Journal of the Neurological Sciences 476 (2025) 123617

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

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

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ARTICLE INFO

Keywords:
Blood-based biomarkers
Glial fibrillary acidic protein (GFAP)
Neurofilament light chain (NfL)
Phosphorylated tau181 (p-tau181)
Neurodegenerative diseases
Parkinson's disease

ABSTRACT

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.

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.

NfL levels were significantly lower in PD and AD compared to atypical parkinsonisms and FTD, effectively distinguishing MSA and PSP from controls. NfL also negatively correlated with Montreal Cognitive Assessment (MoCA) scores in AD and PD, 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.

In conclusion, NfL serves as a sensitive indicator of neurodegeneration, albeit with limited specificity. However, by establishing biomarker concentration thresholds and integrating complementary biomarkers, blood-

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https://doi.org/10.1016/j.jns.2025.123617
Received 18 March 2025; Received in revised form 8 July 2025; Accepted 9 July 2025
Available online 11 July 2025

based assays may enhance the differential diagnosis of neurodegenerative diseases, providing valuable clinical insights.

1. Introduction

The growing recognition of the complexity of pathogenetic mechanisms underlying neurodegenerative disorders has reshaped diagnostic approaches. Integrating morphological and functional data with comprehensive biological profiling now facilitates differential diagnosis and early disease detection in clinical practice [1,2].

Accurate early differentiation between Parkinson's disease (PD) and atypical parkinsonisms, such as multiple system atrophy (MSA) and progressive supranuclear palsy (PSP), is critical for optimizing treatment, particularly with the advent of disease-modifying therapies, including monoclonal antibodies targeting α-synuclein and tau. Similarly, Alzheimer's disease (AD) management has evolved with anti-amyloid beta monoclonal antibodies, which, despite initial safety and efficacy concerns, are now entering clinical use [3]. Consequently, precise differentiation between AD and frontotemporal dementia (FTD) is increasingly important as new therapeutic options emerge. To this end, recent criteria for the biological diagnosis of AD have proposed expanding the array of fluid biomarkers beyond tau and amyloid to include biomarkers of inflammation and neurodegeneration [4].

Blood biomarkers offer a promising, accessible tool for neurological diagnostics, providing insights into glial activation and astrocytosis as well as neuronal damage (e.g., glial fibrillary acidic protein [GFAP] and neurofilament light chain [NfL], respectively) and pathological protein deposition (e.g., phosphorylated tau181 [p-tau181]). The development of highly sensitive single-molecule array technology (Simoa®) has expanded their application across neurodegenerative disorders, multiple sclerosis, peripheral neuropathies, and neurologic adverse events from immune checkpoint inhibitors [5,6].

In parkinsonian syndromes and cognitive disorders, shared pathogenetic features—such as protein aggregation, neurodegeneration, and inflammation—can be quantified through blood biomarkers. Increasing evidence suggests that co-pathology (concurrent deposition of α-syn, TDP-43, and amyloid) is common in neurodegenerative diseases, indicating that characteristic biomarker patterns may aid diagnosis. Furthermore, serum NfL levels have shown potential for monitoring motor and cognitive progression in PD and AD, providing prognostic value [7–9].

In this study, we used Simoa to quantify serum and plasma NfL, GFAP, and pTau181 levels across cohorts of PD, MSA, PSP, AD, and FTD, compared to age-matched controls. We assess their utility for differential diagnosis and potential integration into clinical practice, both individually and in combination.

2. Materials and methods

2.1. Sample and study design

This is an observational retrospective research study on patients who are part of the PADUA-CESNE cohort at the Movement Disorders Unit of Padova University Hospital (Padova, Italy) and at the Regional Brain Aging Center (Selvazzano Dentro, Padova) between November 2017 to April 2024.

Our cohort consisted of 249 participants including, 120 PD patients [age Mdn = 65; f/m = 39/81], 88 with AD [age Mdn = 69; f/m = 51/37], 16 with behavioral-variant FTD [age Mdn = 60; f/m = 8/8], 11 with MSA [age Mdn = 60; f/m = 8/3], and 14 with PSP [age Mdn = 73.5; f/m = 7/7]. Additionally, 30 cognitively unimpaired (CU) individuals [age Mdn = 65.5; f/m = 11/19], sex and age-matched, served as controls and were recruited as part of Italian National Recovery Fund 'AGE-it' project on normal aging (https://ageit.eu/wp/en/). All participants underwent a comprehensive evaluation, including medical history, neurological examination, cognitive assessment, blood sampling and MRI to exclude presence of abnormalities. PD diagnosis was established clinically based on the most recent criteria [10]. Probable PSP patients was diagnosed according to the 2017 Movement Disorder Society (MDS) diagnostic criteria [11], with motor severity assessed with the Progressive Supranuclear Palsy Rating Scale (PSP-RS), yielding a mean total score of 45.31 ± 16.59. Probable MSA was diagnosed according to the second consensus statement proposed by Gilman et al. (2008) [12], and the 2022 MDS diagnostic criteria for MSA [13]. Most MSA patients presented with the parkinsonian variant (MSA-P, $n = 10$), while one exhibited the MSA-cerebellar subtype (MSA-C). Motor disability was evaluated using the Unified Multiple System Atrophy Rating Scale (UMSARS), with patients demonstrating moderate impairment in daily functionality [Part I: 16.91 ± 4.83; Part II: 21.82 ± 6.95], and a mean global disability scale score of 2.55 ± 0.82. All patients with parkinsonian syndromes were diagnosed by movement disorder specialists and followed for at least two years for diagnostic confirmation and ongoing clinical/cognitive assessment. Motor severity was evaluated using the motor subscale of the MDS-Unified Parkinson's Disease Rating Scale (MDS-UPDRS-III). AD patients were diagnosed according to the 2018 research framework criteria [14], and its 2024 revision [4], with classification based on the A/T/N framework. Behavioral-variant FTD diagnosis followed the most recent published criteria [15]. All participants underwent a global cognitive screening by means of Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) [16]. The study protocol was approved by the local ethics committee at Padua University Hospital and conducted according to the Declaration of Helsinki. All study participants gave written informed consent.

2.2. Blood sample analyses

Serum levels of NfL, GFAP and pTau181 were measured across all groups, while plasma levels were assessed in most AD participants ($n =$ 68, 77 %). Of note, before combining serum and plasma biomarkers within the AD group, we run specific analyses to verify potential differences of the two distributions (serum vs. plasma), see Supplementary materials and Supplementary Fig. 1.

NfL, GFAP and pTau181 were tested in serum samples (or K-2 ethylenediaminetetraacetic acid plasma for the AD group) using a research-use-only (RUO) Simoa assay on a semi-automated SR-X platform (Quanterix, USA). The following kits were used: Neuro 2-Plex B Advantage kit (lot numbers 503,866 and 504,131) and pTau181 V2.1 Advantage kit (lot numbers 503,843 and 503,907). To assess analytical variability, two quality control levels (low and high) provided by the manufacturer were tested in each run. The coefficient of variation (CV) was <20 % for low levels and < 15 % for high levels. Samples were aliquoted into polypropylene tubes after centrifugation and stored at −80 °C. Before testing, they were thawed at room temperature for at least 30 min and centrifuged at 10,000*g* for 5 min. All analyses were conducted at the Laboratory Medicine Unit of the University Hospital of Padova. To ensure comparability with published data from the previous version of the Simoa pTau181 Advantage kit (V2), we applied the data transformation recommended by the manufacturer, as detailed in a technical note (TECH-0153 01, Quanterix, 2022; available at Quanterix Portal) [17].

