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Original Article

Assessing Parkinson's Disease Cognitive Impairment Severity via Plasma α-Synuclein, Phosphorylated α-Synuclein, and Neurofilament Light Chain

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SUMMARY

Background: α-synuclein (α-syn), Ser129-phosphorylated α-synuclein (p-α-syn), and neurofilament light chain (NfL) are potential biomarkers associated with cognitive impairment in Parkinson's disease (PD). This study investigates their plasma levels in relation to cognitive severity in PD.
Methods: We measured plasma α-syn, p-α-syn, and NfL levels using immunomagnetic reduction assays in 45 PD patients and 16 healthy controls. Statistical tests included Mann-Whitney U, Kruskal-Wallis, and Spearman's correlation analyses, with Bonferroni correction ($\alpha = 0.0125$).
Results: Levels of α-syn and p-α-syn were significantly higher in PD compared to controls ($p = 0.006$ and $p = 0.001$, respectively; Bonferroni-adjusted $p < 0.0125$; Cohen's $d = 1.2$ and 1.5, respectively). NfL levels were elevated in PD dementia (PDD) compared to controls ($p = 0.048$; Cohen's $d = 0.92$), though this did not meet the Bonferroni-adjusted threshold of $p < 0.0125$. NfL levels were negatively correlated with Mini-Mental State Examination (MMSE) scores ($\rho = -0.35$, $p < 0.0125$), distinguishing PDD from controls but not from PD with normal cognition (PDNC). No significant correlations were observed between NfL levels and cognitive severity or across PD mild cognitive impairment (PDMCI) subtypes.
Conclusion: While α-syn, p-α-syn, and NfL are elevated in PD, only NfL distinguishes PDD from controls, with inconclusive ties to cognitive severity. Larger studies are needed.

1. Introduction

Parkinson's disease (PD), the second most common neurodegenerative disease, is characterized by dopaminergic neuron loss and Lewy body accumulation.[1] It causes motor and non-motor symptoms, including cognitive dysfunction, which significantly impacts patients' quality of life, increases caregiver burden, and escalates healthcare costs. Dementia affects 83% of patients after 20 years.[2] A spectrum of cognitive function rather than clear-cut stages is observed among PD patients, ranging from normal cognition (PDNC) to dementia (PDD), with mild cognitive impairment (PDMCI) as an intermediate stage.[2] PD patients with PDMCI may differ in affected cognitive domains.[3] Early identification of PDMCI is crucial to prevent progression to dementia.

Recent biomarker research has shifted from invasive cerebrospinal fluid (CSF) sampling to plasma-based assays due to their accessibility and patient tolerability.[4] Recent plasma proteomics studies predict PD up to 7 years pre-symptomatically,[5] complementing this shift. However, challenges such as lower analyte concentrations and variability in blood processing persist, necessitating robust validation.[4,6] Identifying reliable plasma markers could accelerate clinical trials for disease-modifying therapies in PD. α-synuclein (α-syn) accumulates abnormally in PD neurons, with pathogenic aggregation into Lewy bodies correlating with cognitive impairment.[2] Post-translational modifications like Ser129-phosphorylation (p-α-syn) contribute to PD progression.[7,8] Both α-syn and p-α-syn are candidate biofluid markers of PD cognitive function in CSF studies,[4] but plasma studies remain inconclusive despite their non-invasive appeal.[4,9]

Neurofilament light chain (NfL), specific to neuronal damage, shows elevated levels in neurodegenerative diseases.[10] Though not PD-specific,[4,11,12] plasma NfL may distinguish cognitive decline severity and monitor PD progression.[13–15]

Identifying biomarkers to predict cognitive decline is vital for therapeutic interventions. This study investigates correlations between plasma α-syn, p-α-syn, and NfL levels with cognitive severity and PDMCI subtypes in PD.

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2. Materials and methods

2.1. Participants

All participants were recruited from Chang Gung Memorial Hospital. This study included 61 participants: 45 patients with PD and 16 healthy controls. Healthy controls were unrelated adult volunteers without neurodegenerative disease. PD was diagnosed by an experienced movement-disorder specialist (YR Wu) according to the United Kingdom Parkinson's Disease Society Brain Bank clinical diagnostic criteria.[16] We recorded age, sex, and evaluated disease presentation using various assessments. Informed consent was obtained, and the study was approved by the Institutional Review Board of Chang Gung Memorial Hospital (ethical license No.: 2019 01005B0C501).

