

Association Between Plasma Biomarkers And Clinical Progression In Parkinson's: Data From The Parkinson's Precision Medicine Initiative

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Plasma neurodegeneration biomarker levels measured early in the disease state associate with cognitive and motor scale scores and predict a greater risk of cognitive and functional decline but not motor decline or changes in DAT SPECT in Neuronal Synuclein Disease cases.

INTRODUCTION

RESULTS

Neuronal synuclein disease (NSD), which includes Parkinson's disease (PD) and dementia with Lewy bodies, is a neurodegenerative disorder associated with intracellular alpha-synuclein-containing Lewy Body (LB) pathology.^{1,2}

Co-occurring neurodegenerative pathologies in NSD are clinically relevant and associate with faster progression and greater symptom burden.³ Blood based markers of P-tau217 and amyloid-beta (Aβ) isoforms have comparable performance to CSF biomarkers and PET imaging to detect brain Aβ pathology in cohorts of established PD.

Plasma glial fibrillary acidic protein (GFAP) is a non-specific marker of neuroinflammation that associates with AD co-pathology,⁴ while neurofilament light chain (NfL) is a non-specific marker of axonal degeneration; Both associate with disease progression in PD.⁵

The objectives are 1) evaluate associations between neurodegeneration biomarker levels measured close to the clinical diagnosis of PD in NSD and symptom disease progression.

METHODS

PPMI Cohorts: Sporadic PD (sPD) and Healthy Control(HC) cohorts. sPD were CSF aSyn-SAA positive and HC were negative. PPMI clinical outcomes were collected for up to 11 years. Domain-based disease milestones were analyzed.⁶

P-tau-217 : Roche Elecsys immunoassay on Cobas® e 801.

Aβ40 and Aβ42: Immunoprecipitation-mass spectrometry (IP/MS) workflow (C2N Diagnostics). **GFAP and NFL**: Quanterix Simoa Platform (NCRAD).

Cohort Baseline Clinical Summary				
	Healthy Control NSD- (N = 97)	Sporadic PD NSD+ (N = 523)	p-values	
			HC vs sPD	
Sex, n (%)				
Male	57 (59%)	323 (62%)		
Female	40 (41%)	200 (38%)		
Age (years), mean (SD)	58.9 (12.4)	62.9 (12.3)		
Median (min, max)	58.4 (30.5, 81.3)	63.7 (33.7, 84.9)		
Disease Duration (years), mean (SD)	NA	0.7 (0.6)		
Median (min, max)	NA	0.5 (0.0, 3.2)		
Race, n (%)				
White	88 (91%)	485 (93%)		
Black/African American	6 (6%)	6 (1%)		
Asian	1 (1%)	10 (2%)		
Other	2 (2%)	17 (3%)		
Missing	0	3		
Revised UPDRS total score, mean (SD)	59.9 (26.5)	10.9 (13.3)		
Median (min, max)	62.5 (2.0, 100.0)	6.0 (1.0, 91.5)		
NSD+, n (%)				
2a	NA	8 (2%)		
2b	NA	74 (14%)		
3	NA	409 (78%)		
4	NA	32 (6%)		
5	NA	0		
Missing	0	0		
MDS-UPDRS total score, mean (SD)	4.2 (4.3)	34.0 (12.7)		
Median (min, max)	3 (0, 17)	33 (7, 70)		
Missing	1	0		
MoCA total score, mean (SD)	28.4 (1.2)	27.1 (2.3)		
Median (min, max)	28 (27, 30)	28 (17, 30)		
Missing	0	0		
SCOPA-AUT total score, mean (SD)	5.7 (3.7)	9.7 (5.8)		
Median (min, max)	5 (0, 18)	9 (0, 39)		
Missing	0	0		
% Aspartate-expected low putamen, mean (SD)	1.00 (0.15)	0.41 (0.14)		
Median (min, max)	1.00 (0.65, 1.35)	0.40 (0.02, 0.99)		
Missing	2	0		
Cognitive Categorization, n (%)				
Normal cognition	245 (100%)	19 (7%)		
Mild Cognitive Impairment	0	0		
Missing	0	259		

Table 2.

