

Leveraging Proteomics To Identify Novel Plasma Biomarkers That Predict Alzheimer’s Disease Progression

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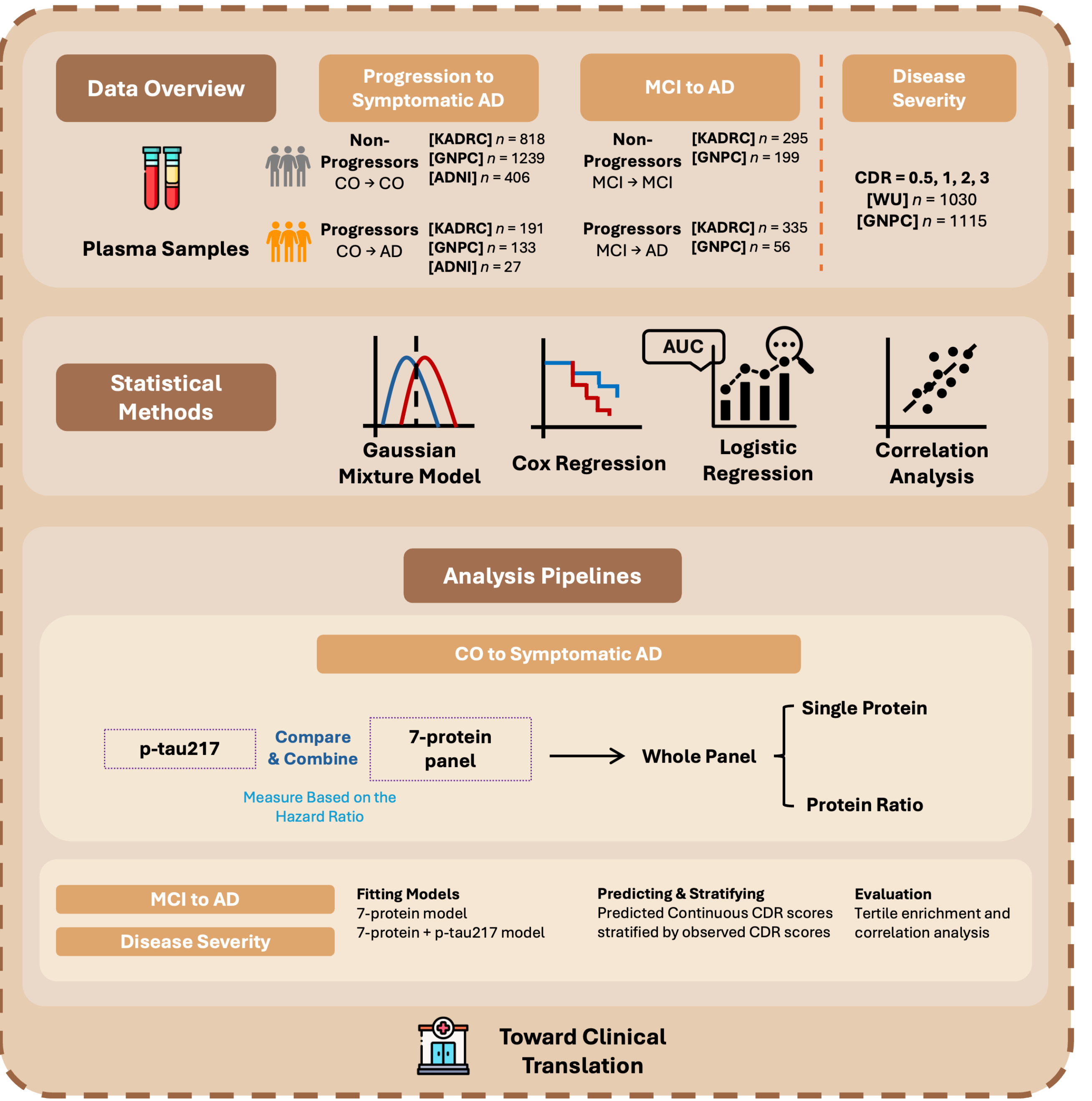
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Introduction