2.2. Diagnosis of Parkinson's disease with mild cognitive impairment or dementia

PDMCI diagnosis followed Movement Disorder Society (MDS) criteria.[17] Impairment in global cognitive ability was defined as Montreal Cognitive Assessment (MoCA) score < 26.[18] In contrast to patients with PDD, a diagnosis of PDMCI requires that the patient's cognitive impairment does not interfere with daily independent function. PDD was diagnosed per MDS criteria,[19] requiring that their deficits be severe enough to impair daily life. Exclusion criteria included cerebrovascular events, brain injury, or secondary Parkinsonian symptoms.

2.3. Neuropsychological evaluation

Disease severity and clinical manifestation were accessed using the Unified Parkinson's Disease Rating Score (UPDRS) and modified Hoehn and Yahr scale.[14] Neuropsychological evaluations covered global and domain-specific cognition. We selected the Montreal Cognitive Assessment (MoCA) over the Mini-Mental State Examination (MMSE) as the primary screening tool due to its greater sensitivity to executive function and visuospatial deficits, which are critical for early detection of PDMCI.[17] Detailed assessments for specific domains, such as memory and attention, were conducted using standardized test (Table 1). Subtyping adhered to MDS recommendations (Table 1).[17]

2.4. Plasma biomarker measurement

Plasma α-syn, p-α-syn, and NfL levels were measured via immunomagnetic reduction assays (IMR) (MagQu; New Taipei City, Taiwan).[20–23] Blood was collected in EDTA tubes, centrifuged within 3 hours of collection at 2,500 $\times$ g for 15 min at 4 °C, and plasma stored at -80 °C. Hemolysis was minimized by excluding samples with visible red discoloration. IMR quantified biomarkers through magnetic signal suppression correlated with biomarker concentration.

2.5. Statistical methods and data analysis

Numerical variables were expressed as the mean $\pm$ standard deviation. Mann-Whitney U and Kruskal-Wallis tests compared groups. Spearman's correlation analyzed biomarker relationships with cognitive scores. To account for multiple comparisons (α-syn, p-α-syn, NfL, and their product), Bonferroni correction adjusted the significance threshold to $\alpha = 0.05/4 = 0.0125$, minimizing the risk of type I errors inherent in testing multiple biomarkers. Effect sizes were calculated using Cohen's d.[24] Post-hoc power analysis was conducted with G*Power 3.1, assuming a medium effect size (d = 0.5), α = 0.0125, and sample size (n = 61), to evaluate the study's ability to detect moderate effects given the limited cohort size. Analyses used SPSS software, version 24 (IBM; Armonk, NY, USA).

3. Results

3.1. Clinical characteristics of participants

The study cohort included 45 patients with PD (15 PDNC, 16 PDMCI, 14 PDD) and 16 healthy controls. Patients with PD were further classified as PD with normal cognition (PDNC), PDMCI, or PDD. Demographic and clinical data are summarized in Table 2. Education

Table 1
Neuropsychological assessments for different cognitive domains applied in this study.

Cognitive domain	Assessments	
Global cognition function	Mini-Mental State Examination (MMSE)	Montreal Cognitive Assessment (MoCA)
Visuospatial function	Judgment of line orientation	Taylor complex figure test (copy)
Executive function	Trail making test	Digits-backward
Memory	California verbal language test-short form	Taylor complex figure test (immediate and delay recall)
Attention and working memory	Digits-forward	Digital symbol modality test
Language	Boston naming test	Similarities

Table 2
Clinical characteristics of participants.