Plasma Biomarkers in Parkinson's Disease and Healthy Control Cohorts			
	Healthy Control NSD- (N = 97)	Sporadic PD NSD+ (N = 523)	p-values
			HC vs sPD
Ptau217, mean (SD)	0.17 (0.10)	0.18 (0.10)	0.5687
Median (min, max)	0.14 (0.06, 0.75)	0.15 (0.06, 0.90)	
Missing	1	200	
Ptau217 Tertile, n (%)			0.4192*
< 0.131	40 (41%)	109 (33%)	
0.131 - 0.174	30 (31%)	112 (34%)	
> 0.174	27 (28%)	110 (33%)	
Missing	0	192	
NFL, mean (SD)	12.03 (7.15)	13.52 (6.24)	0.2445****
Median (min, max)	10.60 (3.13, 49.85)	12.26 (3.77, 62.67)	
Missing	0	1	
NFL Tertile, n (%)			0.0695*
< 9.877	44 (45%)	172 (33%)	
9.877 - 14.538	33 (34%)	163 (31%)	
> 14.538	20 (21%)	187 (36%)	
Missing	0	1	
GFAP, mean (SD)	84.76 (58.45)	98.70 (55.51)	0.1372***
Median (min, max)	66.56 (19.75, 403.48)	87.19 (14.55, 531.82)	
Missing	0	1	
GFAP Tertile, n (%)			0.0305*
< 64.478	45 (46%)	144 (28%)	
64.478 - 105.341	30 (31%)	191 (37%)	
> 105.341	22 (23%)	187 (36%)	
Missing	0	1	
C2N Aβ40, mean (SD)	NA	387.67 (59.12)	NA
Median (min, max)	NA	391.32 (209.95, 538.38)	
Missing	97	423	
C2N Aβ40 Cutoffs, n (%)			NA
< 374.886	0	37 (37%)	
374.886 - 422.785	0	40 (40%)	
> 422.785	0	23 (23%)	
Missing	97	423	
C2N Aβ42, mean (SD)	NA	43.31 (7.54)	NA
Median (min, max)	NA	42.74 (27.75, 68.55)	
Missing	97	423	
C2N Aβ42/40, mean (SD)	NA	0.11 (0.02, 0.20)	NA
Median (min, max)	NA	0.11 (0.09, 0.20)	
Missing	97	423	
C2N Aβ42 Cutoffs, n (%)			NA
< 40.219	0	32 (32%)	
40.219 - 45.870	0	37 (37%)	
> 45.870	0	31 (31%)	
Missing	97	423	

* P-values calculated using PROC LOGISTIC adjusted for age and sex.
*** P-values calculated using a log-transformed model.
**** P-values calculated using a square-root-transformed model.
***** P-values calculated using a squared-value (power-2) transformation.
***** P-values calculated using a rank-based nonparametric model.