2.3. Statistical analyses

The Shapiro–Wilk test was used to assess the normality of the data

distribution. Categorical variables were analyzed using the chi-square test. For normally distributed data, one-way ANOVA with Welch's correction for unequal variances was adopted, followed by Games-Howell or Tukey's post-hoc test, when in presence of unequal and equal variance, respectively. Due to the skewed distribution of the blood biomarker concentrations, these were log-transformed to normalize their distribution. In addition, given their association with age, ANCOVA models were run to compare their concentration's difference across groups, including age as covariate. Spearman's correlations (*rs*) were conducted to investigate the association between blood-based biomarkers (NfL, GFAP, pTau181) and cognitive/clinical features. False discovery rate (FDR) corrections were adopted for multiple comparisons correction.

Receiver operating characteristic (ROC) curve analysis was performed to assess diagnostic value. Differential diagnosis accuracy was quantified using the area under the curve (AUC), along with sensitivity and specificity values. To determine whether combining biomarkers improved diagnostic performance over individual markers, all tested blood-based biomarkers were included in a binary logistic regression model to calculate individual probabilities, ultimately deriving a combined probability.

Multinomial logistic regression was performed to assess whether NfL, GFAP and pTau181 concentrations could predict neurodegenerative disorders (PD, AD, FTD, MSA, PSP vs. CU), by including diagnoses as dependent variable and blood-based biomarkers as independent continuous predictors. All the statistical analyses were performed using R (version 4.2.3) and IBM SPSS Statistics (version 24), with statistical significance set at $p \leq 0.05$. Furthermore, in the Supplementary Materials, we provide the results of all analyses repeated after excluding the plasma samples from the AD group to demonstrate the comparability of the present findings, which include both plasma and serum data.

3. Results

3.1. Sample demographic and clinical features

All demographic, cognitive, clinical characteristics, and blood-based marker levels are shown in Table 1. AD patients were significantly older than PD [$t = -3.20(205.5)$, $p = 0.019$], FTD [$t = 3.40(18.9)$, $p = 0.030$], and MSA [$t = 3.90(12.4)$, $p = 0.019$]. Additionally, PSP patients were older than both FTD and MSA patients [$t = -3.62(28.0)$, $p = 0.013$ and $t = -4.02(22.9)$, $p = 0.007$, respectively].

In terms of educational level, the AD group exhibited significantly lower education levels compared to the CU groups [$t = 3.91(240)$, $p = 0.002$]. Regarding sex, we observed a statistically significant difference in AD and PD subgroups. The AD group had a higher proportion of females (58 %, $p < 0.001$), while PD group had a higher proportion of males (68 %, $p < 0.001$).

3.2. Blood-based biomarkers

3.2.1. NfL

As shown in Fig. 1A, compared to CU, NfL levels were higher in PD [$t = -2.93(269)$, $p = 0.042$], FTD [$t = -4.75(269)$, $p < 0.001$], MSA [$t = -4.32(269)$, $p < 0.001$] and PSP [$t = -4.60(269)$, $p < 0.001$]. PD showed statistically significant lower level of NfL compared to FTD [$t = -3.30(269)$, $p = 0.014$], MSA [$t = -2.94(269)$, $p = 0.041$] and PSP [$t = -3.20(269)$, $p = 0.019$]; similarly, AD had statistically significant lower level of NfL than FTD [$t = -4.17(269)$, $p < 0.001$], MSA [$t = -3.72(269)$, $p = 0.003$] and PSP [$t = -4.11(269)$, $p < 0.001$].

3.2.2. GFAP

As compared to CU, PD and AD showed significant higher levels of GFAP [$t = -3.34(270)$, $p = 0.012$; $t = -6.61(270)$, $p < 0.001$, respectively]. Further, GFAP levels were higher in AD patients compared to PD [$t = -5.07(270)$, $p < 0.001$] (see Fig. 1B), and a similar trend was found compared to FTD [$t = 2.66$ (270), $p < 0.087$].

3.2.3. pTau181

Statistically significant higher levels of pTau181 were observed in AD patients compared to CU [$t = -5.20(257)$, $p < 0.001$], PD [$t = -5.23(257)$, $p < 0.001$], and FTD [$t = -6.54(257)$, $p < 0.001$]. PD patients also showed significant higher pTau181 levels than FTD patients [$t = -3.95(257)$, $p < 0.001$] (see Fig. 1C).

3.3. Cognitive and clinical features

Regarding global cognitive functioning, all disease groups exhibited greater cognitive impairments than CU as assessed by the MoCA (see Table 1): PD (p < 0.001), AD ($p < 0.001$), FTD ($p < 0.010$), MSA ($p = 0.013$) and PSP ($p = 0.002$). Further, AD patients showed a worse global cognitive profile than PD ($p = 0.007$) and MSA ($p = 0.002$), while PSP patients were more cognitively impaired than MSA ($p = 0.040$), and FTD patients were more impaired than MSA ($p = 0.044$).Regarding the MMSE, this brief scale was less sensitive in detecting cognitive impairment, as only PD and AD showed worse global cognitive profiles than CU ($p < 0.001$).

PD patients exhibited a significantly longer disease duration compared to all the other disease groups: AD ($p < 0.001$), FTD ($p < 0.001$), MSA ($p < 0.001$) and PSP ($p < 0.001$). No further differences in disease duration were observed between the other disease groups.

Regarding motor severity, as assessed by MDS-UPDRS motor part, PD patients showed lower motor severity than MSA and PSP groups ($p = 0.005$ and $p < 0.001$, respectively).

3.4. Relationship between blood biomarkers and cognitive/ clinical characteristics

As shown in Fig. 2A, in the overall PD group ($n = 120$), significant positive correlations were found between the three blood-biomarkers (NfL, GFAP and pTau181) and age (all $p_{FDR} < 0.001$). In addition, a significant positive correlation was observed between the NfL concentration and disease duration ($rs = 0.273$; $p_{FDR} = 0.009$) or motor severity (MDS-UPDRS-III) ($rs = 0.246$; $p_{FDR} = 0.019$). A significant negative correlation was also observed between NfL levels and global cognitive functioning, as assessed by the MoCA ($rs = -0.308$; $p_{FDR} < 0.001$), as well as GFAP concentrations negatively correlated with MoCA ($rs = -0.234$; $p_{FDR} = 0.026$). No other significant correlations were found.

Similarly, in the overall AD sample ($n = 88$), as shown in Fig. 2B, we found a significant positive correlation between NfL levels and age ($rs = 0.282$; $p_{FDR} = 0.024$), and a significant negative correlation with global cognition, as assessed by MMSE and MoCA ($rs = -0.461$; $p_{FDR} < 0.001$, and $rs = -0.598$; $p_{FDR} = 0.037$, respectively). Notably, negative correlations were also observed between MMSE and GFAP, as well as pTau181 levels ($rs = -0.481$; $p_{FDR} < 0.001$, and $rs = -0.363$; $p_{FDR} = 0.014$, respectively).

