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ORIGINAL RESEARCH

Diagnostic Value of Carotid Intima-Media Thickness Combined with Periventricular White Matter Hyperintensities for Mild Cognitive Impairment in Parkinson's Disease

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Purpose: To determine the independent association of carotid intima-media thickness (CIMT) and periventricular white matter hyperintensities (PWMHs) with mild cognitive impairment in Parkinson's disease (PD-MCI) and evaluate the diagnostic value of CIMT combined with PWMHs for PD-MCI.

Patients and Methods: A prospective cohort of 541 PD patients was enrolled, and all patients underwent carotid artery ultrasound for mean CIMT measurement and 3T brain MRI for PWMH volume quantification. PD-MCI was diagnosed via comprehensive neuropsychological assessment (10 tests across 5 domains) based on established criteria, ie, at least two tests demonstrated abnormal results, either one impaired test in two different cognitive domains or two impaired tests in a single cognitive domain. Multivariate analysis was conducted to determine the independent association, and the receiver operating characteristic (ROC) curve was employed to assess the diagnostic values, and the *Z* test was employed to compare the area under curve (AUC).

Results: PD-MCI prevalence was 45.5% (246/541). Multivariate analysis, adjusting for education duration, Cys C levels, disease duration, total brain WMHs, hypertension, hyperlipidemia, and age, identified PWMHs [odds ratio (OR): 2.114, 95% confidence interval (CI): 1.391–4.586], CIMT (OR: 2.027, 95% CI: 1.485–4.281), homocysteine (OR: 1.551, 95% CI: 1.172–2.680), Hoehn and Yahr stage (OR: 2.243, 95% CI: 1.534–4.736), and MDS-UPDRS part III score (OR: 1.416, 95% CI: 1.158–2.465) as independent PD-MCI predictors. ROC analysis demonstrated significantly higher diagnostic value for the combination of CIMT and PWMHs (AUC: 0.908, 95% CI: 0.882–0.934) compared to either marker alone (AUC: 0.705, 95% CI: 0.661–0.750 for PWMHs; AUC: 0.722, 95% CI: 0.678–0.765 for CIMT; both $P < 0.001$).

Conclusion: The combination of CIMT and PWMHs provides significantly superior diagnostic value for PD-MCI compared to either marker individually, and this integrated model suggests a potential tool for identifying PD patients at high risk for cognitive decline.

Keywords: Parkinson's disease, mild cognitive impairment, carotid intima-media thickness, periventricular white matter hyperintensities, prediction

Introduction

Parkinson's disease (PD), the second most common neurodegenerative disorder after Alzheimer's disease (AD), affects > 1% of adults aged ≥ 65 years and is characterized by motor symptoms (eg, bradykinesia, rigidity) and non-motor manifestations.[1] Among non-motor manifestations, cognitive impairment is common, potentially occurring at any disease stage. Mild cognitive impairment (MCI) represents a critical intermediate stage between normal cognition and dementia in PD, with a pooled prevalence of ≥ 40%.[2,3] Mild cognitive impairment in Parkinson's disease (PD-MCI) confers a substantially elevated risk of progression to Parkinson's disease dementia (PDD),[4] with individuals six times more likely to develop dementia than age-matched controls and a long-term PDD prevalence reaching 80% after 15–20 years of disease duration.[5] This progression

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severely compromises patients' quality of life, functional independence, and survival,[6,7] underscoring the urgent need for early biomarkers to predict and intercept cognitive decline.