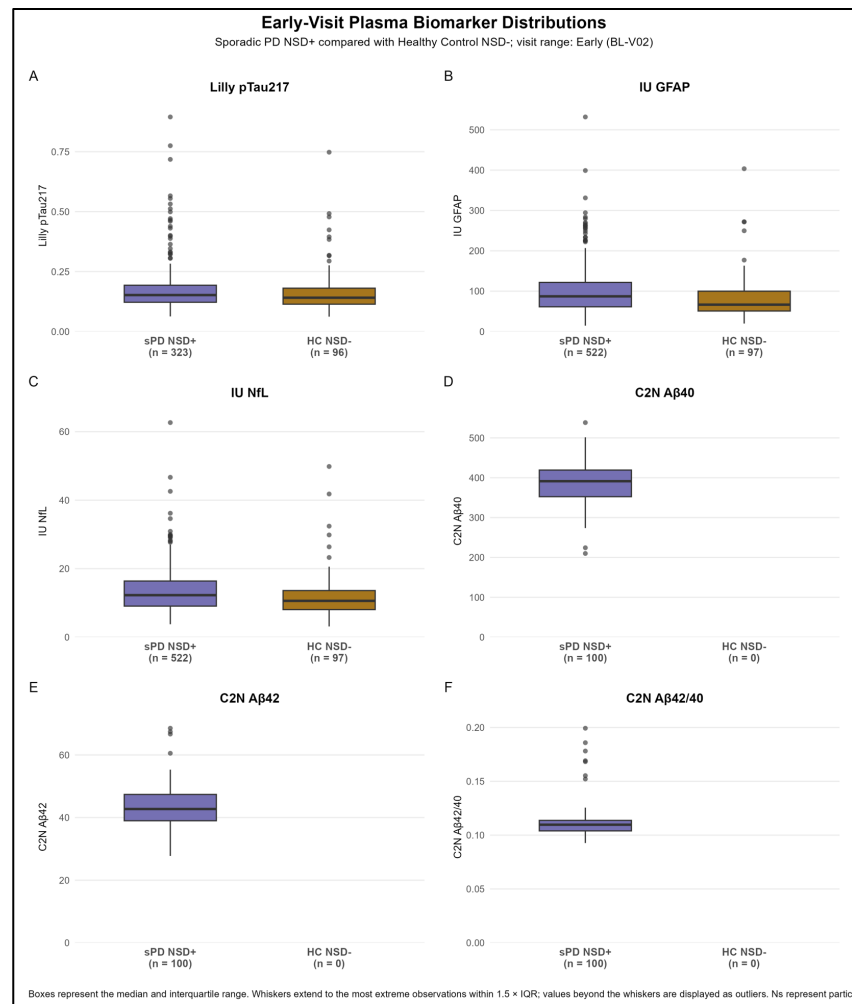


Figure 1 (ABOVE): Box and Whisker Plots showing the median (IQR) for all biomarkers measured in sporadic Parkinson's disease (sPD) and Healthy Control (HC) Cohorts. No differences are identified between groups for any biomarker.