Lastly, in the MSA, PSP, and FTD groups, no significant correlations were found.

3.5. Diagnostic accuracy of blood-based biomarkers

ROC curve analyses were conducted to assess the ability of blood-based biomarkers (NfL, GFAP, and pTau181), individually and in combination, to differentiate between various neurodegenerative conditions (Table 2; Fig. 3).

In distinguishing CU individuals from those with neurodegenerative diseases, the highest accuracy was observed in the CU vs. PSP comparison (Fig. 3E). NfL demonstrated excellent diagnostic performance (AUC: 0.98), while GFAP and pTau181 showed moderate accuracy (AUC: 0.75 and 0.72, respectively). Notably, combining all three markers further improved accuracy to 0.99. Similarly, these biomarkers were effective in differentiating CU from AD (Fig. 3B), with GFAP and

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 (5259)	**<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 (5270)	**<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 (5257)	**<0.001**
pTau181(ng/L) **–transformed**	1 (0.3)	0.2–2.25	1.5 (0.7)	0.1–6.9	2.4 (0.9)	0.35–7.9	0.9 (0.5)	0.03–2.6	1.3 (0.3)	0.7–2.3	1.5 (0.35)	0.7–2.25		
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**

Note. NfL, neurofilament light chain; GFAP, glial fibrillary acidic protein; pTau181, phosphorylated tau 181; MMSE, Mini-mental State Examination; MoCA, Montreal Cognitive Assessment; MDS-UPDRS, MDS-Unified Parkinson's Disease Rating Scale. CU, cognitive unimpaired individuals; PD, Parkinson's disease, AD, Alzheimer's disease, FTD, frontotemporal dementia; MSA, multiple system atrophy; PSP, progressive supranuclear palsy.

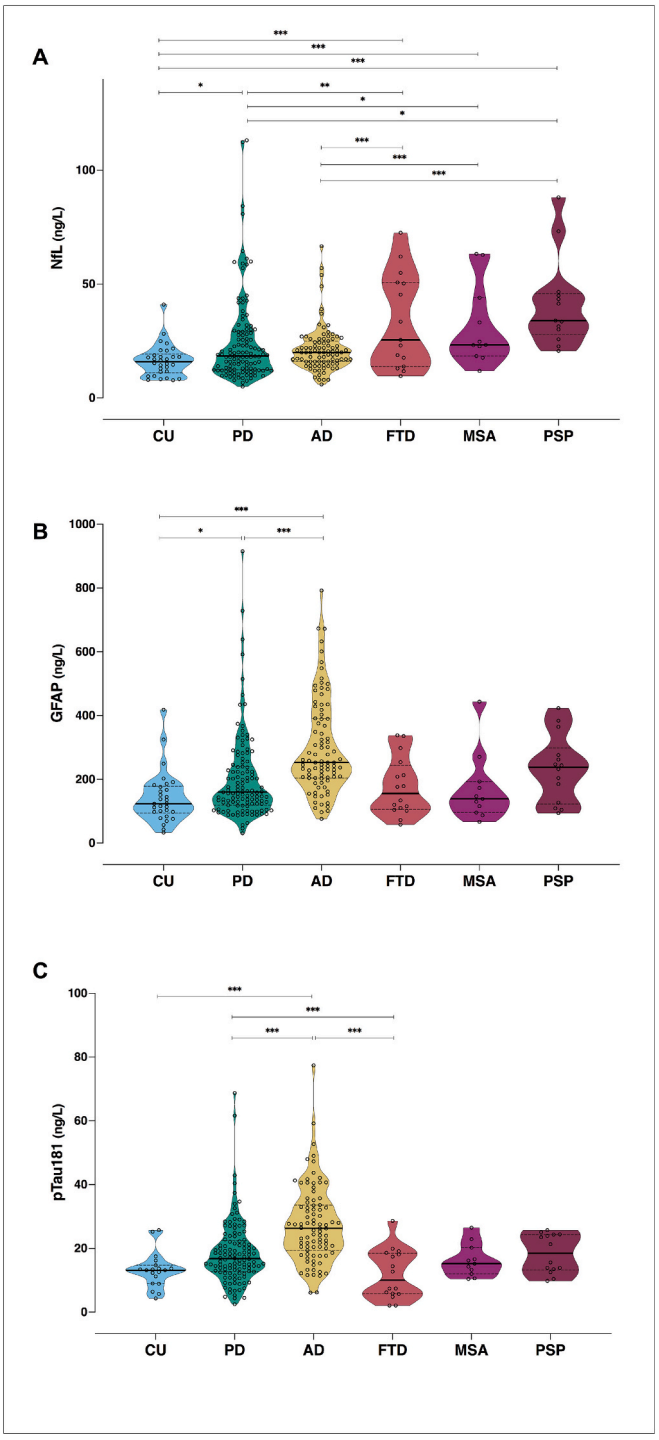

Fig. 1. Blood-based biomarkers (NfL, GFAP and pTau181) differences between groups.