	HC (n = 16)	PD (n = 45)				p value
		All PD (n = 45)	PDNC (n = 15)	PDMCI (n = 16)	PDD (n = 14) [a]	
Age (years)	60.00 $\pm$ 8.49	70.64 $\pm$ 10.67	61.38 $\pm$ 9.13	73.69 $\pm$ 8.08	77.50 $\pm$ 7.11	***
Gender (male, %)	44	47	40	56	43	0.809
MMSE	28.88 $\pm$ 1.20	24.07 $\pm$ 5.80	28.67 $\pm$ 1.18	25.94 $\pm$ 2.79	15.71 $\pm$ 5.04	***
MoCA	27.19 $\pm$ 1.47	19.67 $\pm$ 7.64	27.27 $\pm$ 1.44	19.63 $\pm$ 2.75	10.57 $\pm$ 2.93	***
UPDRS total	N.A.	32.26 $\pm$ 15.68	21.93 $\pm$ 12.04	34.06 $\pm$ 14.51	52.55 $\pm$ 14.96	***
UPDRS part I	N.A.	2.37 $\pm$ 1.91	1.53 $\pm$ 1.13	2.69 $\pm$ 2.27	4.09 $\pm$ 2.30	*
Modified H-Y scale	N.A.	2.4 $\pm$ 1.1	1.5 $\pm$ 0.6	2.3 $\pm$ 0.9	3.5 $\pm$ 0.6	***
LEDD (mg)	N.A.	614.45 $\pm$ 405.33	494.86 $\pm$ 404.40	658.34 $\pm$ 467.40	692.42 $\pm$ 320.08	0.141

* $p \leq 0.05$; *** $p \leq 0.001$.
HC, healthy control; LEDD, Levodopa Equivalent Daily Dose; MMSE, Mini-Mental State Examination; modified H-Y scale, modified Hoehn and Yahr scale; MoCA, Montreal Cognitive Assessment; N.A., not available; NfL, neurofilament light chain; PDD, PD with dementia; PDNC, Parkinson's disease with normal cognition; PDMCI, PD with mild cognitive impairment; p-α-synuclein, Ser129-phosphorylated α-synuclein; UPDRS, Unified Parkinson's Disease Rating score.
[a] 3 out of 14 patients with PDD were unable to perform UPDRS because of their poor motor and/or cognitive conditions.

levels varied across groups (e.g., mean 12.5 years in PDNC vs. 9.8 years in PDD), potentially influencing cognitive test performance. Disease duration was notably longer in PDD (mean 8.2 years) compared to PDNC (mean 3.5 years), reflecting disease progression. Three of 14 PDD patients could not complete UPDRS due to poor motor/cognitive conditions.

3.2. Plasma biomerkers

Plasma α-syn and p-α-syn were higher in all PD groups than controls (α-syn: p = 0.006, d = 1.2; p-α-syn: p = 0.001, d = 1.5; Bonferroni-adjusted p < 0.0125), while NfL was elevated in PDD patients (p = 0.048, d = 0.92). A significant difference (p = 0.015) in NfL levels was observed between controls and PD patients as a single group. No significant biomarker differences were observed among PD subgroups (p > 0.0125) (Table 3) (Figure 1). Correlations between α-syn and p-α-syn were positive (ρ = 0.45, p < 0.0125), but no correlation was found between α-syn or p-α-syn and NfL (Figure 2). Biomarker ratios lacked discriminatory power (Table 4). The product of α-syn, p-α-syn, and NfL was higher in PD (p < 0.001, d = 1.8) but did not distinguish cognitive status (Figure 3).

3.3. Correlation between investigated proteins and neuropsychological assessments

Plasma levels of α-syn and p-α-syn did not correlate with either MMSE or MoCA scores (p > 0.0125). Plasma NfL correlated negatively with MMSE (ρ = -0.35, p < 0.0125) and MoCA (ρ = -0.32, p < 0.05) (Figure 4). This negative correlation suggests that greater axonal damage, as reflected by higher NfL levels, is associated with more pronounced cognitive decline, particularly evident in PDD patients where neurodegeneration is advanced. Domain-specific neuropsychological tests revealed significant differences between PDNC and PDMCI groups (Supplementary Table 1), but no biomarker correlations were observed in PDMCI (Supplementary Table 2). Post-hoc power analysis (d = 0.5, α = 0.0125, n = 61)

Table 3
Plasma biomarker levels by group.

	HC (n = 16)	PDNC (n = 15)	PDMCI (n = 16)	PDD (n = 14)	p value (vs. HC)*	p value (PD subgroups)**
α-synuclein (pg/mL)	0.095 ± 0.026	0.138 ± 0.032	0.140 ± 0.064	0.146 ± 0.050	0.006***	0.817
p-α-synuclein (pg/mL)	0.00085 ± 0.000340	0.00168 ± 0.000640	0.00156 ± 0.000916	0.00136 ± 0.000524	0.001***	0.431
NfL (pg/mL)	8.534 ± 2.478	10.542 ± 2.989	10.833 ± 3.923	12.729 ± 4.343	0.048	0.336

