). Categorical: n (%).

COHORT PATHOLOGY MAP

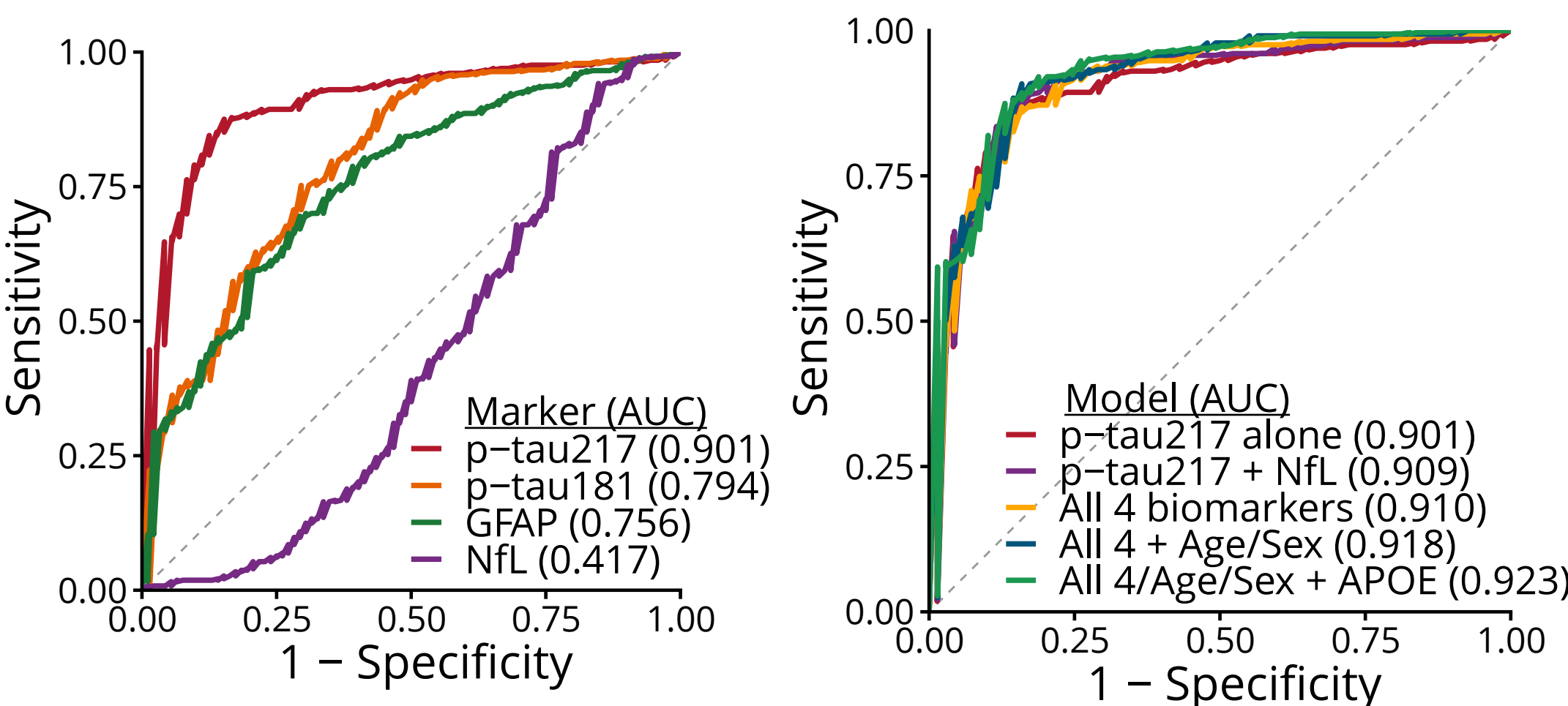


PLASMA BIOMARKERS ACROSS ADNC SEVERITY