- AD pathology starts early:** Amyloid and tau can accumulate **15–20 years before dementia**, but symptom onset varies across individuals.
- Prediction gap:** Many people with positive amyloid or p-tau217 do not develop clinical dementia, highlighting the need for better prognostic markers.
- Beyond tau alone:** Additional plasma proteins related to **synaptic and neuronal processes** may improve risk prediction.
- Study aim:** Test whether a **7-protein plasma panel**, alone or simplified, improves prediction of progression when combined with p-tau217, with replication across cohorts and platforms.

Graphical Abstract



Methods

- Cohorts:** Discovery in Knight ADRC, with replication in GNPC and ADNI.
- Proteomics platforms:** SomaScan (Knight ADRC, GNPC) and Alamar (Knight ADRC validation, ADNI replication).
- Cutoffs:** Biomarker “low/high” defined using **Gaussian mixture modeling** (ratios computed first, then z-scored).
- Statistics:** Kaplan–Meier curves and Cox regression to estimate hazard ratios; resampling used to assess stability.
- Secondary analyses:** Applied similar framework to MCI → AD progression and cross-sectional disease severity.

Cohort	Group	Count	Female	Mean Age [SD]	APOE4+	Time to event Mean [SD]
WU	Non-Progressors	818	58.68%	72.42 [9.84]	31.78%	4.93 [3.08]
	Progressors	191	59.16%	80.10 [7.33]	36.65%	3.51 [2.46]
GNPC	Non-Progressors	1239	58.35%	65.33 [9.38]	24.37%	5.13 [2.71]
	Progressors	133	47.37%	71.86 [8.56]	17.29%	4.38 [2.60]
ADNI	Non-Progressors	406	61.33%	71.60 [6.20]	28.33%	6.69 [3.63]
	Progressors	39	48.72%	75.92 [4.15]	46.15%	5.56 [3.59]