* p value (vs. HC): Comparison between healthy controls (HC) and all PD patients (PDNC, PDMCI, PDD combined), using Mann-Whitney U test. ** p value (PD Subgroups): Comparison among PD subgroups (PDNC vs. PDMCI vs. PDD), using Kruskal-Wallis test. *** Indicates significance after Bonferroni correction (α = 0.0125, adjusted for 4 comparisons: α-syn, p-α-syn, NfL, product).
HC: healthy control; NfL: neurofilament light chain; PDD: PD with dementia; PDNC: Parkinson's disease with normal cognition; PDMCI: PD with mild cognitive impairment; p-α-synuclein: Ser129-phosphorylated α-synuclein.

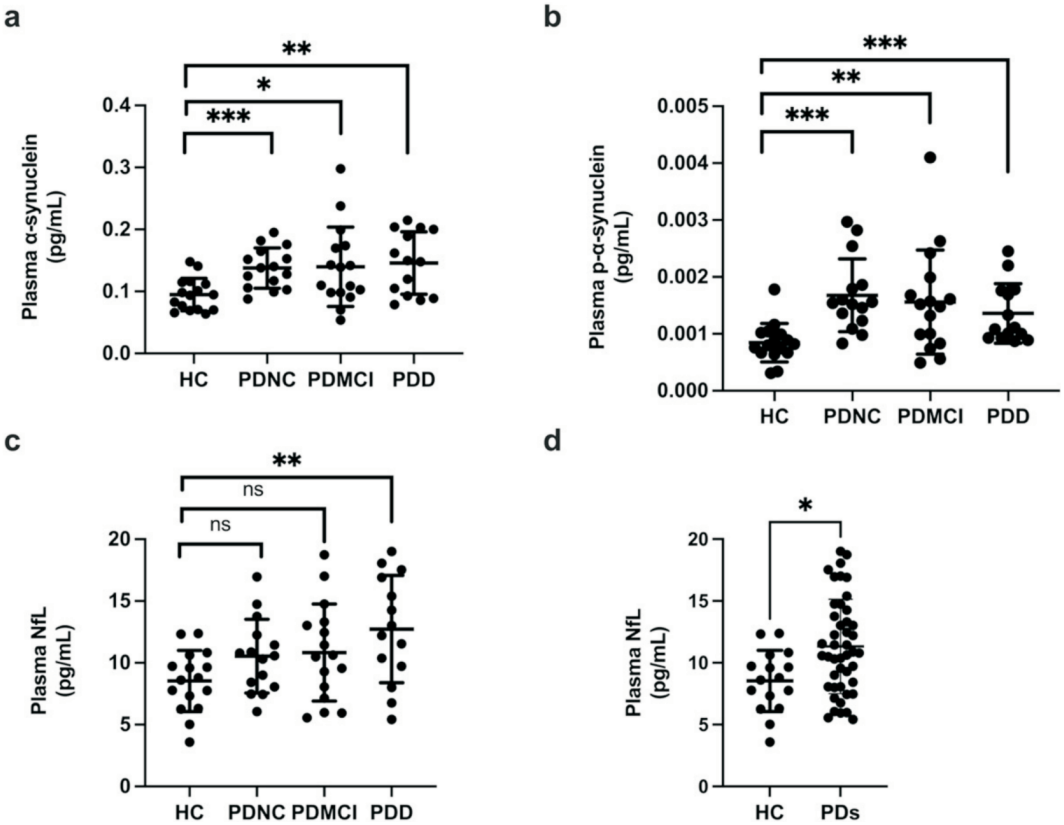

Figure 1. Comparison of α-synuclein (A), p-α-synuclein (B), and NfL (C, D) concentrations between groups. Data were compared using the two-tailed Mann-Whitney U test. *** p ≤ 0.001; ** p ≤ 0.01; * p < 0.05; HC, healthy control; NfL, neurofilament light chain; ns, p > 0.05; PDD, Parkinson's disease with dementia; PDMCI, Parkinson's disease with mild cognitive impairment; PDNC, Parkinson's disease with normal cognition; PDs, patients with Parkinson's disease as a single group; p-α-synuclein, Ser129-phosphorylated α-synuclein.