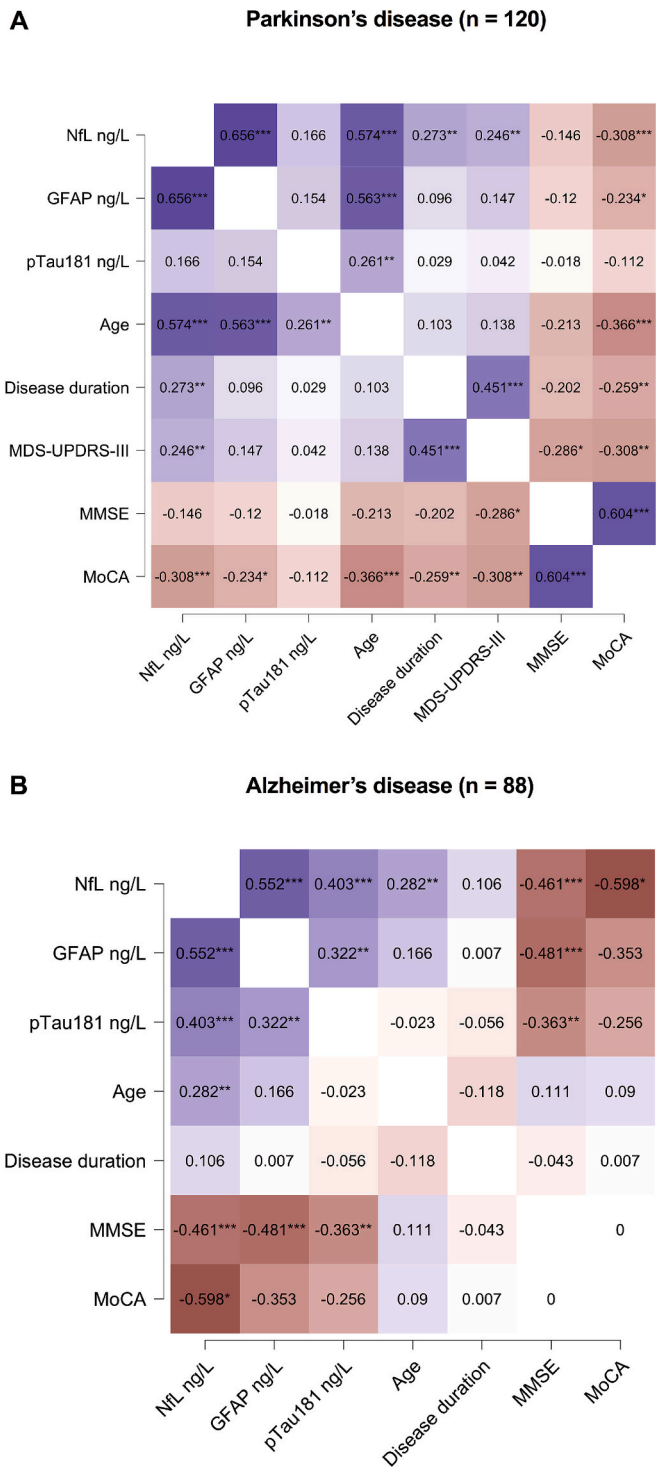

Fig. 2. Heatmap presenting results of Spearman correlation analyses for blood-based markers versus clinical variables in Parkinson's and Alzheimer's disease groups.

pTau181 exhibiting good diagnostic accuracy (AUC: 0.84 and 0.88, respectively), which increased to 0.91 when combined. For CU vs. MSA and CU vs. FTD, NfL emerged as the most accurate marker, demonstrating a good accuracy in MSA (AUC: 0.89; Fig. 3D) and FTD (AUC: 0.81; Fig. 3C). In contrast, for CU vs. PD, both NfL and pTau181 displayed fair accuracy (AUC: 0.70), which improved when combined (AUC: 0.77; Fig. 3A).

GFAP and pTau181 played a key role in differentiating AD from FTD and MSA. In the AD vs. FTD comparison, GFAP exhibited good accuracy (AUC: 0.80), while pTau181 demonstrated an excellent performance (AUC: 0.91; Fig. 3J). Their combination further improved accuracy to 0.95. Similarly, in AD vs. MSA, both GFAP and pTau181 showed good performance (AUC: 0.82 and 0.81, respectively), with the combined panel achieving an AUC of 0.89 (Fig. 3K). However, in AD vs. PD, GFAP and pTau181 showed only moderate accuracy (AUC: 0.74), improving to 0.82 when combined (Fig. 3F).

NfL levels were particularly relevant in differentiating PSP from other conditions. In the PSP vs. AD comparison, NfL demonstrated

Table 2
Diagnostic performance of blood-based biomarkers (NfL, GFAP and pTau181) and their combination.

		AUC [95 %CI]	*p* value		AUC [95 %CI]	*p* value		AUC [95 %CI]	*p* value
CU[§]	**NfL (ng/L)**	0.70 [0.59–0.82]	0.004	PD[§]	0.52 [0.44–0.60]	0.594	AD	0.31 [0.13–0.48]	0.035
vs.	**GPAP (ng/L)**	0.64 [0.5–0.78]	0.046	vs.	0.74 [0.68–0.81]	<0.001	vs.	**0.81** [0.66–0.97]	0.001
PD	**pTau181 (ng/L)**	0.70 [0.59–0.82]	0.005	AD	0.74 [0.67–0.81]	<0.001	MSA[§]	**0.82** [0.71–0.93]	0.001
(Fig. 3A)	**Combined panel**	0.77 [0.66–0.87]	<0.001	(Fig. 3F)	**0.82** [0.76–0.88]	<0.001	(Fig. 3K)	**0.89** [0.77–1.00]	<0.001
CU[§]	**NfL (ng/L)**	0.76 [0.64–0.88]	<0.001	PD	0.36 [0.20–0.52]	0.079	AD[§]	**0.90** [0.82–0.97]	<0.001
vs.	**GPAP (ng/L)**	**0.84** [0.73–0.95]	<0.001	vs.	0.56 [0.41–0.72]	0.424	vs.	0.37 [0.22–0.52]	0.124
AD	**pTau181 (ng/L)**	**0.88** [0.8–0.95]	<0.001	FTD[§]	0.74 [0.61–0.88]	0.002	PSP	0.27 [0.15–0.38]	0.005
(Fig. 3B)	**Combined panel**	**0.91** [0.85–0.97]	<0.001	(Fig. 3G)	**0.80** [0.68–0.92]	<0.001	(Fig. 3L)	**0.95** [0.91–1.00]	<0.001
CU[§]	**NfL (ng/L)**	**0.81** [0.66–0.96]	0.002	PD[§]	0.68 [0.53–0.82]	0.053	FTD[§]	0.51 [0.28–0.74]	0.959
vs.	**GPAP (ng/L)**	0.58 [0.38–0.77]	0.435	vs.	0.41 [0.23–0.59]	0.31	vs.	0.49 [0.25–0.72]	0.897
FTD	**pTau181 (ng/L)**	0.42 [0.2–0.63]	0.405	MSA	0.44 [0.29–0.59]	0.487	MSA	0.71 [0.51–0.91]	0.073
(Fig. 3C)	**Combined panel**	**0.83** [0.69–0.98]	0.001	(Fig. 3H)	0.71 [0.53–0.88]	0.025	(Fig. 3M)	0.73 [0.54–0.93]	0.046
CU[§]	**NfL (ng/L)**	**0.89** [0.76–1]	0.001	PD[§]	**0.84** [0.76–0.92]	<0.001	FTD[§]	0.65 [0.44–0.86]	0.176
vs.	**GPAP (ng/L)**	0.56 [0.35–0.77]	0.591	vs.	0.62 [0.47–0.78]	0.131	vs.	0.69 [0.49–0.88]	0.089
MSA	**pTau181 (ng/L)**	0.67 [0.46–0.87]	0.132	PSP	0.53 [0.38–0.68]	0.718	PSP	0.79 [0.62–0.96]	0.008
(Fig. 3D)	**Combined panel**	**0.89** [0.75–1]	<0.001	(Fig. 3I)	**0.84** [0.76–0.93]	<0.001	(Fig. 3N)	**0.83** [0.67–0.99]	0.003
CU[§]	**NfL (ng/L)**	**0.98** [0.95–1]	<0.001		0.37 [0.17–0.56]	0.096	MSA[§]	0.72 [0.51–0.93]	0.067
vs.	**GPAP (ng/L)**	0.75 [0.58–0.92]	0.016		**0.80** [0.68–0.92]	<0.001	vs.	0.68 [0.46–0.91]	0.125
PSP	**pTau181 (ng/L)**	0.72 [0.54–0.9]	0.03	AD vs. FTD[§]	**0.91** [0.84–0.97]	<0.001	PSP	0.59 [0.36–0.82]	0.46
(Fig. 3E)	**Combined panel**	**0.99** [0.96–1.00]	<0.001	(Fig. 3J)	**0.95** [0.89–1.00]	<0.001	(Fig. 3O)	0.76 [0.57–0.95]	0.029

Note. NfL, neurofilament light chain; GFAP, glial fibrillary acidic protein; pTau181, phosphorylated tau 181; CU, cognitive unimpaired individuals; PD, Parkinson's disease, AD, Alzheimer's disease, FTD, frontotemporal dementia; MSA, multiple system atrophy; PSP, progressive supranuclear palsy. In parentheses are reported the corresponding figures (see Fig. 3). §, reference group.

excellent accuracy (AUC: 0.90; Fig. 3L), further improving to 0.95 when combined with GFAP and pTau181. In PSP vs. PD, NfL outperformed other biomarkers (AUC: 0.84; Fig. 3I), though its accuracy did not increase with the combined panel.

pTau181 was especially useful in distinguishing FTD from PD and PSP. In PD vs. FTD, it exhibited moderate-to-good accuracy (AUC: 0.74; Fig. 3G), improving to 0.80 with the combined panel. Similarly, in FTD vs. PSP, pTau181 showed moderate accuracy (AUC: 0.79; Fig. 3N), increasing to 0.83 when combined with other markers.