Carotid intima-media thickness (CIMT), a surrogate marker of subclinical atherosclerosis measured via ultrasonography, is an independent predictor of cognitive decline in middle-aged and elderly populations.[8] In PD, CIMT correlates with cognitive dysfunction and disease progression,[9,10] reflecting an underlying vascular pathology. Concurrently, periventricular white matter hyperintensities (PWMHs), visualized on T2-weighted or FLAIR MRI sequences, are indicative of cerebral small vessel disease and chronic hypoperfusion.[11] The vascular pathology represented by CIMT may thus synergize with the cerebral small vessel disease evident as PWMHs, collectively exacerbating cognitive decline in PD. Indeed, PWMHs are highly prevalent in PD and are strongly associated with MCI,[12] with particular detrimental effects on executive function and processing speed.[13,14] Recent studies continue to underscore the role of WMHs in PD-related cognitive and motor outcomes.[15–17] While CIMT and PWMHs individually demonstrate associations with PD-MCI, their combined diagnostic utility remains unexplored. No study has yet integrated these vascular and neuroimaging markers into a unified model to discriminate PD-MCI patients from those with normal cognition in a cross-sectional setting.

In this study, PD-MCI was diagnosed based on a comprehensive neuropsychological assessment according to the criteria described in the Methods section, aiming to bridge this gap by evaluating the synergistic potential of CIMT and PWMHs in diagnosing PD-MCI. We hypothesize that their combination will enhance diagnostic accuracy beyond either marker alone, offering a clinically accessible tool for early risk stratification and intervention.

Patients and Methods

Participants

Between January 2021 and March 2024, we prospectively enrolled a consecutive cohort of PD patients from Chongqing University Jiangjin Hospital. This study was approved by the Chongqing University Jiangjin Hospital Ethics Committee (JJ2021017036) and conducted in accordance with the *Declaration of Helsinki*. All participants provided written informed consent.

Inclusion criteria comprised: ① Newly diagnosed PD meeting the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria;[18] ② De novo status, defined as cumulative levodopa exposure ≤2 weeks and no use within 4 weeks prior to recruitment; ③ Age 45–80 years; ④ Ability to complete neuropsychological evaluation.

Exclusion criteria included: ① Medication-induced parkinsonism; ② Features suggestive of progressive supranuclear palsy or multiple system atrophy per consensus criteria;[19,20] ③ Documented severe normal-pressure hydrocephalus (NPH) or vascular encephalopathy on MRI; ④ History of deep brain stimulation (DBS); ⑤ Significant renal/hepatic impairment, or severe cardiovascular, respiratory, hematologic, wasting, or metabolic disorders; ⑥ Prior carotid endarterectomy (CEA) or carotid artery stenting (CAS) for carotid stenosis; ⑦ Current use of medications with potential cognitive adverse effects.

All participants underwent baseline MRI and cognitive assessment. Patients with Clinical Dementia Rating (CDR) ≥ 0.5, indicating possible dementia, were excluded to enhance the specificity of the PD-MCI diagnosis.

Data Collection

Clinical, demographic, and laboratory data were collected for all participants. These included age, gender, body mass index (BMI), hypertension status, diabetes status, hyperlipidemia status, smoking history, disease duration, educational duration, current non-PD and PD medications, homocysteine (Hcy), total cholesterol (TC), triglycerides (TG), cystatin C (Cys C), apolipoprotein B (Apo B), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C). Trained research personnel performed clinical evaluations, including the Hoehn and Yahr (H&Y) stage and the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS).

Neuropsychological Evaluation

Participants underwent a comprehensive neuropsychological assessment comprising 10 tests evaluating five cognitive domains: memory, attention/working memory, visuospatial function, executive function, and language. Two tests assessed each domain:

① Memory: Rey-Osterrieth Complex Figure (ROCF) delayed recall and Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) word list learning with delayed recall;
② Attention/Working Memory: Wechsler Memory Scale-Fourth Edition (WMS-IV) Symbol Span and Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV) Digit Span Backward;
③ Visuospatial Function: Benton Judgment of Line Orientation (BJLOT) and Rey-Osterrieth Complex Figure (ROCF) copying test;
④ Executive Function: Frontal Assessment Battery (FAB) and Fruit Fluency Test (FFT);
⑤ Language: WAIS-IV Similarities and Boston Naming Test (BNT).

