The role of blood-based biomarkers in Parkinsonian disorders, Alzheimer's disease and frontotemporal dementia

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Background and Aims

The complexity of neurodegenerative disorders necessitates an integrative approach that incorporates morphological, functional, and molecular biomarkers. The advent of highly sensitive single-molecule array (Simoa®) assays has significantly enhanced the accuracy of blood-based biomarker quantification, including glial fibrillary acidic protein (GFAP), neurofilament light chain (NfL), and phosphorylated tau181 (p-tau181). This study evaluates the diagnostic utility of these biomarkers in neurodegenerative diseases.

Methods

We analyzed data from 279 individuals from the PADUA-CESNE cohort: 120 with Parkinson's disease (PD), 88 with Alzheimer's disease (AD), 16 with frontotemporal dementia (FTD), 11 with multiple system atrophy (MSA), 14 with progressive supranuclear palsy (PSP), and 30 cognitively unimpaired controls.

See **Table 1**.

Results

NfL levels were significantly lower in PD and AD compared to atypical parkinsonisms and FTD, effectively distinguishing MSA and PSP from controls (**Fig. 1**). NfL also negatively correlated with Montreal Cognitive Assessment (MoCA) scores in AD and PD (**Fig. 2**), indicating its association with cognitive decline. Elevated GFAP levels were observed in both PD and AD and inversely correlated with global cognition. Combining GFAP and p-tau181 improved AD differentiation from PD and other parkinsonian disorders, while the integration of all three biomarkers facilitated the distinction between AD and FTD. Notably, lower NfL levels (<20 ng/L) in conjunction with elevated p-tau181 were indicative of AD, whereas NfL levels below 40 ng/L were suggestive of PD (**Fig. 3**).

Conclusions

NfL can serve as a sensitive indicator of neurodegeneration, albeit with **limited specificity**. However, by establishing **biomarker concentration thresholds** and **integrating complementary biomarkers**, blood-based assays may enhance the differential diagnosis of neurodegenerative diseases, providing valuable clinical insights.

Fig 1. Blood-based biomarkers (NfL, GFAP and pTau181) differences between groups

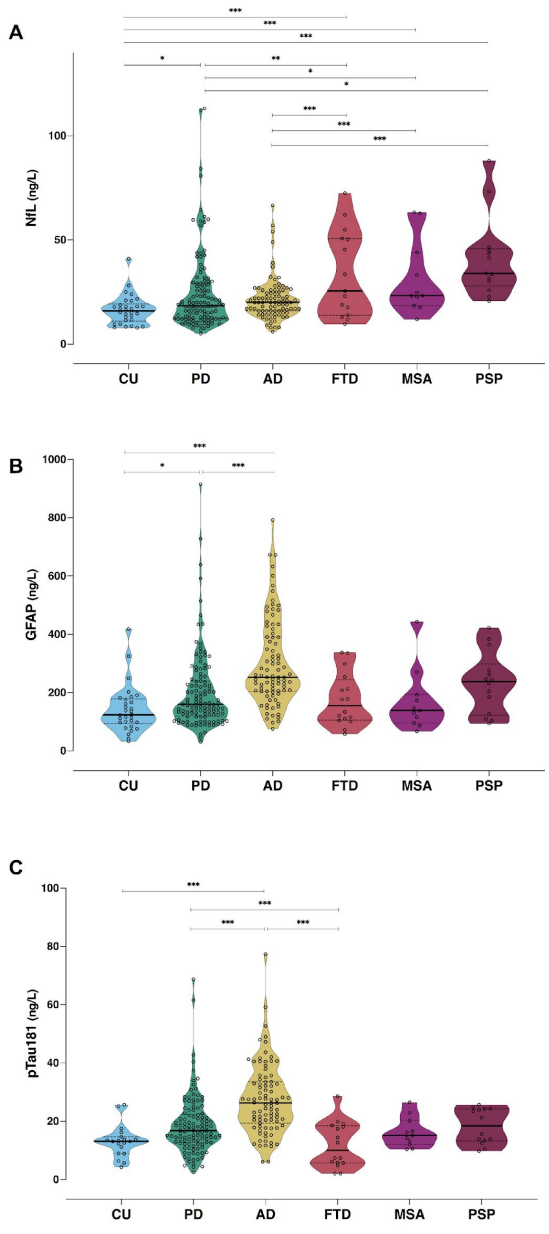

Fig 2. Spearman correlation analyses for blood-based markers vs. clinical variables in PD and AD

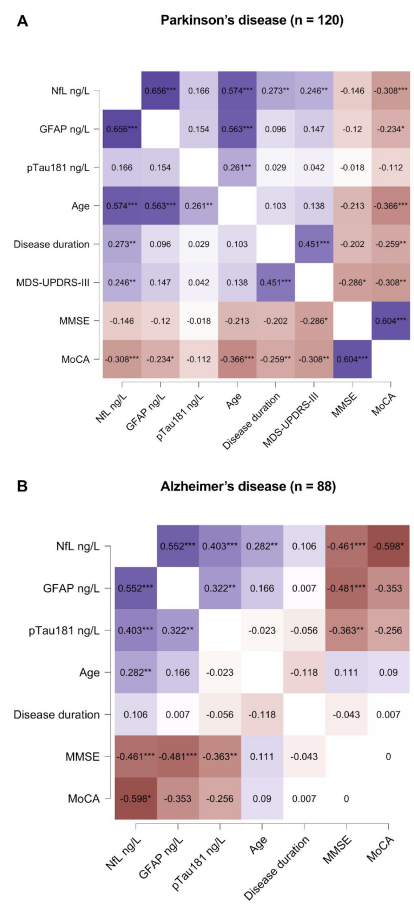

Fig 3. Multinomial logistic regression results: Predicted probabilities of disease diagnoses relative to blood-based biomarkers concentrations.