For other differential diagnoses, as summarized in Table 2, biomarker accuracy was generally fair to moderate (see Fig. 3H, M-O).

3.6. Multinomial logistic regression results

We observed that a steep increase in serum NfL concentrations, reaching approximately ~40 ng/L, was more predictive of PD. By contrast, higher NfL concentrations exceeding ~70 ng/L were more commonly associated with PSP, with the highest levels strongly indicative of this condition and exhibiting a rising trend. Conversely, lower NfL concentrations, below ~20 ng/L, were more consistent with an AD diagnosis (Fig. 4A). As shown in Table 3, NfL levels were significantly associated with the diagnosis of PD, PSP, MSA and FTD (all $p < 0.05$).

Higher levels of GFAP and pTau181 were more suggestive of AD (Fig. 4B and C), whereas lower concentrations of GFAP and pTau181, below ~20 ng/L and ~ 100 ng/L respectively, were more commonly associated with PD. However, only pTau181 but not GFAP, was significantly relevant in predicting both AD and PD diagnoses according to the regression model (Table 3).

4. Discussion

The aim of our study was to investigate the role of three blood-based biomarkers—NfL, GFAP and pTau181—both individually and in combination, in patients with neurodegenerative conditions who are part of our PADUA-CESNE collection and were diagnosed according to clinical criteria. Consistently with the current literature, our findings demonstrated that NfL is highly sensitive in differentiating patients with neurodegenerative diseases from control subjects [18,19]. However, its specificity was limited, despite our cohort showing significantly lower NfL levels in PD and AD compared to other parkinsonian syndromes and FTD. The elevated NfL levels observed in MSA and PSP relative to PD likely reflect the more rapid disease progression characteristic of atypical parkinsonian syndromes, which are associated with greater white matter and axonal degeneration [20]. Overall, NfL emerged as the most effective blood-based marker for distinguishing MSA and PSP from control subjects (AUCs 0.89 and 0.98, respectively). Further, our study confirmed that NfL concentrations positively correlated with disease duration and motor severity in PD, while showing a negative correlation with the MoCA scores in both AD and PD patients, prompting the use of this biomarker as a possible predictor of clinical and cognitive progression, as previously suggested [7].

GFAP is a brain-specific intermediate filament protein and considered as an established marker of reactive astrogliosis [21]. Elevated GFAP expression has been reported in several neurodegenerative disorders, and when the central nervous system is damaged, astrocytes rapidly release GFAP into the peripheral blood [22,23]. The assessment of GFAP levels in CSF and blood has been successfully utilized to characterize distinct neuroinflammatory profiles in neurodegenerative diseases and is considered a potential biomarker for diagnosis and prognosis [23,24]. Furthermore, astrocyte reactivity appears to be a critical early event linking Aβ and tau pathology in preclinical AD [25].

In line with previous studies [26,27], we observed significantly elevated GFAP levels in both PD and AD patients compared to controls, with AD exhibiting the highest levels. Moreover, GFAP concentrations negatively correlated with the global cognitive status in both PD and AD patients, suggesting that intrinsic neuroinflammatory processes, particularly reactive astrogliosis, may be strongly associated to the underlying neuropathological processes and might contribute to cognitive

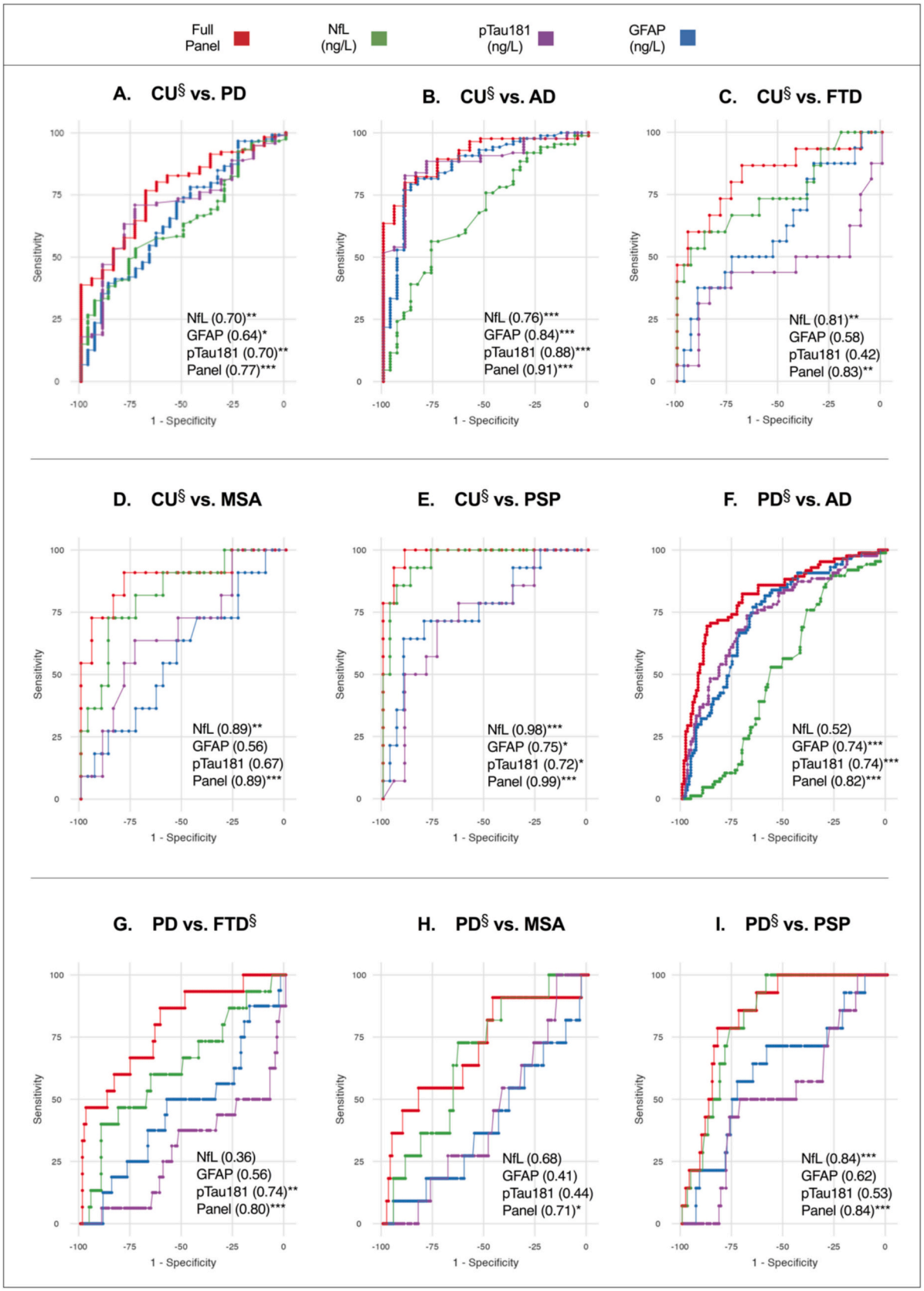

Fig. 3. ROC curves analyses of blood-based biomarkers (NfL, GFAP and pTau181).
Note. NfL, neurofilament light chain; GFAP, glial fibrillary acidic protein; pTau181, phosphorylated tau 181; CU, cognitive unimpaired individuals; PD, Parkinson's disease, AD, Alzheimer's disease, FTD, frontotemporal dementia; MSA, multiple system atrophy; PSP, progressive supranuclear palsy. §, reference group.