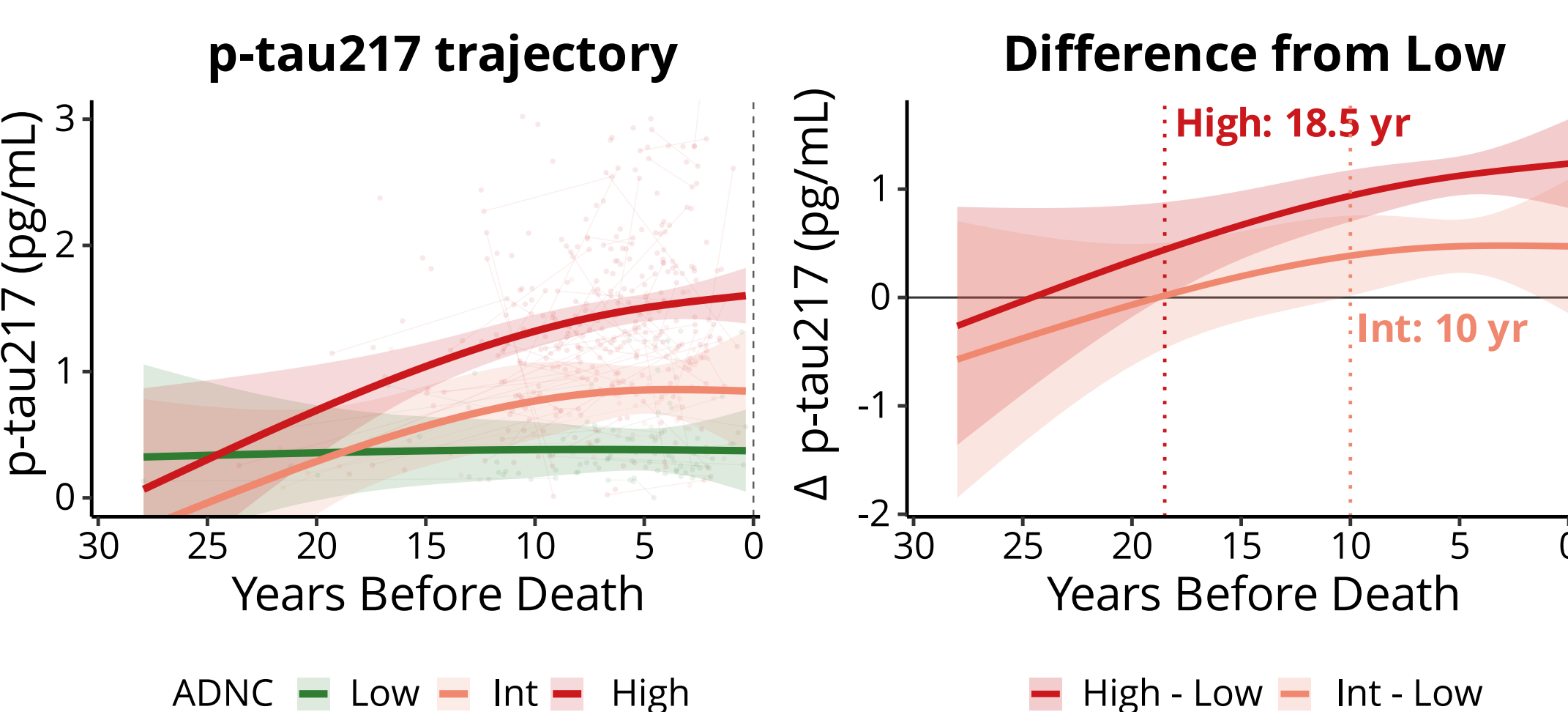
p-tau217, p-tau181 and GFAP rise with ADNC severity, NfL does not