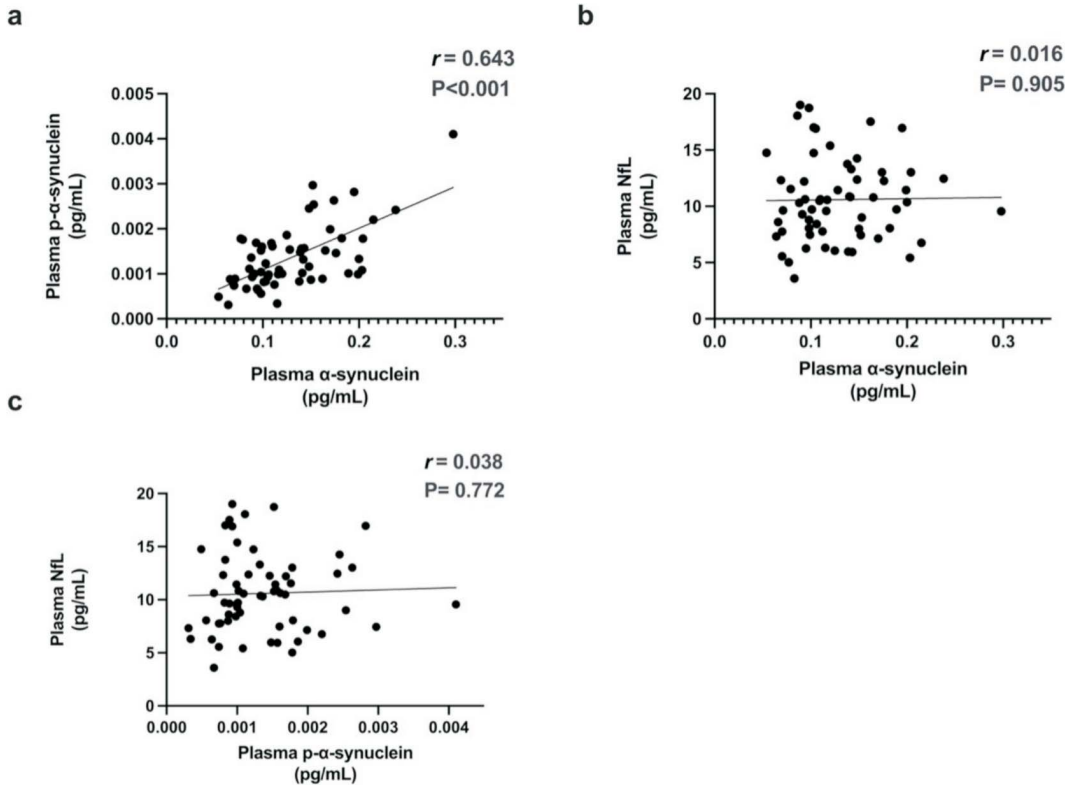

Figure 2. Correlation between α-synuclein and p-α-synuclein (A), α-synuclein and NfL (B), p-α-synuclein and NfL (C). p value was determined by Spearman's rank correlation. NfL, neurofilament light chain; p-α-synuclein, Ser129-phosphorylated α-synuclein

Table 4
Biomarker ratios and combinations by group.

	HC (n = 16)	PDNC (n = 15)	PDMCI (n = 16)	PDD (n = 14)	p value	p value (HC excluded)
p-α-synuclein/α-synuclein	0.00938 ± 0.00457	0.01228 ± 0.00376	0.01104 ± 0.00325	0.01037 ± 0.00531	0.088	0.248
α-synuclein/NfL	0.0120 ± 0.0045	0.0139 ± 0.00046	0.0146 ± 0.0078	0.0143 ± 0.0102	0.678	0.692
p-α-synuclein/NfL	0.000109 ± 0.000073	0.000175 ± 0.000093	0.000162 ± 0.000104	0.000125 ± 0.000075	0.057	0.315
Product of 3 biomarkers	0.000729 ± 0.000514	0.002585 ± 0.002043	0.002783 ± 0.003031	0.002342 ± 0.001250	< 0.001	0.823

HC, healthy control; NfL, neurofilament light chain; PDD, Parkinson's disease with dementia; PDNC, Parkinson's disease with normal cognition; PDMCI, Parkinson's disease with mild cognitive impairment; p-α-synuclein, Ser129-phosphorylated α-synuclein.

yielded a power of 0.60, indicating limited sensitivity for moderate effects.