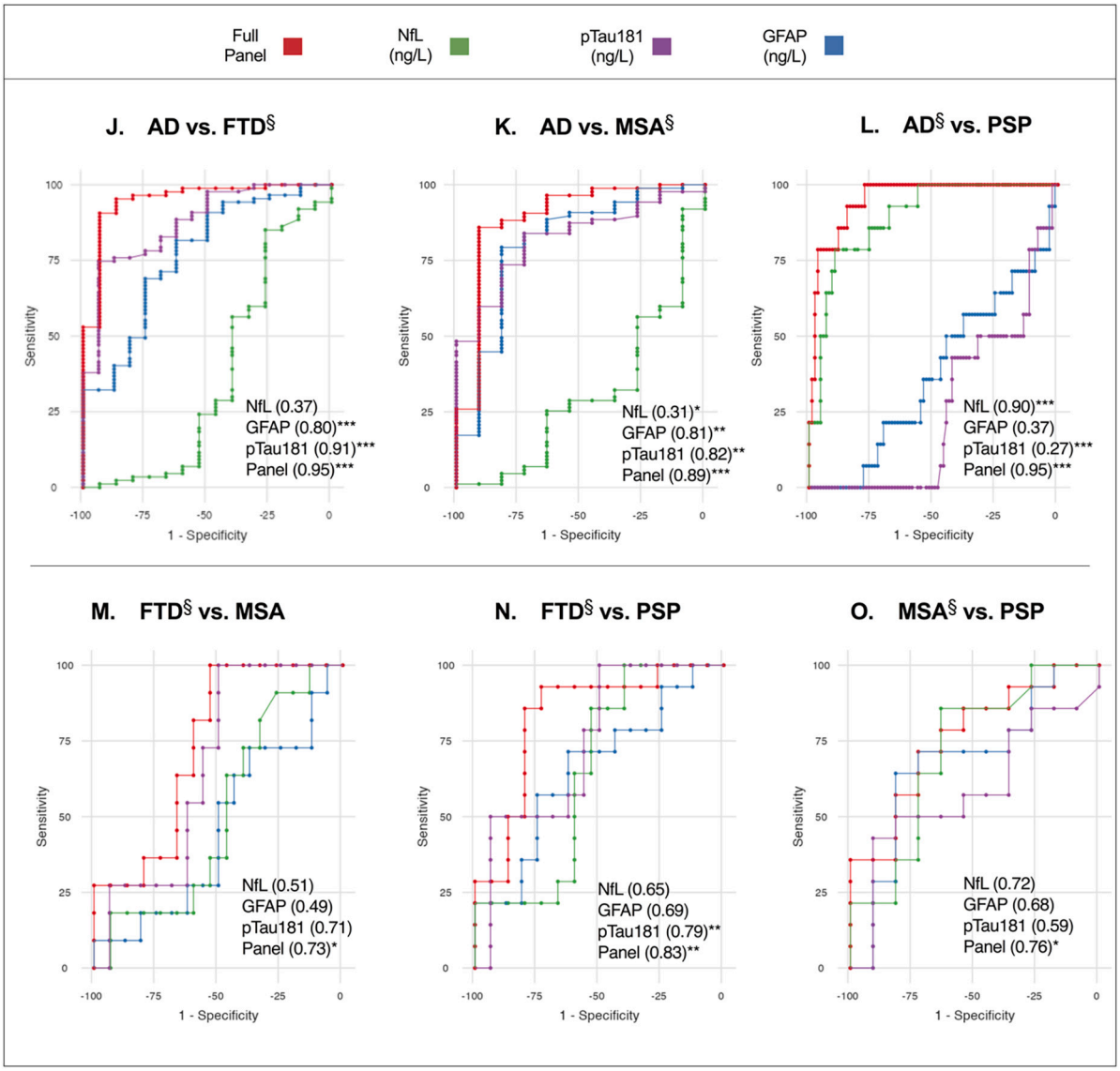

Fig. 3. (*continued*).

decline.

These findings support the potential for neuroprotective approaches targeting this pathway, particularly in AD [28,29] or in presence of AD co-pathology [30]. Given the complexity of the molecular mechanisms underlying neurodegenerative disease, a multifaceted approach is required for both the diagnosis and the treatment [31].

Building on this, we found that combining GFAP and pTau181 better differentiated AD versus CU, FTD, MSA, and PSP (AUC: 0.89–0.95) compared to using single biomarkers. Specifically, for differentiating neurodegenerative dementias (AD vs. FTD), the combination of all three biomarkers yielded an AUC of 0.95—outperforming individual markers (NfL: 0.37, GFAP: 0.80, pTau181: 0.91). Further, our results align with previous evidence, showing that incorporating NfL may enhance diagnostic accuracy, given that AD is characterized by higher GFAP and pTau181 but lower NfL levels [24,32,33]. Interestingly, unlike prior studies, we did not observe significantly higher blood GFAP levels in AD versus FTD, though a trend toward significance was noted. This discrepancy may be attributed to our relatively small FTD sample size, which may have limited statistical power to detect this difference [24].

In line with available literature, our cohort revealed significantly elevated pTau181 levels in AD patients compared to the other subgroups (PD and FTD) and to controls. Notably, in AD, pTau181 showed a significant negative correlation with the MMSE scores but not with the MoCA, indicating the contribution of AD-pathology to cognitive deterioration [34].

The diagnostic utility of pTau181 could be further enhanced when combined with other blood-based markers such as GFAP and NfL, suggesting potential limitations in its sensitivity and specificity as a standalone prognostic biomarker. Indeed, current AD criteria endorse the use of GFAP and NfL alongside ptau181 to detect inflammation and neuronal dysfunction [4].

Moreover, recent studies have highlighted the superior diagnostic performance of pTau217 over other pTau isoforms [35], particularly in detecting amyloid and tau pathology and distinguishing individuals in intermediate-to-advanced AD stages from early stages [36–38]. Hence, given its higher accuracy in identifying amyloid co-pathology in PD, integrating pTau217 into a multimarker panel would further improve diagnostic precision [39].