DISCRIMINATION OF AUTOPSY-CONFIRMED ADNC

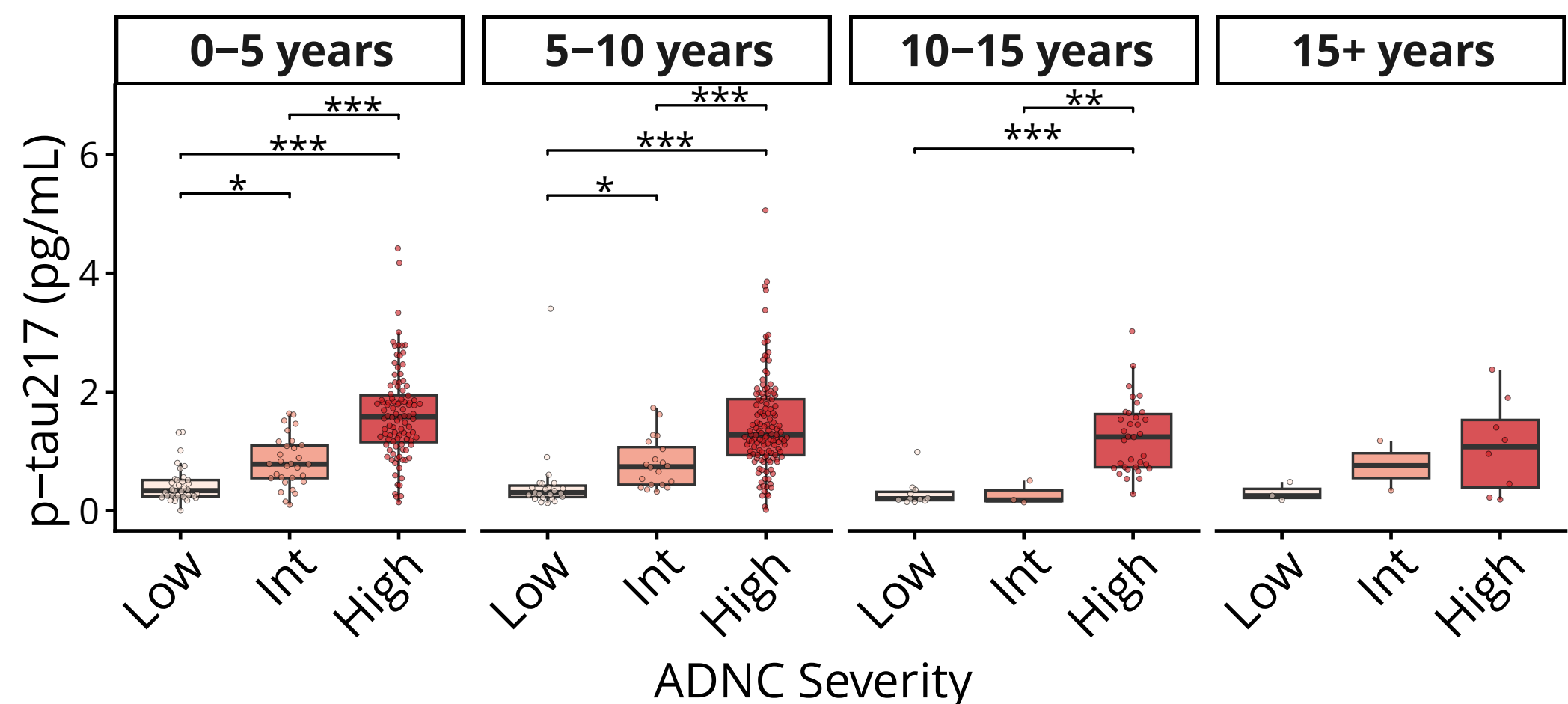


p-tau217 separates Intermediate/High from Low ADNC at AUC 0.901 (0.861–0.941), above p-tau181 (0.794), GFAP (0.756) and NfL (0.417). Combining markers, demographics, and APOE genotype added little (0.901 to 0.923).

