

Plasma GFAP as a predictor of mild cognitive impairment progression in cognitively normal older adults

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Background

- Plasma glial fibrillary acidic protein (GFAP) is a promising biomarker for early Alzheimer’s disease (AD).
- However, its prognostic value in predicting the conversion from cognitively normal (CN) to mild cognitive impairment (MCI) and its interactions with other biomarkers remain unclear.
- This study evaluated whether baseline plasma GFAP predicts this conversion and examined whether this relationship is moderated by other biomarkers, including amyloid beta (Aβ) 42/40 ratio, neurofilament light chain (NfL), and phosphorylated tau at threonine 217 (p-tau217).

Methods

- From the Alzheimer's Disease Neuroimaging Initiative database, we initially identified 1,303 participants with available baseline blood plasma analysis data. The following inclusion criteria were then applied: (1) baseline CN status, defined by a Mini-Mental State Examination (MMSE) score of 24–30 and a Clinical Dementia Rating (CDR) of 0; (2) a minimum longitudinal follow-up of 6 months; and (3) a clinical trajectory remaining CN or progressing to MCI at the final visit. This selection process resulted in 354 participants, with a maximum follow-up period of up to 7 years.
- Concentrations of p-tau217, Aβ42, and Aβ40 were determined using the Fujirebio Lumipulse G1200 automated immunoassay platform, while GFAP and NfL were measured via the Quanterix SIMOA HD-X high-sensitivity platform. The blood plasma values were log-transformed and z-score standardized.
- We evaluated the effect of baseline GFAP on the risk of MCI progression and the moderation effect of other biomarkers on GFAP using Cox proportional hazards model, adjusted for age, sex, and apolipoprotein ε4 allele positivity.

Results

Table 1. Association of baseline plasma glial fibrillary acidic protein levels and risk for incident mild cognitive impairment

	HR	95% CI	Wald z	p
Model A				
GFAP (1SD)	2.084	1.644, 2.642	6.069	< .001
Low	Ref			
High	2.604	1.647, 4.119	4.092	< .001
Model B				
GFAP (1SD)	1.844	1.419, 2.397	4.575	< .001
Low	Ref			
High	2.214	1.342, 3.653	3.111	.002

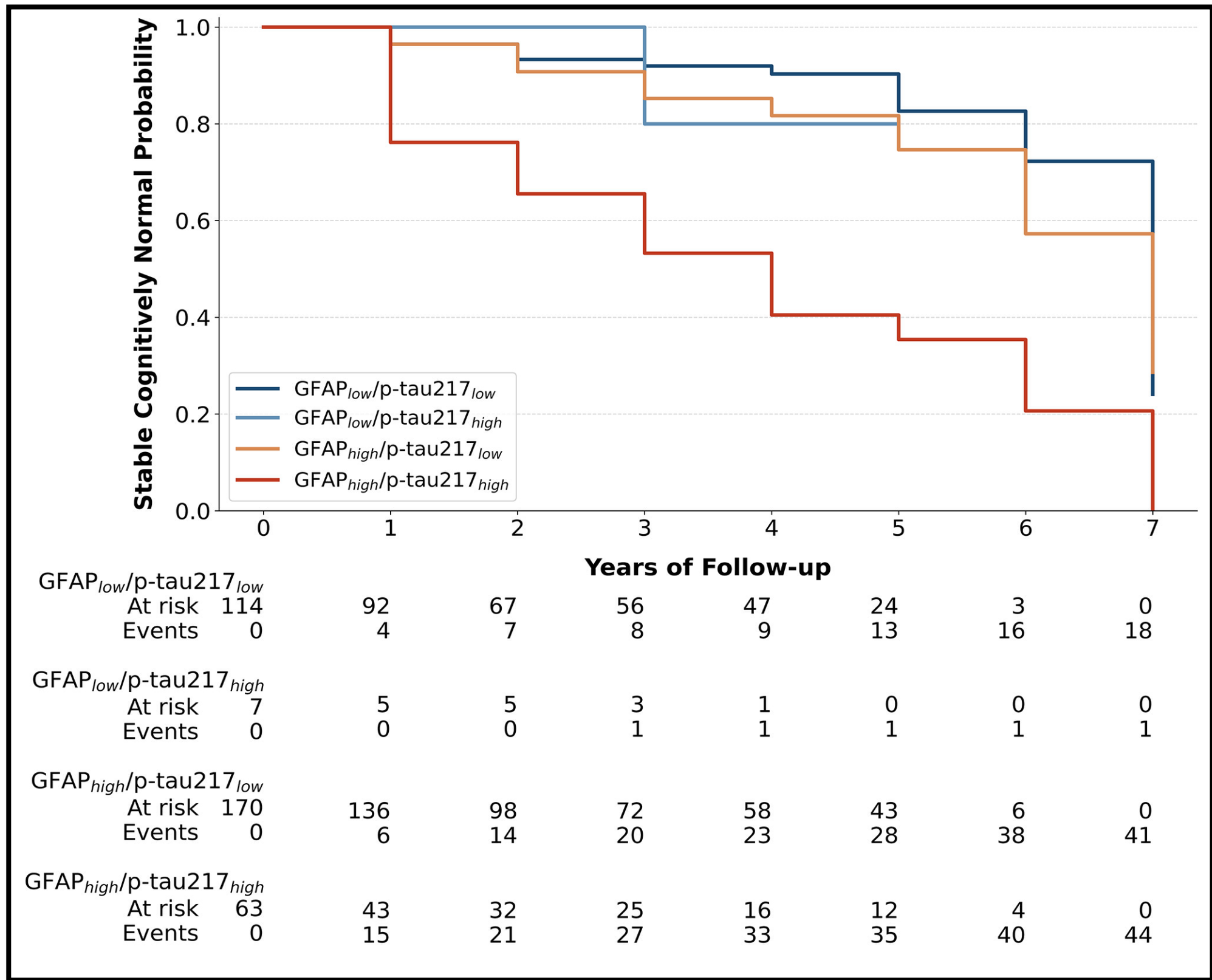
Cox proportional hazards models demonstrating the effect of baseline plasma GFAP in predicting risk for cognitively normal to mild cognitive impairment progression. Model A: Adjusted for Age, sex and APOE ε4 carrier status; Model B: Adjusted for the covariates of Model A, plus Aβ42/40 ratio, p-tau217, and NfL

Table 2. Moderation effects of plasma biomarkers on the association of glial fibrillary acidic protein on the risk of incident mild cognitive impairment

Moderator	β (interaction)	SE	z interaction	p interaction
Aβ42/40	-0.211	0.127	-1.664	.096
p-tau217	0.137	0.067	2.045	.041
NfL	-0.025	0.124	-0.202	.840

Cox proportional hazards models were used to examine the association of plasma GFAP on the risk of MCI, including interactions with other plasma biomarkers. Age, sex and APOE ε4 carrier status are included as covariates.

Figure 1. The Kaplan-Meier survival curves for mild cognitive impairment conversion according to plasma glial fibrillary acidic protein and p-tau217 levels.



Conclusion

- Plasma GFAP serves as a potent independent predictor of MCI conversion, with its prognostic strength moderated by p-tau217.
- These findings suggest that GFAP can be utilized as a clinically valuable biomarker for identifying high-risk individuals in the preclinical stage and implementing personalized monitoring strategies for AD.

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