4. Discussion

This study confirms elevated plasma α-syn and p-α-syn in PD patients compared to controls, consistent with previous IMR studies,[20] and elevated NfL in PDD patients.[15] However, only NfL negatively correlated with MMSE (ρ = -0.35, p < 0.0125), distinguishing PDD from controls, with no biomarkers differentiating PDNC, PDMCI, or PDD subgroups.

Cortical α-syn pathology strongly correlates with cognitive decline in PD.[2] Lin et al.,[25] using IMR, reported higher plasma α-syn in PDD (4.09 pg/mL) versus PDNC (0.42 pg/mL), contrasting our sub-pg/mL levels (e.g., 0.146 ± 0.050 pg/mL in PDD), which align with Chang et al. (0.2566 ± 0.0502 pg/mL).[26] These discrepancies may reflect plasma processing differences — e.g., centrifugation timing or hemolysis control[4,6] — as α-syn is sensitive to erythrocyte contamination.[27] Our rigorous protocol (centrifugation within 3 hours, hemolysis exclusion) likely reduced such artifacts, yet α-syn and p-α-syn showed no cognitive severity gradient.

Methodologically, IMR's sub-pg/mL sensitivity contrasts with ELISA's wider range (2.6–177,100 pg/mL),[28] possibly due to antibody affinity or aggregation states.[29] Structural isoforms (e.g., α-syn112) or phosphorylation (pY125) might alter IMR detection,[27,29] though this remains unconfirmed. Cognitive assessments also vary: Lin et al. used MMSE,[25] while our MoCA-based PDMCI diagnosis may miss subtle MMSE-specific trends.[18,30]

Biologically, p-α-syn's lack of cognitive correlation, despite elevated plasma levels in PD patients (p = 0.001, d = 1.5), suggests it reflects motor-related Lewy body burden rather than cortical pathology driving cognitive decline.[2,21] Braak's model links cognitive decline to cortical Lewy bodies,[31] but co-pathologies like amyloid-beta and tau in PDD may dilute α-syn's signal.[4,32] Emerging plasma markers like GFAP and p-tau suggest additional neurodegenerative mechanisms influence PDD progression,[33,34] potentially explaining our null findings for α-syn and p-α-syn across cognitive stages. NfL's elevation in PDD (p = 0.048, d = 0.92) and MMSE correlation align with axonal damage in advanced PD,[13,15] yet its lack of subgroup specificity echoes mixed findings — e.g., no PDNC-control difference in Batzuet al.[35] The rise in NfL likely reflects widespread white matter damage and axonal degeneration, consistent with the severe cognitive deficits observed in PDD, whereas α-syn and p-α-syn may predominantly contribute to motor-related Lewy body pathology rather

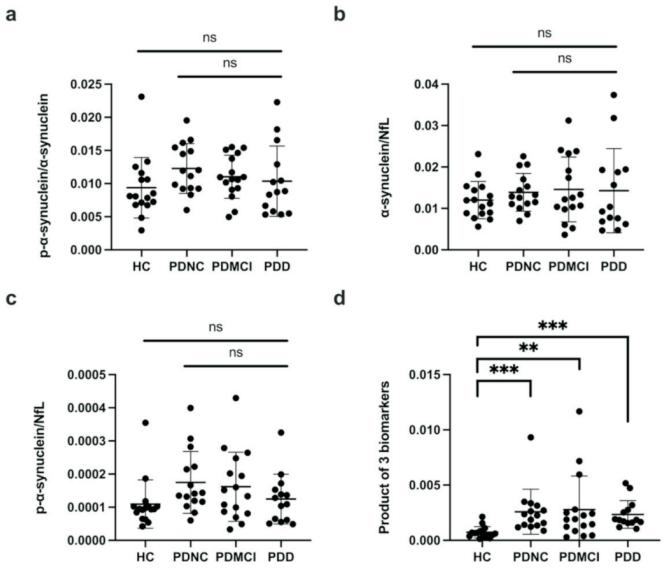

Figure 3. Comparison of p-α-synuclein/α-synuclein (A), α-synuclein/NfL (B), p-α-synuclein/NfL (C), and the product of α-synuclein, p-α-synuclein and NfL (D) between groups. Data were compared using the two-tailed Mann-Whitney U test. *** $p \leq 0.001$; ** $p \leq 0.01$; * $p < 0.05$; HC, healthy control; NfL, neurofilament light chain; ns, $p > 0.005$; PDD, Parkinson's disease with dementia; PDMCI, Parkinson's disease with mild cognitive impairment; PDNC, Parkinson's disease with normal cognition; p-α-synuclein, Ser129-phosphorylated α-synuclein.