In our cohort, we also explored the stratification of NfL concentrations to aid differential diagnosis in neurodegenerative disorders. Lower NfL levels (<20 ng/L), combined with elevated pTau181, were more indicative of AD, while NfL levels below 40 ng/L suggested PD. In contrast, higher NfL concentrations were associated with PSP and MSA. Overall, atypical parkinsonisms and FTD exhibited significantly

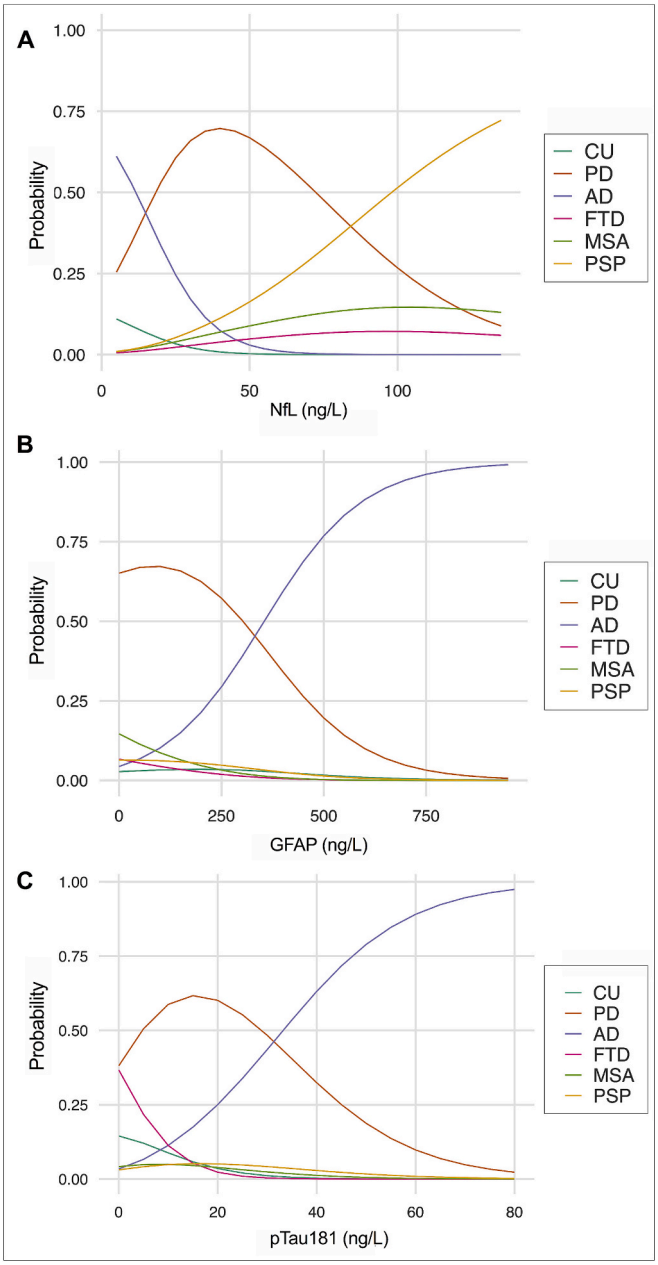

Fig. 4. Predicted probabilities of disease diagnoses relative to blood-based biomarkers concentrations.
Note. NfL, neurofilament light chain; GFAP, glial fibrillary acidic protein; pTau181, phosphorylated tau 181; CU, cognitive unimpaired individuals; PD, Parkinson's disease, AD, Alzheimer's disease, FTD, frontotemporal dementia; MSA, multiple system atrophy; PSP, progressive supranuclear palsy.

elevated NfL levels compared to both PD and AD, reinforcing the notion that neuronal damage is more severe in these conditions and likely driven by heterogeneous mechanisms.

Our current work presents limitations. First, in the AD group, we combined plasma and serum biomarkers. Although we accounted for biomarker distribution, this approach prevented us from establishing specific cutoffs. However, our transformed pTau181 values for both the AD, and control groups aligned with previous findings [40–42]. Namely, the transformed blood-based pTau181 levels in CU individuals were equal to 1 ± 0.3 in our sample, while equal to 1.1, 1.55 and 2.23 (ng/L) in other studies analyzing plasma [40–42]; a similar mean score was observed in serum 0.6 and 0.9 (ng/L) [40,43]. Regarding AD patients, these showed transformed pTau181 levels equal to 2.4 in our sample,

Table 3
Multinomial logistic regression results: Association between blood-based biomarkers (NfL, GFAP and pTau181) and diagnoses.

Diagnoses	Predictor	Estimate	SE	Z	*p* value	Odds ratio [95 % CI]
PD vs. CU	Intercept	−1.23	0.8	−1.53	0.125	0.29 [0.06, 1.41]
	NFL ng/L	0.1	0.05	2.18	**0.029**	1.1 [1.01, 1.21]
	GFAP ng/L	0	0	−0.31	0.757	1 [0.99, 1.01]
	pTau181 ng/L	0.09	0.04	2.13	**0.033**	1.1 [1.01, 1.2]
AD vs. CU	Intercept	−3.39	0.9	−3.78	<0.001	0.03 [0.01, 0.2]
	NFL ng/L	0.01	0.05	0.29	0.771	1.01 [0.92, 1.11]
	GFAP ng/L	0.01	0	1.87	0.061	1.01 [1, 1.01]
	pTau181 ng/L	0.17	0.05	3.75	**<0.001**	1.19 [1.09, 1.3]
FTD vs. CU	Intercept	−0.75	1.08	−0.69	0.488	0.47 [0.06, 3.92]
	NFL ng/L	0.15	0.05	3.08	**0.002**	1.16 [1.06, 1.28]
	GFAP ng/L	−0.01	0.01	−1.61	0.107	0.99 [0.98, 1]
	pTau181 ng/L	−0.08	0.07	−1.23	0.218	0.92 [0.81, 1.05]
MSA vs. CU	Intercept	−2.89	1.2	−2.42	0.016	0.06 [0.01, 0.58]
	NFL ng/L	0.14	0.05	2.95	**0.003**	1.15 [1.05, 1.27]
	GFAP ng/L	−0.01	0.01	−1.46	0.145	0.99 [0.98, 1]
	pTau181 ng/L	0.06	0.06	1.04	0.298	1.06 [0.95, 1.2]
PSP vs. CU	Intercept	−4.42	1.17	−3.77	<0.001	0.01 [0, 0.12]
	NFL ng/L	0.15	0.05	3.09	**0.002**	1.16 [1.06, 1.27]
	GFAP ng/L	0	0	−0.52	0.604	1 [0.99, 1.01]
	pTau181 ng/L	0.08	0.06	1.51	0.131	1.09 [0.98, 1.21]

Note. NfL, neurofilament light chain; GFAP, glial fibrillary acidic protein; pTau181, phosphorylated tau 181; CU, cognitive unimpaired individuals; PD, Parkinson's disease, AD, Alzheimer's disease, FTD, frontotemporal dementia; MSA, multiple system atrophy; PSP, progressive supranuclear palsy.

while in other works the range was between 3.59 and 3.37 (ng/L) in plasma samples [41,42]. Additional limitations include the small sample size of certain disease groups (i.e., MSA, PSP and FTD), which may limit the generalizability of our findings and reduce the reliability of the threshold values identified for these subgroups. Therefore, we acknowledge the need for replication and validation in larger multicenter cohorts, recruiting more patients with rare disorders. By contrast the PD and AD group, due to their larger sample sizes, exhibited greater variability in NfL and GFAP concentrations, with a few patients appearing as outliers. Notably, this heterogeneity may reflect differences in disease stage, as increased levels of GFAP and NfL have been previously associated with disease progression [7,44]. However, we believe documenting this variability is important, given that all clinical diagnoses were confirmed through multiple follow-ups. To improve the clinical utility of blood-based biomarkers, future studies should aim to establish cutoffs that account for relevant factors such as age, disease severity, clinical phenotype, and comorbidities (e.g., renal dysfunction). A further major limitation is the lack of neuropathological confirmation and the cross-sectional design of our study, which limits the ability to assess biomarker trajectories or their prognostic value over time. Longitudinal studies are warranted to determine whether these blood-based markers can reliably predict disease progression or therapeutic

response, thereby enhancing their clinical relevance. Furthermore, our cohort consisted of patients already in the clinical phase of disease, which prevents us from drawing definitive conclusions about the utility of blood biomarkers in preclinical or early diagnostic stages.