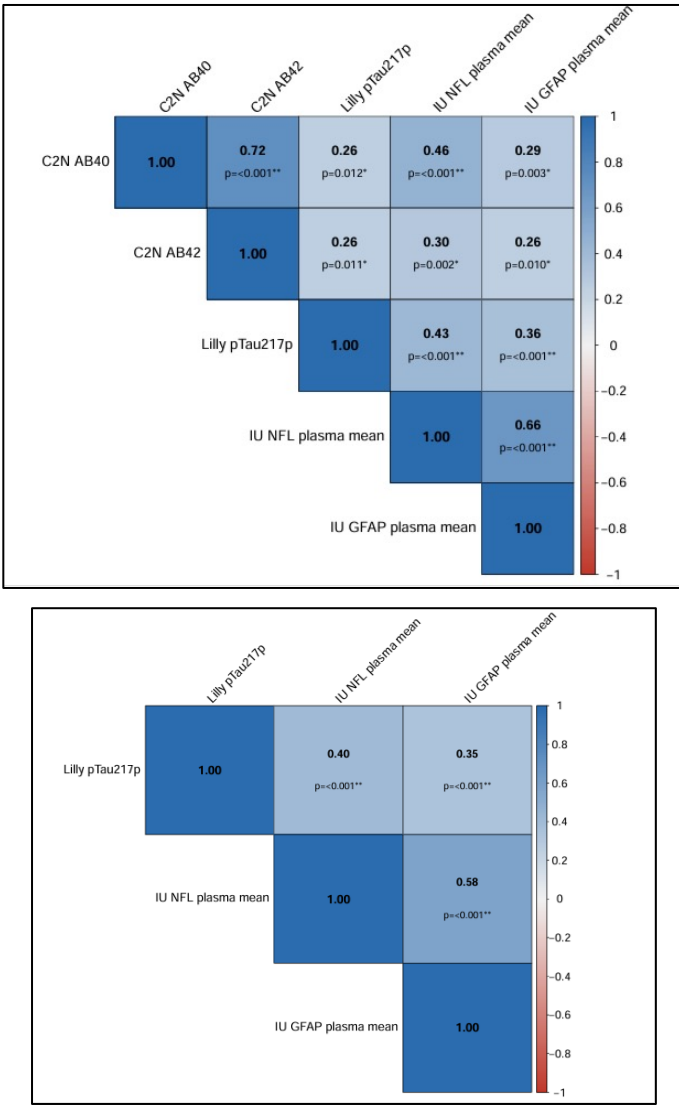


Figure 2 (ABOVE): Correlograms showing Spearman correlation coefficients in sporadic PD (TOP) and Healthy Control (Bottom) cohorts. Blue indicates positive correlation, Red indicates negative correlation. P-values are shown below each correlation coefficient.

Figure 3 (LEFT): Association between biomarker tertile and cognitive outcomes in PD cohort. Left shows predicted curves of linear mixed effects models (Age, Sex, baseline MoCA corrected) for each biomarker. Right shows Cox Proportional Hazards models (Age, Sex corrected) for risk of a cognitive composite outcome. Omnibus test and pairwise comparisons are shown below graphs.