DETECTABLE NEARLY TWO DECADES BEFORE DEATH



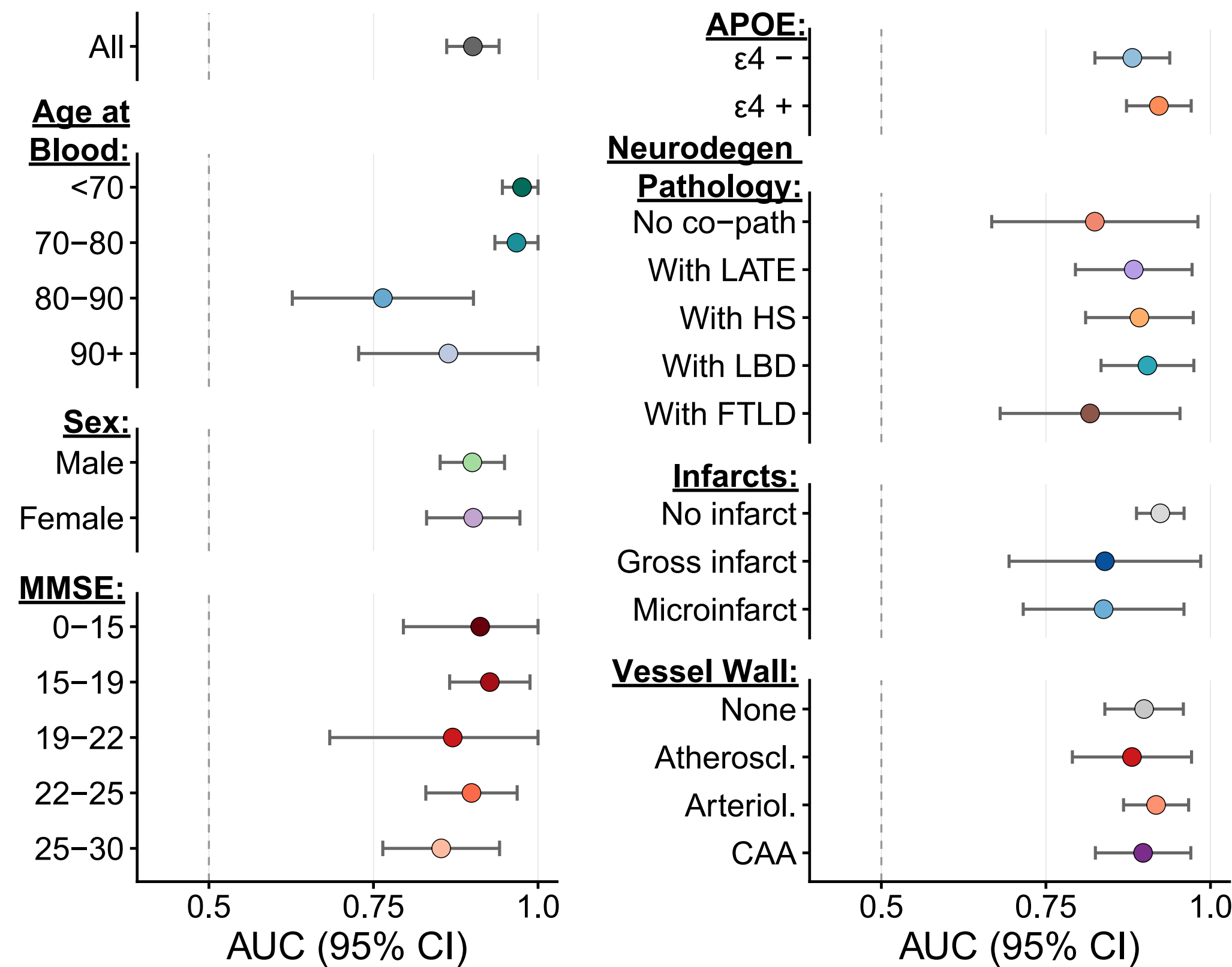
Modeled p-tau217 separates future High ADNC from Low ADNC 18.5 years before death and Intermediate ADNC 10.0 years before death.



Separation holds at every blood-to-death interval, AUC 0.90–0.91 from 0–5 through 10–15 years

