



The Effect of Chronic Comorbidities on Predicting Amyloid Status Using Blood-Based Biomarkers

Vanderbilt Memory & Alzheimer's Center

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Background

- The diagnostic accuracy of blood-based biomarkers (BBMs) of Alzheimer's disease (AD) is known to be impacted by comorbid conditions such as chronic kidney disease and obesity. The effect of other chronic medical conditions on BBM accuracy is less understood.
- This study examines the moderating effect of various chronic medical conditions on the ability of BBMs to diagnose amyloid positivity.

Methods

- Participants:** Vanderbilt Memory and Aging Project participants, free of clinical dementia or stroke (n=154, 72±6 years, 37% mild cognitive impairment (MCI)), completed baseline fasting blood draw, lumbar puncture and self-reported medical history form; see **Table 1**.
- Biomarkers and Medical Conditions:** plasma p-tau231, glial fibrillary acidic protein (GFAP), neurofilament light (NfL), β -amyloid₄₂, β -amyloid₄₀, and β -amyloid_{42/40} were quantified using the Quanterix Simoa platform. Amyloid positivity was defined as cerebrospinal fluid A β _{42/40} ratio of <0.072. Over 25 medical conditions were assessed as present/absent.
- Statistical Analysis:** Logistic regression models related BBMs to amyloid positivity. Models included *BBM x chronic medical condition* interaction terms. Significant interactions were followed by stratified analyses to compare associations among participants with and without the condition.

Table 1. Participant Characteristics Stratified by Amyloid Status

	Combined (n=154)	No (n=82)	Yes (n=72)	p-value ^a
Age, years	72.4 ± 6.4	71.4 ± 6.0	73.5 ± 6.6	0.055
Education, years	16.1 ± 2.8	16.3 ± 2.9	15.8 ± 2.6	0.16
Race, % non-Hispanic White	7.0	9.0	6.0	<0.001
Cognitive diagnosis, %MCI	37.0	24.0	51.0	0.002
APOE-ε4, % carrier	33.0	11.0	58.0	<0.001
FSRP score	11.6 ± 3.7	10.9 ± 3.4	12.3 ± 4.0	0.04
Baseline Cerebrospinal Fluid Variables				
A β ₄₂ , pg/mL	4.8 ± 2.6	4.9 ± 2.4	4.8 ± 2.8	0.46
A β ₄₀ , pg/mL	70 ± 35	68 ± 38	74 ± 33	0.63
GFAP, pg/mL	192 ± 104	154 ± 74	236 ± 116	<0.001
NfL, pg/mL	30 ± 21	27 ± 12	33 ± 27	0.14
p-Tau ₂₃₁ , pg/mL	6.8 ± 4.4	5.5 ± 3.6	8.2 ± 4.7	<0.001
A β _{42/40}	0.10 ± 0.084	0.109 ± 0.089	0.090 ± 0.078	<0.001

Note. Values are denoted as mean±standard deviation or frequency. A β =amyloid beta; APOE=apolipoprotein E gene; FRSF; Framingham Stroke Risk Profile; GFAP=glial fibrillary acidic protein; NfL=neurofilament light; MCI=mild cognitive impairment; p-Tau231=phosphorylated Tau231; ^aWilcox's test was used for continuous variables and Pearson's chi-square test was used for categorical variables.

Table 2. Biomarker Diagnostic Strength and Amyloid Status with Comorbid Conditions

	Comorbidity	OR With (95% CI)	p-value ^a	OR Without (95% CI)	p-value
GFAP	Hypertension	1.03 (1.01-1.04)	0.0006	1.00 (0.99-1.01)	0.30
NfL	Cancer History	1.12 (0.96-1.3)	0.16	0.99 (0.97-1.01)	0.56
NfL	Hypercholesterolemia	0.96 (0.91-1.00)	0.06	1.02 (0.96-1.08)	0.49

Note. Odds ratios delineate effect size. ^aFDR-adjusted p-values represent stratified models.

Results

Interaction models:

- GFAP interacted with hypertension (p=0.01) and NfL with cancer (p=0.04) and hypercholesterolemia (p=0.03) in predicting amyloid positivity; see **Figure 1; Table 2**.
- No other *BBM x chronic medical condition* associations were significant (p>0.05).

Stratified models

- GFAP was significantly related to amyloid status in individuals with hypertension. (OR=1.03, p=0.0006) but not in those without hypertension (OR=1.00, p=0.30).
- NfL showed stronger association with amyloid positivity in participants with a history of cancer (OR=1.12 vs. 0.99) and in those without hypercholesterolemia (OR=1.02 vs. 0.96); however, neither cancer or hypercholesterolemia associations reached thresholds for statistical significance (p-values>0.05); see **Table 2**.