Despite its limitations, the present study emphasizes the potential for incorporating blood-based biomarkers—NfL, GFAP, and p-tau181—into clinical practice, both individually and in combination, across a range of complex neurodegenerative disorders, including rare conditions such as MSA, PSP and FTD. To the best of our knowledge, no previous works compared these neurodegenerative conditions in the same study, providing detailed demographic, clinical and cognitive data for these disorders, while analyzing multiple blood-based biomarker panels (e.g., [18,44]). Our findings demonstrate the added diagnostic value of multimarker panels, which better reflect the multifactorial pathophysiology of these diseases. We also propose preliminary biomarker thresholds that, if validated in other centers using Simoa assays, could reduce the need for invasive and costly procedures, such as CSF analysis or PET imaging. Additionally, the observed inverse correlations between NfL/GFAP levels and MoCA scores in AD and PD highlight their potential utility in disease monitoring and support their integration into clinical protocols.

To conclude, our study confirmed the efficacy of NfL as a sensitive marker of neurological dysfunction. Although its specificity is limited, establishing concentration thresholds to aid in the differential diagnosis of neurodegenerative disorders could be a valuable diagnostic tool. Regarding diagnostic utility, both GFAP and pTau181 demonstrated low sensitivity and specificity, highlighting the need for more accurate biomarkers. However, relying on a single biomarker may be insufficient, as it fails to capture the complex pathophysiological mechanisms underlying these disorders. Neurodegenerative diseases begin developing in the body many years before the onset of noticeable symptoms. Therefore, identifying reliable biomarkers in easily accessible biofluids is crucial. Such biomarkers may facilitate early and rapid diagnosis, enabling timely therapeutic interventions before significant neurological damage occurs. This approach holds promise for improving patient outcomes by initiating treatment at the earliest stages of disease.

Ethical compliance statement

Ethical approval was obtained by the local ethic committee at Padua University Hospital and conducted according to the Declaration of Helsinki. All study participants gave written informed consent. All authors confirm that they have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

CRediT authorship contribution statement

Marta Campagnolo: Writing – original draft, Investigation. **Eleonora Fiorenzato:** Writing – original draft, Formal analysis, Data curation. **Giulia Musso:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Valentina Misenti:** Writing – review & editing, Methodology, Data curation. **Simone Cauzzo:** Writing – review & editing, Data curation. **Annachiara Cagnin:** Writing – review & editing, Supervision. **Roberta Biundo:** Writing – review & editing, Investigation. **Cinzia Bussè:** Writing – review & editing, Investigation. **Carmelo Alessandro Fogliano:** Writing – review & editing, Investigation. **Stefano Mozzetta:** Writing – review & editing, Investigation. **Alessandra Codemo:** Writing – review & editing, Investigation. **Elisabetta Gasparoli:** Writing – review & editing, Investigation. **Stefania Moz:** Writing – review & editing, Methodology, Investigation, Data curation. **Marco Narici:** Writing – review & editing, Methodology, Conceptualization. **Paola Pizzo:** Writing – review & editing, Methodology, Investigation. **Maurizio Corbetta:** Writing – review & editing. **Martina Montagnana:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Angelo Antonini:** Writing – review & editing, Supervision, Resources, Funding acquisition, Conceptualization.

Funding

Antonini A. has received compensation for consultancy and speaker related activities from UCB, Boehringer Ingelheim, Britannia, AbbVie, Kyowa Kirin, Zambon, Bial, Neuroderm, Theravance Biopharma, Roche; he receives research support from Chiesi Pharmaceuticals, Lundbeck, Horizon 2020 - Grant 825,785, Horizon2020 Grant 101,016,902, Ministry of Education University and Research (MIUR) Grant ARS01_01081, Cariparo Foundation. He serves as consultant for Boehringer–Ingelheim for legal cases on pathological gambling. Disclosures to report. Corbetta M. was supported by Fondazione Cassa di Risparmio di Padova e Rovigo (CARIPARO)—Ricerca Scientifica di Eccellenza 2018 (Grant Agreement number 55403); Italian Ministero della Salute, Brain connectivity measured with high-density electroencephalography: a novel neurodiagnostic tool for stroke (NEUROCONN; RF-2018-1,236,689); Celeghin Foundation Padova (CUP C94I20000420007); BIAL foundation grant (No. 361/18); Horizon 2020 European School of Network Neuroscience—European School of Network Neuroscience (euSNN), H2020-SC5–2019-2 (Grant Agreement number 860563); Horizon 2020 research and innovation program; Visionary Nature Based Actions For Heath, Wellbeing & Resilience in Cities (VARCITIES), Horizon 2020-SC5–2019-2 (Grant Agreement number 869505); Italian Ministero della Salute: Eye-movement dynamics during free viewing as biomarker for assessment of visuospatial functions and for closed-loop rehabilitation in stroke (EYEMOVINSTROKE; RF-2019-12,369,300). Pizzo P.'s research is funded by Italian Ministry of University and Scientific Research grants (PRIN2022943TH9 and PRIN P20225R4Y5, financed by the European Union, NextGenerationEU); Cure Alzheimer's Fund (USA) and Alzheimer's Association grant (USA; E2A-23-1148250); Next Generation EU and Italian Ministry of Research, NRRP-National Recovery and Resilience Plan grant, National Centre of Research 'Development of gene therapy and drugs with RNA technology', CN3 'Neurodegenerative Diseases'. Campagnolo M. was supported by Italian Ministry of University and Scientific Research grant PRIN-PNRR 2022FJAXY8 'Amyloid-related cortical excitability in patients with MCI due to Alzheimer's disease'. Musso G. has received compensation from Novartis Farma for scientific consultancy.

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. All the other authors declare that there are no additional disclosures to report.

Acknowledgments

We acknowledge co-funding from Next Generation EU, in the context of the National Recovery and Resilience Plan, Investment PE8 – Project Age-It: 'Ageing Well in an Ageing Society'. This resource was co-financed by the Next Generation EU [DM 1557 11.10.2022]. The views and opinions expressed are only those of the authors and do not necessarily reflect those of the European Union or the European Commission. Neither the European Union nor the European Commission can be held responsible for them. Of note, this funding source has no potential conflicts of interest related to the research covered in the article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2025.123617.

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