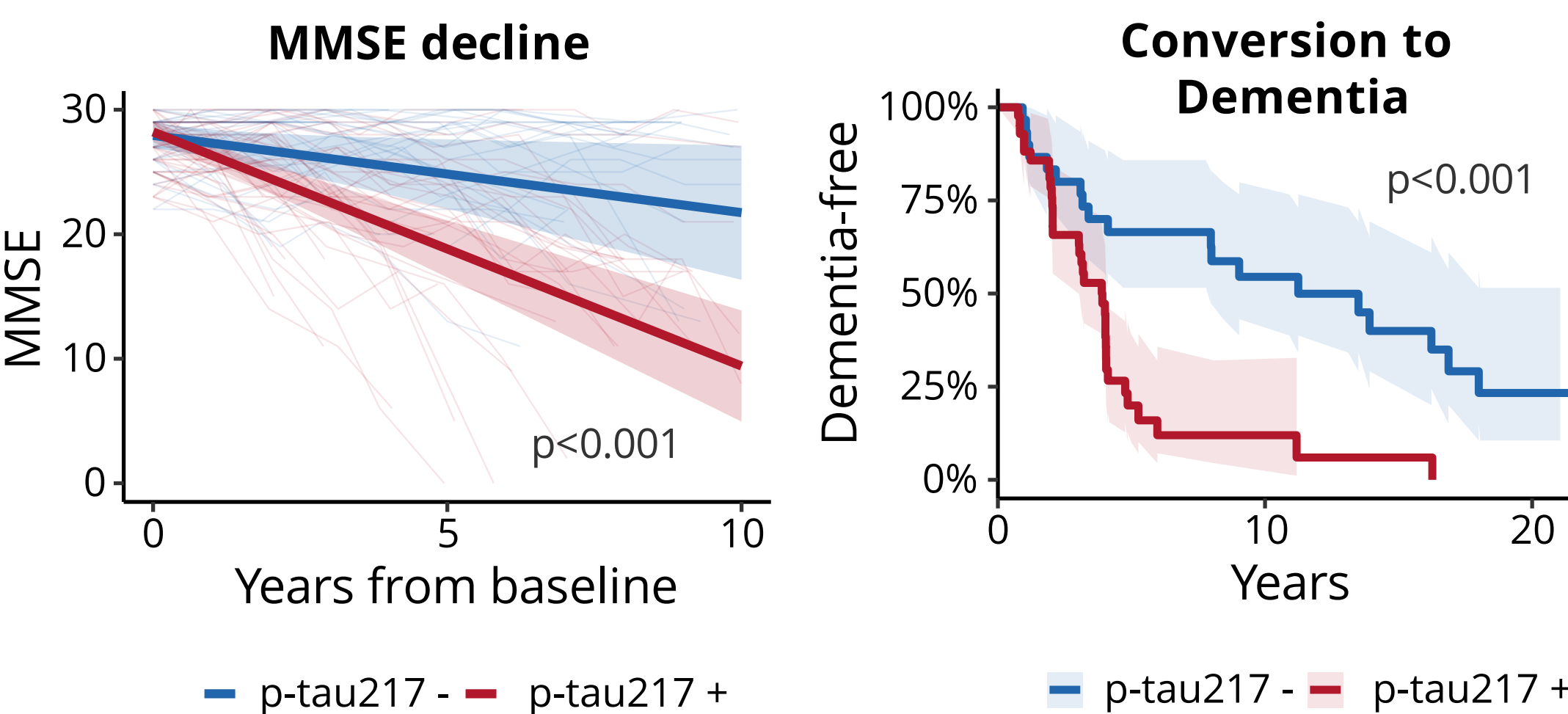
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ROBUST ACROSS HETEROGENEITY



p-tau217 AUC holds across sex, age, APOE, near-normal cognition (MMSE 25–30, AUC 0.852), co-pathology (LBD 0.904, LATE-NC 0.883, FTLD 0.817) and vascular disease (infarcts, CAA, arteriolosclerosis).

PREDICTS COGNITIVE DECLINE AND DEMENTIA



Among participants non-demented at baseline, p-tau217 positivity predicts steeper MMSE decline (left) and a 3.4-fold higher hazard of progression to dementia (right, HR 3.43, 1.80–6.54).

CONCLUSIONS

Strong Discrimination: Plasma p-tau217 separated Int/High ADNC from low ADNC with an AUC of 0.901, outperforming p-tau181, GFAP and NfL.

Early and durable: The signal was present 18.5 years before death and remained stable across blood-to-death intervals through 15 years

Robust: Discrimination held across age, sex, APOE genotype, cognitive stage and mixed pathology, including Lewy body disease, LATE-NC, FTLD and vascular disease.

Prognostic: Among non-demented participants, p-tau217 positivity predicted faster decline and a 3.4-fold higher hazard of dementia. Together these findings support plasma p-tau217 as a durable, autopsy anchored marker of clinically meaningful ADNC for early detection and prognosis.