Figure 1. Interactions of Plasma Biomarkers with Comorbid Medical Conditions in Predicting Amyloid Status

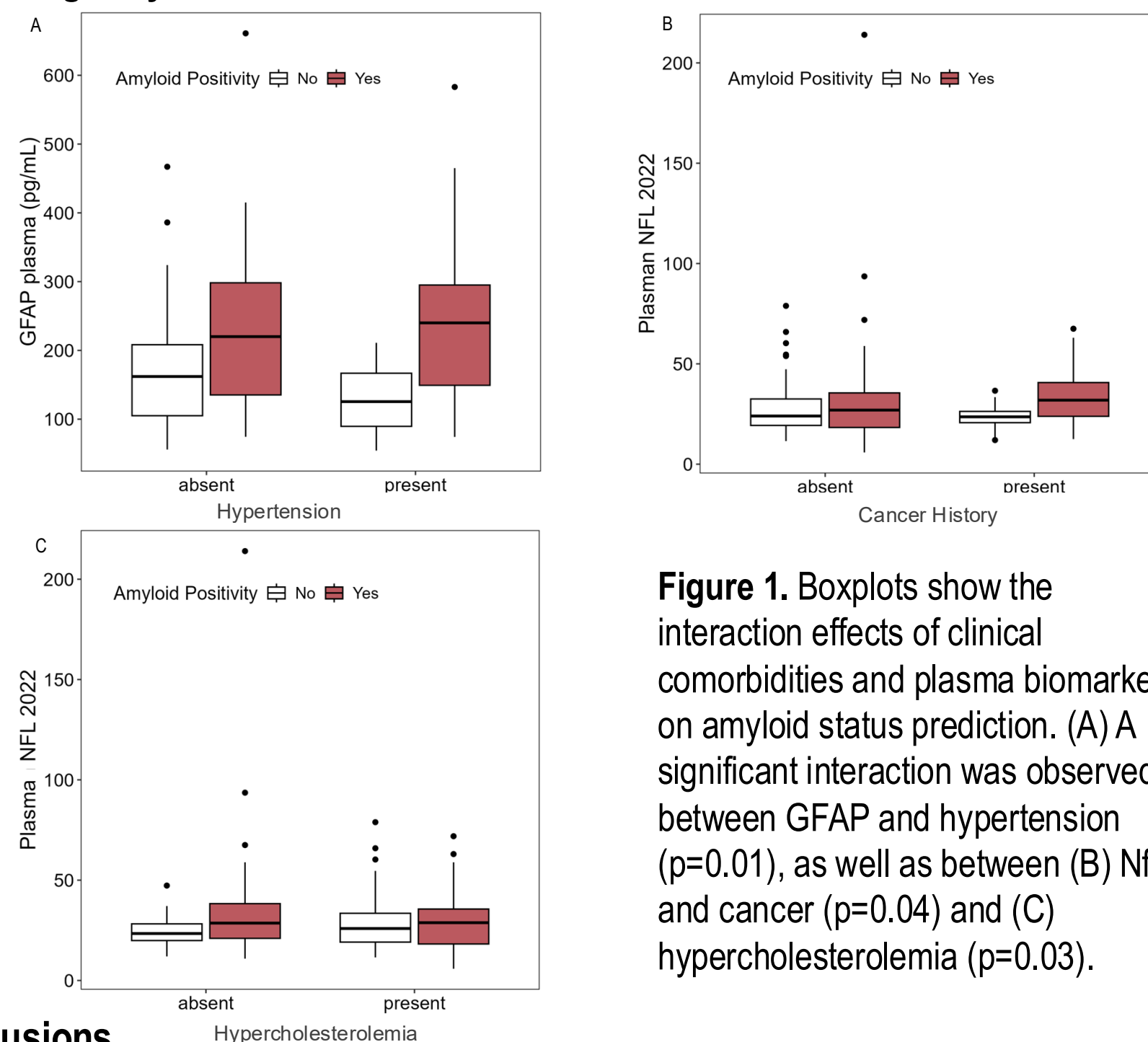


Figure 1. Boxplots show the interaction effects of clinical comorbidities and plasma biomarkers on amyloid status prediction. (A) A significant interaction was observed between GFAP and hypertension (p=0.01), as well as between (B) NfL and cancer (p=0.04) and (C) hypercholesterolemia (p=0.03).

Conclusions

- In older adults free of dementia, several chronic medical conditions modified BBM performance for diagnosing amyloid status.
- These results suggest that prevalent conditions such as hypertension can influence BBM-based detection of AD pathology.
- Further investigation is warranted to clarify underlying mechanisms and whether comorbidities similarly affect BBM prediction of other clinically relevant outcomes.