MCI in PD patients was defined by abnormal performance on at least two tests, meeting either of the following criteria: ① one impaired test in each of two different cognitive domains, or ② two impaired tests within a single cognitive domain. A test score falling 1.5 standard deviations below the normative mean, adjusted for age and education where available, was considered impaired.

Quantification of WMHs

MRI was performed using a 3T Skyra system (Siemens Healthineers, Erlangen, Germany). The acquisition parameters for each sequence were as follows: ① T1-weighted Magnetization Prepared-Rapid Gradient Echo (MP RAGE): 1900 / 2. 44 ms of repetition time (TR)/echo time (TE), 256×253 of matrix size, 900 ms of inversion time (TI), 250×250 of field of view (FOV), and 1 mm of slice thickness; ② Fluid-Attenuated Inversion Recovery (FLAIR): 7000 / 132 ms of TR/TE, 256×256 of matrix size, 2.2102e + 03 ms of TI, 220×220 of field of view, 150°of flip angle and 4 mm of slice thickness.

Image preprocessing was implemented using custom scripts in MATLAB R2017b (The MathWorks, Natick, MA, USA) and SPM8 (https://www.fil.ion.ucl.ac.uk/spm/). The processing pipeline consisted of: ① Segmentation & Coregistration: T1-weighted images were segmented into tissue classes using a priori SPM8 tissue probability maps. The resulting tissue segments were then coregistered to the corresponding FLAIR images; ② Intensity Correction & White Matter Segmentation: Non-uniformity intensity correction and segmentation of white matter tissue on FLAIR images were performed using the "new segment" function within SPM8;[21] ③ WMH Quantification: White matter hyperintensity (WMH) volumes for the total brain and periventricular region were calculated based on the segmented FLAIR images.

Carotid Artery Ultrasound Examination

Carotid artery ultrasound examination was performed using a GE LOGIQ E9 color Doppler ultrasound system (GE Healthcare, USA). CIMT was defined as the distance between the media-adventitia interface and the lumen-intima interface. CIMT was measured bilaterally at the following sites: the common carotid artery, carotid bulb, and the proximal and distal walls of the internal carotid artery (ICA). The mean CIMT value was computed from these twelve measurement points.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics (version 20.0; SPSS Inc., Chicago, IL, USA). A two-sided P value < 0.05 was considered statistically significant. Normality of continuous variables was assessed using the Kolmogorov–Smirnov test. Normally distributed data are presented as mean ± standard deviation (SD) and were compared between groups using the independent samples t test. Non-normally distributed data are presented as median (M) and interquartile range (IQR) and were compared between groups using the Mann–Whitney U-test. Categorical data are presented as percentages (%) and were compared between groups using the chi-square test (χ^2 test). Multicollinearity was assessed using Variance Inflation Factors (VIF), and a VIF value of ≥ 5 was considered indicative of significant collinearity.

Variables yielding a two-sided P value < 0.10 in univariate analysis were entered into a binary *logistic* regression model to identify independent risk factors for MCI in patients with PD. Receiver operating characteristic (ROC) curve analysis was employed to evaluate predictive values. The DeLong test (Z test for AUC comparison) was used to compare the areas under the ROC curves (AUCs).

Results

General Data

During the study period, 601 patients with PD were recruited. Of these, 60 patients were excluded: 30 for declining study participation, 17 due to signs or symptoms suggestive of other (atypical) disorders, 6 because of prior PD medication use, 4 due to the occurrence of NPH, and 3 for exhibiting predominant postural tremor and polyneuropathy. Consequently, 541 patients were included in the final analysis.

The study cohort comprised 306 males (56.6%) and 235 females (43.4%), with a mean age of 64.07 ± 9.15 years. The mean disease duration was 14.28 ± 8.16 months. MCI was identified in 246 PD patients, yielding a prevalence of 45.5%.