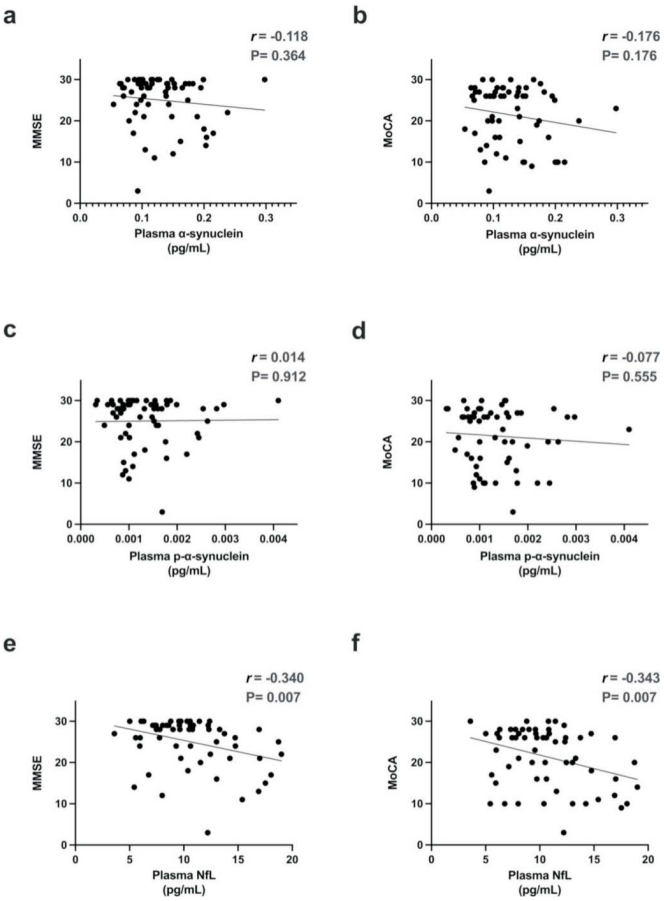

Figure 4. Correlation between MMSE or MoCA and α-synuclein (A, B), MMSE or MoCA and p-α-synuclein (C, D), and MMSE or MoCA and NfL (E, F). p value was determined by Spearman's rank correlation. MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; NfL, neurofilament light chain; p-α-synuclein, Ser129-phosphorylated α-synuclein.

than cortical cognitive decline.[21]

The selective correlation of NfL with PDD suggests its utility as a prognostic marker for advanced cognitive decline, potentially aiding in patient stratification for clinical trials.[15,35] PDMCI's heterogeneity[3] — e.g., executive versus memory deficits — complicates biomarker correlations.[36,37] Our comprehensive neuropsychological battery (Table 1) revealed PDNC-PDMCI differences (Supplementary Table 1), but no biomarker ties, possibly due to small subtype samples (n = 11 for PDMCI correlations). The cross-sectional design and small cohort (n = 61) limit progression insights and power (0.60 for d = 0.5), despite large effects for α-syn (d = 1.2) and p-α-syn (d = 1.5).[24]

This study's strengths include evaluating a diverse range of PD cognitive stages and conducting comprehensive neuropsychological testing across multiple domains. Limitations include sample size, cross-sectional nature, and unassessed hemoglobin effects on α-syn.[27] Future studies need larger cohorts (n > 100) for power > 0.8,[24] longitudinal tracking,[15] and multi-marker CSF-imaging integration.[4,38] Combining plasma biomarkers with PET imaging (e.g., tau or amyloid scans) could elucidate the dynamic transition from PDMCI to PDD, while integrating genetic factors like APOE may uncover additional drivers of cognitive progression. Such approaches promise to refine these biomarkers' roles in PD cognition and guide targeted interventions.

In conclusion, while plasma α-syn, p-α-syn, and NfL are elevated in PD, only NfL distinguishes PDD from controls with a negative MMSE correlation, highlighting its prognostic potential; their limited ties to cognitive progression underscore the need for broader, longitudinal validation to refine their diagnostic roles in PD cognition.

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Declaration of conflicts of interest

None.

Supplementary materials

Supplementary materials for this article can be found at http://www.sgecm.org.tw/ijge/journal/view.asp?id=35.

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