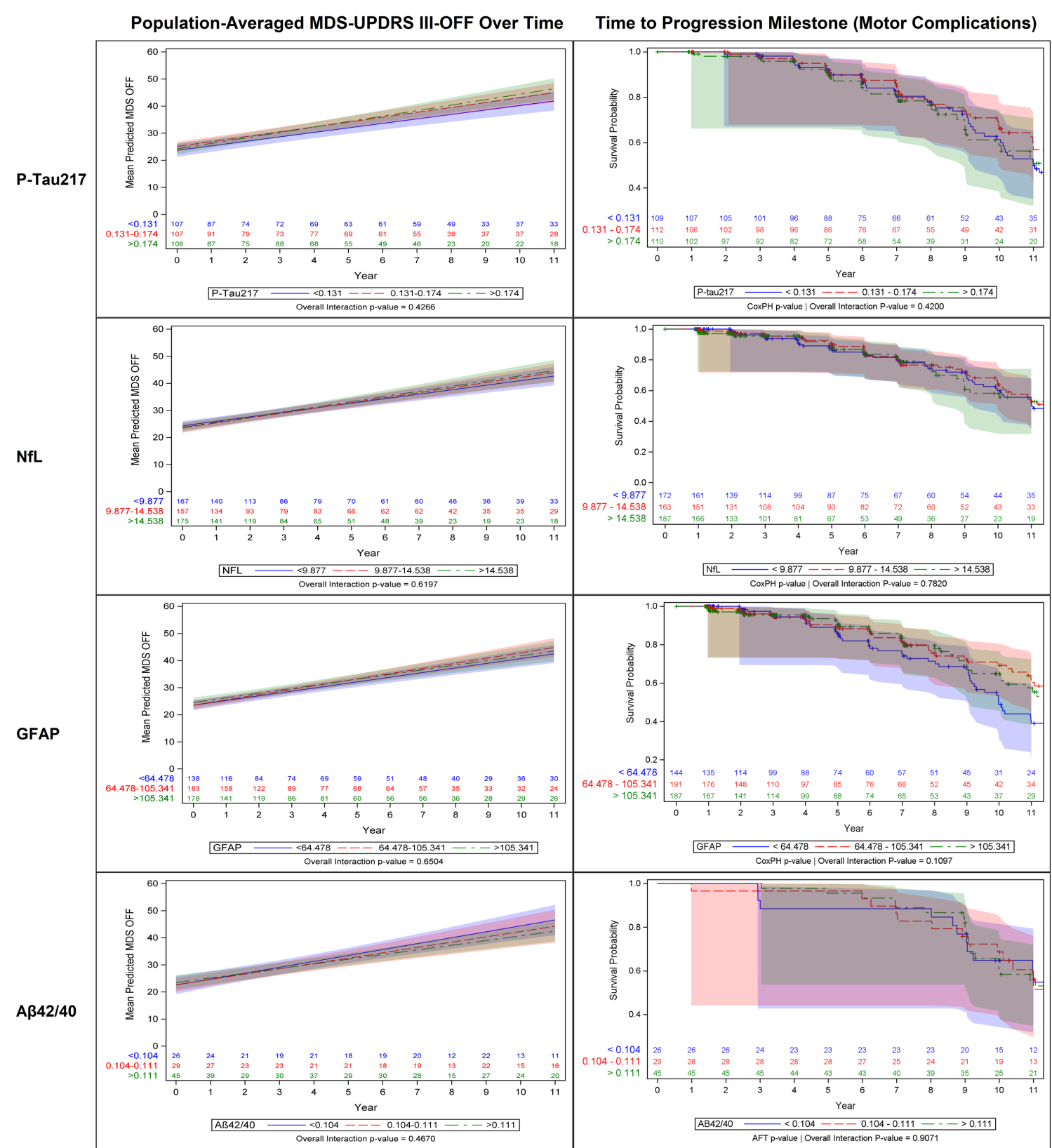


Figure 4 (ABOVE): Association between biomarker tertile and motor outcomes in PD. Omnibus test and pairwise comparisons are shown below graphs.

Figure 5 (BELOW): Association between biomarker tertile and non-motor outcomes in PD. Omnibus test and pairwise comparisons are shown below graphs.