Univariate Analysis

Univariate analysis was performed comparing PD patients with MCI to those without MCI. The results (Table 1) demonstrated statistically significant differences ($P < 0.05$) in hypertension, disease duration, duration of education, MDS-UPDRS part III score, Hoehn and Yahr stage, total brain WMHs, PWMHs, CIMT, Hcy levels, and Cys C levels. No significant differences ($P > 0.05$) were observed for the remaining variables, although age and hyperlipidemia prevalence exhibited trends towards significance ($P < 0.10$).

Multivariate Analysis

To identify risk factors for MCI in PD patients, variables including hypertension, disease duration, education duration, MDS-UPDRS part III score, Hoehn and Yahr stage, total brain WMHs, PWMHs, CIMT, Hcy levels, Cys C levels, age, and hyperlipidemia were included in a binary *logistic* regression model for multivariate analysis. After adjustment for confounders

Table 1 Results of Univariate Analysis Between MCI Group and Non-MCI Group in PD Patients

	PD Patients (541)	MCI Group (246)	Non-MCI Group (295)	χ^2/t	*P*
Age (years, mean±SD)	64.07±9.15	64.83±9.30	63.44±9.02	1.755	0.083
Male (n, %)	306 (56.6%)	133 (54.1%)	173 (58.6%)	1.145	0.285
BMI (Kg/m^2, mean±SD)	24.15±3.48	24.29±3.52	24.03±3.45	0.863	0.407
Hypertension	244 (45.1%)	123 (50.0%)	121 (41.0%)	4.372	0.037
Diabetes	91 (16.8%)	47 (19.1%)	44 (14.9%)	1.684	0.194
Hyperlipidemia	264 (48.8%)	131 (53.3%)	133 (45.1%)	3.581	0.059
Smoking	107 (19.8%)	51 (20.7%)	56 (19.0%)	0.259	0.611
Disease duration (months, mean±SD)	14.28±8.16	13.45±8.32	14.97±8.03	−2.150	0.035
Duration of education (years, mean±SD)	10.69±3.97	10.20±4.03	11.10±3.92	−2.619	0.009
MDS-UPDRS part III score (mean±SD)	21.05±9.94	22.46±10.31	19.87±9.63	2.998	0.003
Hoehn and Yahr stage (mean±SD)	1.81±0.52	1.87±0.55	1.76±0.49	2.433	0.016
Levodopa equivalent daily dose (mg/d, mean±SD)	158.97±59.88	158.42±60.83	159.43±59.09	−0.195	0.856
Total brain WMHs (cm^3, mean±SD)	1.20±0.69	1.27±0.78	1.14±0.61	2.127	0.037
PWMHs (cm^3, mean±SD)	1.06±0.57	1.19±0.61	0.95±0.54	4.799	<0.001
Hcy (μmol/L, mean±SD)	15.03±5.12	15.99±4.85	14.23±5.34	4.014	<0.001
TC (mmol/L, mean±SD)	4.19±1.16	4.25±1.21	4.14±1.12	1.089	0.296
TG (mmol/L, mean±SD)	1.28±0.61	1.25±0.56	1.31±0.65	−1.153	0.264
Cys C (mg/L, mean±SD)	0.94±0.37	0.98±0.40	0.91±0.34	2.168	0.033
Apo B (g/L, mean±SD)	0.84±0.32	0.85±0.33	0.83±0.31	0.721	0.477
HDL-C (mmol/L, mean±SD)	1.28±0.59	1.26±0.55	1.30±0.62	−0.795	0.441
LDL-C (mmol/L, mean±SD)	2.69±1.14	2.73±1.18	2.66±1.11	0.706	0.485
CIMT (mm, M, IQR)	0.7 (0.2)	0.8 (0.3)	0.6 (0.2)	4.533	<0.001

Abbreviations: PD, Parkinson's disease; MCI, Mild cognitive impairment; BMI, Body mass index; MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale; WMHs, White matter hyperintensities; PWMHs, Periventricular white matter hyperintensities; Hcy, Homocysteine; TC, Total cholesterol; TG, Triglyceride; Cys C, Cystatin C; Apo B, Apolipoprotein B; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; CIMT, Carotid intima-media thickness; SD, Standard deviation; M, Median; IQR, Interquartile range.