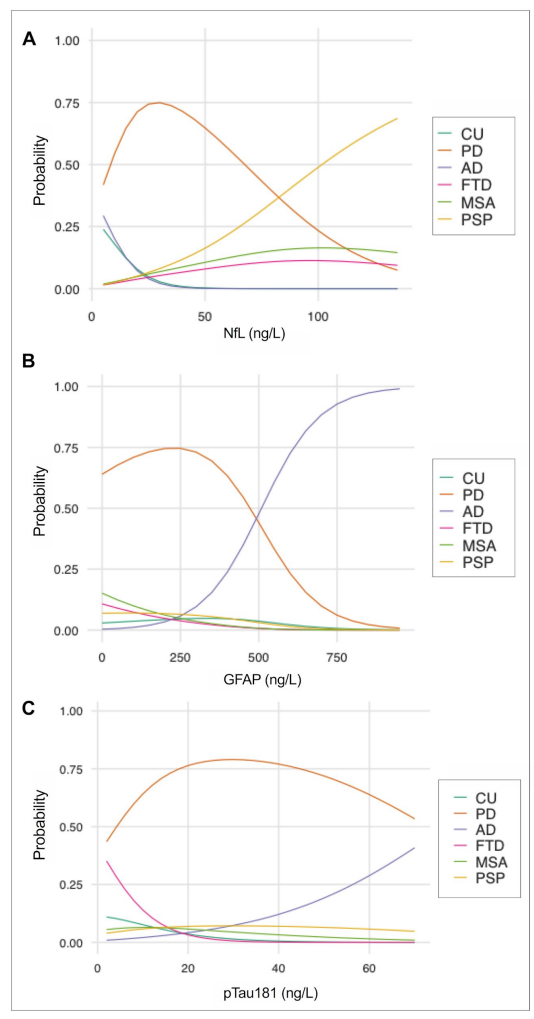

Table 1. Demographic, clinical, cognitive and blood-based biomarker levels for each group.

	CU (n=30)		PD (n=120)		AD (n=88)		FTD (n=16)		MSA (n=11)		PSP (n=14)		Total sample (N = 279)	
	Mean (SD)	min-max	Mean (SD)	min-max	Mean (SD)	min-max	Mean (SD)	min-max	Mean (SD)	min-max	Mean (SD)	min-max	F (df1,df2) / χ^2 (df)	p value
Age (yrs)	64.07 (7.72)	40-74	64.13 (10.15)	30-92	67.95 (7.06)	52-82	60.25 (8,54)	46-78	58.73 (7.43)	48-71	70.93 (7.64)	55-81	6.8 (5,46.13)	**<0.001**
Education (yrs)	15.67 (3.81)	8-21	12.55 (4.08)	5-24	11.02 (4.09)	5-19	13.13 (5.29)	6-23	11.89 (3.44)	7-17	12.75 (5.93)	5-22	3.87 (5,34.91)	**0.007**
Sex (f/m)	11/19		39/81		51/37		8/8		8/3		7/7		18.11 (5)	**0.003**
NfL (ng/L)	16.4 (7.11)	7.8-41	24.52 (19.14)	5-113	21.36 (10.15)	6-66.6	33.51 (20.71)	9.6-72.5	31.38 (17.76)	11.9-63.3	41.24 (19.58)	20.7-88.10	10.07 (5,259)	**<0.001**
GFAP (ng/L)	142.02 (80.81)	33-418.2	202.24 (135.38)	30.9-915	302.61 (149.59)	76-792	176.17 (90.65)	58.2-338	169.29 (106.91)	67.3-443.4	232.63 (105.51)	94.1-423	13.41 (5,270)	**<0.001**
pTau181 (ng/L)	13.16 (5.55)	4.3-25.7	18.6 (9.95)	2.5-68.7	27.54 (12.07)	6.1-77.4	11.89 (7.77)	2.1-28.6	16.2 (5.13)	10.4-26.5	18.41 (6.07)	9.8-25.7	14.63 (5,257)	**<0.001**
MMSE	29.47 (0.52)	29-30	27.92 (2.63)	16-30	23.6 (5.36)	6-30	21 (8.02)	5-27	28.89 (0.93)	27-30	25.6 (4.45)	17-30	18.3 (5,26.78)	**<0.001**
MoCA	27.5 (1.74)	23-30	23.34 (4.37)	8-30	16.69 (6.16)	5-29	13.4 (9.55)	0-23	24.44 (1.88)	22-28	18.42 (5.73)	10-25	18.83 (5,30.70)	**<0.001**
Disease duration (yrs)			9.12 (7.39)	0-34	3.25 (2.06)	1-9	2.53 (1.81)	0-6	3.18 (1.94)	0-7	3.07 (1.94)	0-6	18.01 (4,39.21)	**<0.001**
MDS-UPDRS-III			26.33 (16.3)	4-73					42.91 (16.69)	11-68	54.5 (16.85)	29-82	18.12 (2,16.47)	**<0.001**

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