Result

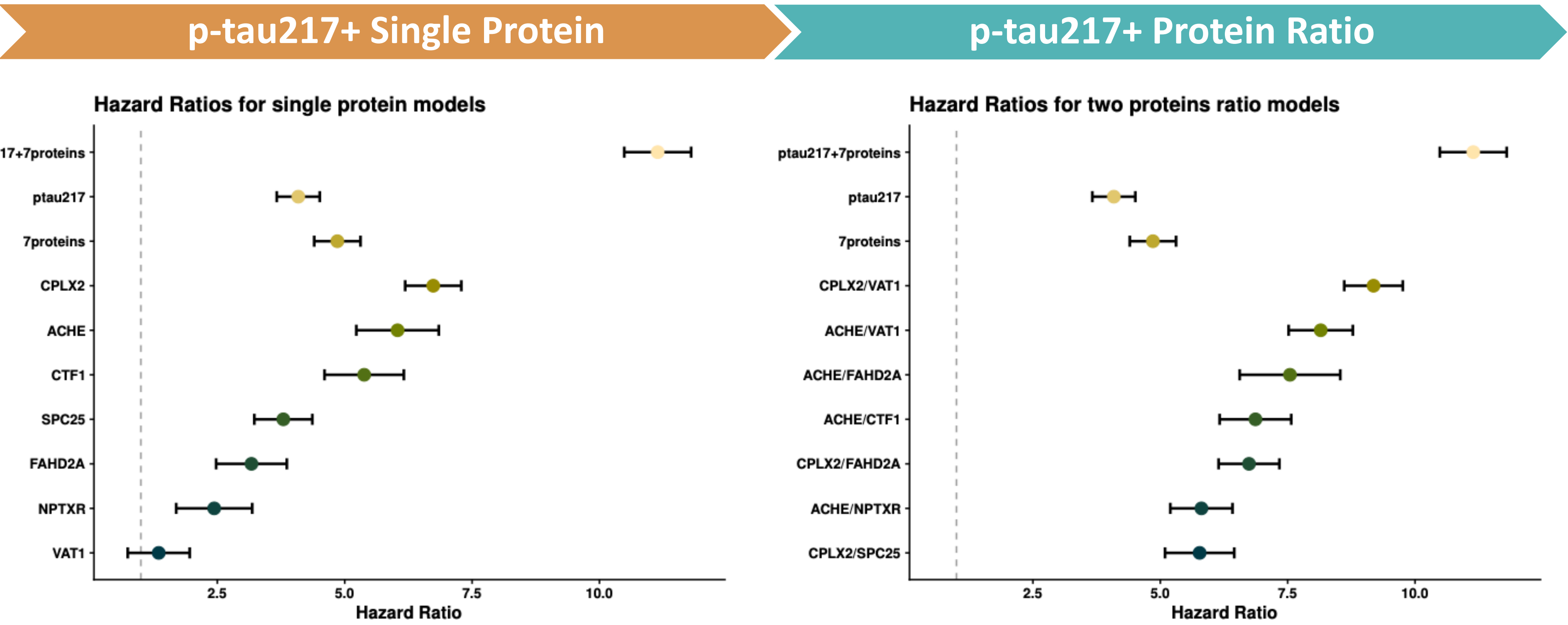


Fig1: Forest plots of hazard ratios (points) with 95% confidence intervals (error bars) for simplified models. Left: p-tau217 combined with single protein. Right: p-tau217 combined with protein ratios. Each hazard ratio was estimated from 100 repeated model iterations, and summary HRs with corresponding 95% confidence intervals are shown.

Table. 1 | Demographic information for replicate cohort

Cohort	Status	N	APOE4+ (%)	Female (%)	Mean Age [SD]	Mean Time to Event [SD]
ADNI	Non-Progressor	406	28.33	61.33	71.60 [6.20]	6.69 [3.63]
	Progressor	39	46.15	48.72	75.92 [4.15]	5.56 [3.59]

Table. 2 | Comparison of Hazard Ratios Across Cohort

	Biomarker	p-tau217	Knight-ADRC Alamar	ADNI Alamar
ACHE	+	-	0.933	17.650
	-	+	3.812	7.492
NPTXR	+	+	6.085	8.539
	-	-	0.707	1.667
	-	+	4.813	8.811
ACHE/NPTXR	+	+	3.074	8.314
	-	-	REF	REF
	+	-	9.476	6.571
ACHE/NPTXR	+	+	4.113	6.336
	-	+	4.113	6.336

Figure 2. Alamar-based replication of p-tau217 and ACHE/NPTXR ratio risk stratification. Kaplan–Meier survival curves show time to Alzheimer’s disease conversion after stratifying participants by joint p-tau217 and ACHE/NPTXR ratio status. (a) Replication using Knight-ADRC samples measured on the Alamar platform. (b) Replication using ADNI samples measured on the Alamar platform. Participants were stratified by p-tau217 and ACHE/NPTXR ratio status, with participants negative for p-tau217 grouped with biomarker-negative and biomarker-positive individuals as the reference group and compared against p-tau217-positive participants with low or high ACHE/NPTXR ratio. Across both cohorts, elevated p-tau217 and/or elevated ACHE/NPTXR ratio was associated with lower survival probability.

Conclusion

- p-tau217 alone predicted progression** from cognitively unimpaired to symptomatic AD (HR ~4), confirming its strong prognostic value.
- Adding the 7-protein panel substantially improved stratification:** the combined p-tau217 + 7-protein model separated participants into four groups, with the dual-positive group reaching HR ~11, clearly exceeding p-tau217 alone
- Simplified models retained signal but were less powerful:** the best single-protein pairing (p-tau217 + CPLX2) reached HR ~6.7, while selected two-protein ratios (e.g., CPLX2/VAT1) achieved HR ~9, approaching the full panel.
- Overall conclusion:** Integrating p-tau217 with selected plasma proteins enables **graded and reproducible risk stratification**, with simplified configurations offering translational potential for **early risk assessment and trial enrichment** in AD.