Table 2 Results of Multivariate Analysis Between MCI Group and Non-MCI Group in PD Patients

Variables	β	SE	Wald χ^2	OR	95% CI	*P*
PWMHs	0.748	0.283	6.993	2.114	1.391–4.586	0.008
CIMT	0.706	0.251	7.924	2.027	1.485–4.281	0.005
Hcy	0.439	0.187	5.509	1.551	1.172–2.680	0.019
Hoehn and Yahr stage	0.808	0.256	9.958	2.243	1.534–4.736	0.002
MDS-UPDRS part III score	0.348	0.162	4.623	1.416	1.158–2.465	0.032
Duration of education	0.189	0.148	0.604	1.208	0.606–1.579	0.439
Cys C	0.382	0.240	2.527	1.465	0.619–2.195	0.112
Disease duration	0.242	0.173	1.004	1.274	0.691–1.667	0.317
Total brain WMHs	0.331	0.265	1.349	1.392	0.725–2.584	0.245
Hypertension	0.553	0.358	2.391	1.739	0.783–3.318	0.122
Hyperlipidemia	0.487	0.334	2.128	1.627	0.733–3.185	0.144
Age	0.183	0.135	0.664	1.201	0.599–1.522	0.416

Notes: OR units: PWMHs (OR per 1 cm^3 increase: 2.114), CIMT (OR per 1 mm increase: 2.027), Hcy (OR per 1 μmol/L increase: 1.551), Hoehn and Yahr stage (OR per 1 stage increase: 2.243), and MDS-UPDRS part III score (OR per 1 point increase: 1.416).

Abbreviations: PD, Parkinson's disease; MCI, Mild cognitive impairment; MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale; WMHs, White matter hyperintensities; PWMHs, Periventricular white matter hyperintensities; Hcy, Homocysteine; CIMT, Carotid intima-media thickness; Cys C, Cystatin C; β, Regression coefficient; SE, Standard error; OR, Odds ratio; CI, Confidence interval.

(education duration, Cys C levels, disease duration, total brain WMHs, hypertension, hyperlipidemia, and age; all $P > 0.05$), multivariate analysis revealed that PWMHs [odds ratio (OR): 2.114, 95% confidence interval (CI): 1.391–4.586, $P = 0.008$], CIMT (OR: 2.027, 95% CI: 1.485–4.281, $P = 0.005$), Hcy levels (OR: 1.551, 95% CI: 1.172–2.680, $P = 0.019$), Hoehn and Yahr stage (OR: 2.243, 95% CI: 1.534–4.736, $P = 0.002$), and MDS-UPDRS part III score (OR: 1.416, 95% CI: 1.158–2.465, $P = 0.032$) were independently associated with MCI in PD patients, as shown in Table 2.

Predictive Values

The ROC curve was used to assess the predictive value of PWMHs, CIMT, and their combination for MCI in PD patients. The results (Figure 1) demonstrated that the AUCs were 0.705 [standard error (SE): 0.023, 95% confidence interval (CI): 0.661–0.750, $P < 0.001$) for PWMHs, 0.722 (SE: 0.022, 95% CI: 0.678–0.765, $P < 0.001$) for CIMT, and 0.908 (SE: 0.013, 95% CI: 0.882–0.934, $P < 0.001$) for the combination. A Z test revealed that the AUC of the combination prediction was significantly higher than those of the individual predictions (combination vs PWMHs: 0.908 vs 0.705, $Z = 7.684$, $P < 0.001$; combination vs CIMT: 0.908 vs 0.722, $Z = 7.279$, $P < 0.001$). The ROC curve for the combination prediction was based on probabilities derived from the logistic regression model.