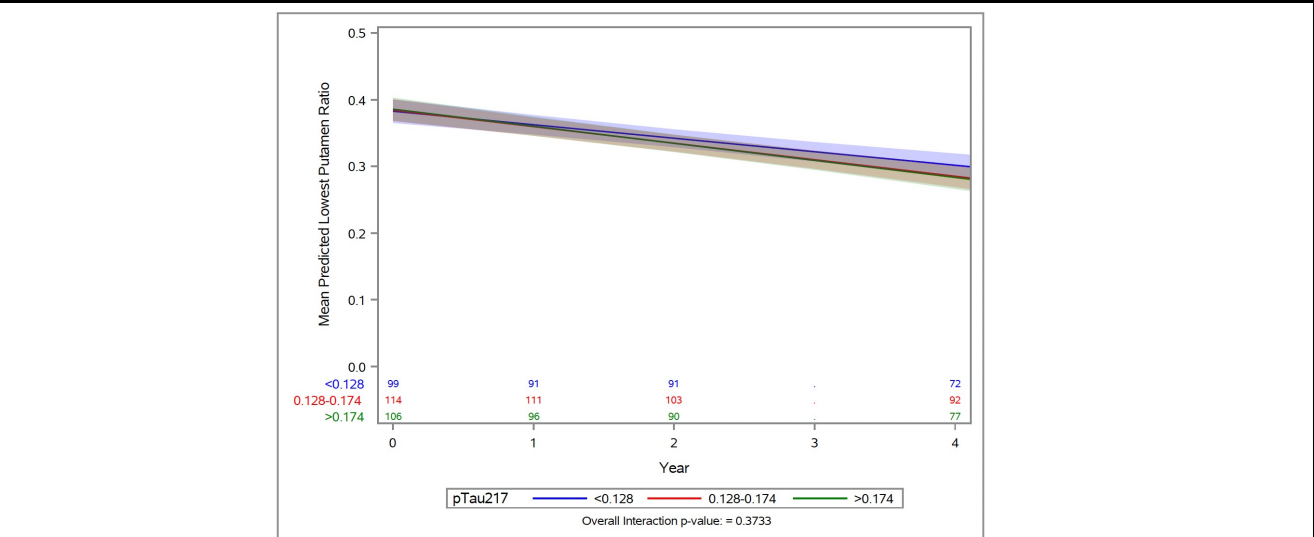
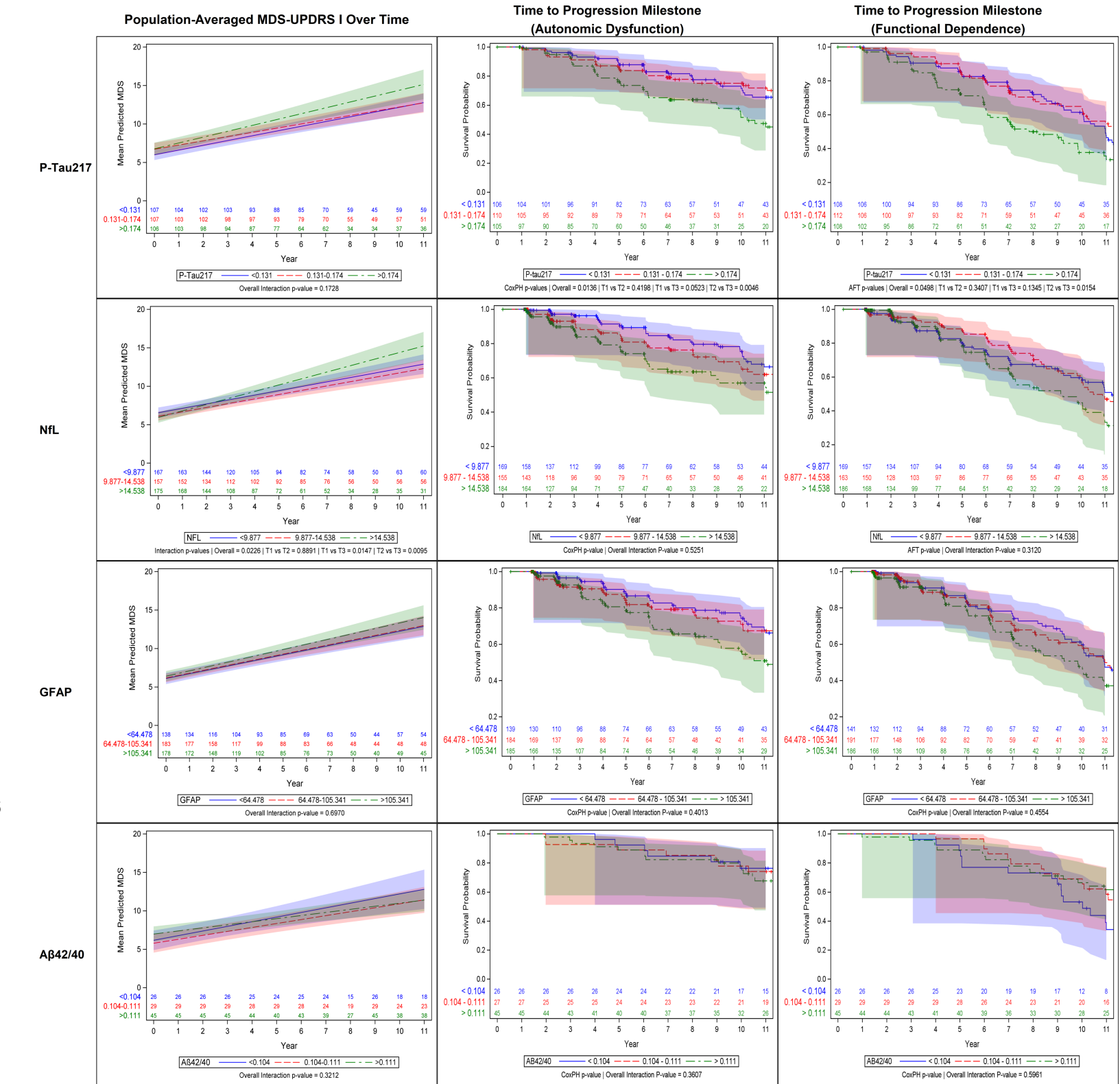


Figure 6: Association between biomarker tertile and DaT SPECT lowest putamen ratio. Omnibus test is shown below graph.

CONCLUSIONS

Elevated levels of plasma neurodegeneration biomarkers, and particularly p-tau217, in early NSD+PD predict longitudinal cognitive and functional decline, but not motor or dopaminergic imaging outcomes.

Taken together, these findings indicate that p-tau217 is a promising prognostic biomarker in NSD that may be informative to enrich cohorts in clinical trials of disease modifying therapies.

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