Discussion

This study demonstrated, for the first time, the synergistic diagnostic value of CIMT and PWMHs for discriminating PD-MCI. Our key finding-that the combination of CIMT (AUC = 0.722) and PWMHs (AUC = 0.705) yielded a significantly superior diagnostic accuracy (AUC = 0.908)-suggested these biomarkers capture complementary aspects of PD-related cognitive vulnerability rooted in intersecting vascular and neurodegenerative pathways.

CIMT, a validated marker of subclinical atherosclerosis,[22] has been shown to correlate significantly with cognitive decline in both middle-aged/elderly populations and AD patients.[8,23,24] The potential mechanisms linking atherosclerosis to cognitive dysfunction involve four primary pathways: First, atherosclerosis-induced carotid calcification and elevated CIMT promote hippocampal degeneration and atrophy.[25] Second, cerebral hypoperfusion and hypoxia secondary to atherosclerosis accelerate β-amyloid (Aβ) production.[26] Third, Aβ clearance may be impaired through disruption of the blood-brain barrier (BBB), perivascular pathways, glymphatic drainage, and enzymatic degradation. Fourth, atherosclerosis-mediated neurovascular unit dysfunction triggers oxidative stress and subsequent neuroinflammatory

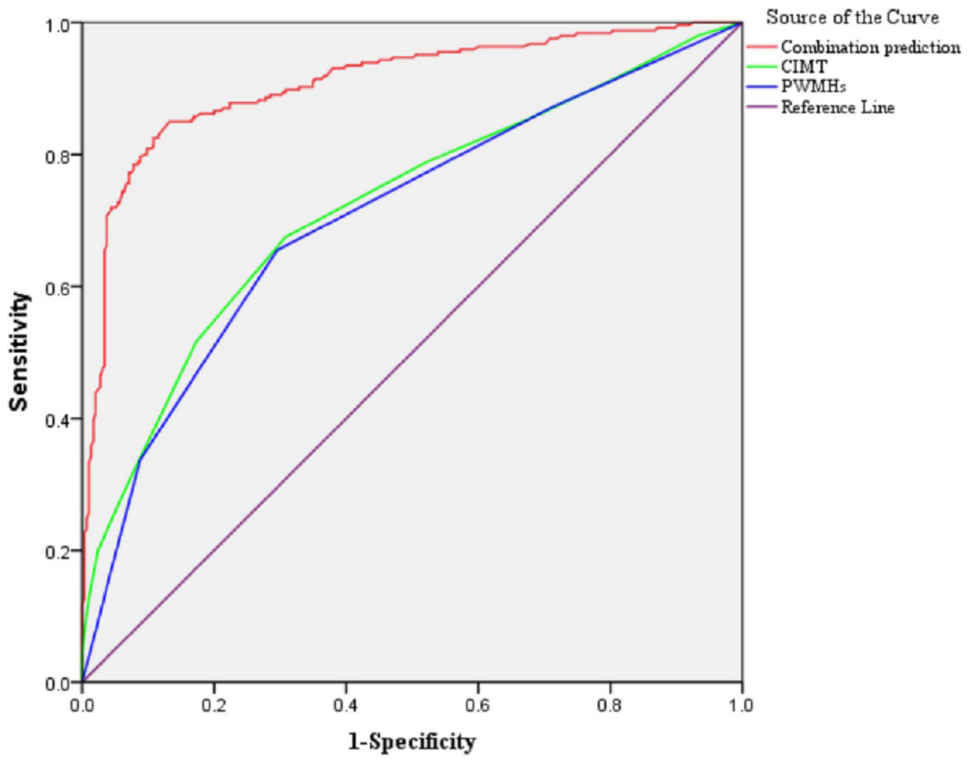

Figure 1 Receiver operating characteristic (ROC) curves for PWMHs, CIMT, and their combination in discriminating PD-MCI. The AUC (95% CI) for the combination model was 0.908 (0.882–0.934). The combination curve is based on the probabilities derived from the *logistic* regression model including PWMHs and CIMT.

responses.[27,28] PWMHs, visualized on MRI, signify cerebral small vessel disease (SVD) and chronic hypoperfusion.[11] They disrupt frontal-subcortical circuits critical for executive function and processing speed-domains frequently impaired in PD-MCI.[13,14] PWMHs may accelerate neurodegeneration by promoting BBB disruption, neuroinflammation, and axonal damage within vulnerable periventricular white matter tracts.[29]

Prior studies support the individual relevance of the two biomarkers. In PD, Yan et al demonstrated that increased CIMT correlated with longer disease duration and higher Hoehn & Yahr stage,[9] while Peng et al reported its association with cognitive impairment.[10] Similarly, Huang et al and Mak et al found that PWMH burden independently predicted MCI in early PD, particularly affecting executive functions.[13,14] Our previous study further showed that combining PWMHs with homocysteine discriminated PD-MCI with moderate accuracy (AUC=0.701).[11] The current results aligned closely with these findings: CIMT alone achieved an AUC of 0.722 (95% CI: 0.678–0.765) and PWMHs an AUC of 0.705 (95% CI: 0.661–0.750), confirming robust yet imperfect individual diagnostic capacity.

The marked increase in diagnostic power (AUC=0.908) when combining CIMT and PWMHs underscored their complementary roles. While CIMT reflects systemic macrovascular atherosclerosis and associated hemodynamic risks, PWMHs indicate cerebral microvascular damage and localized white matter integrity loss. Their integration likely captures a broader spectrum of vascular contributions to PD-MCI pathogenesis-spanning large-vessel atherosclerosis impacting global perfusion and SVD affecting specific cognitive networks.[30]

Both CIMT (via carotid ultrasound) and PWMHs (via routine brain MRI) are highly accessible in standard neurology or vascular clinics. Ultrasound is portable, low-cost, and non-invasive,[31] while brain MRI is already routinely performed in many PD patients for differential diagnosis or monitoring. This contrasts with research-centric biomarkers like PET amyloid imaging or CSF analysis, which are expensive and lack widespread availability.[32] Implementing this two-marker panel could facilitate early identification of high-risk PD-MCI patients during routine clinical assessments, enabling timely intervention. Potential interventions include rigorous cardiovascular risk factor management (eg, hypertension control, statin therapy) or cognitive rehabilitation programs, which may be most effective in the pre-symptomatic or early

MCI stages. However, the clinical applicability of this combined model is weakened by the lack of model calibration and validation, warranting further investigation.

Our findings resonate with the growing recognition of vascular contributions to PD pathology and cognitive decline. The high long-term prevalence of PDD (80% at 15–20 years)[5] underscores the need for early, accessible predictors like those identified here. The AUC of 0.908 approaches the diagnostic range for established clinical tools, suggesting genuine utility for risk stratification.

Our study has several limitations. First, the cross-sectional design precludes causal inference and true prediction of incident MCI; longitudinal studies are needed. Second, we reported discrimination using AUC but did not assess model calibration or perform internal validation (eg, bootstrapping), which limits the estimation of the model's performance in new populations and its immediate clinical utility. Third, although VIF diagnostics did not indicate severe multicollinearity, the inclusion of both PWMHs and total WMHs requires careful interpretation. Fourth, the intra- and inter-rater reliability for CIMT and PWMH measurements were not systematically assessed. Fifth, although we included de novo PD patients, some heterogeneity in disease duration existed. Future studies with larger, more homogeneous cohorts are warranted.

Conclusion

This study demonstrated that the combination of CIMT and PWMHs provided a potential tool for identifying PD-MCI. This integrated model significantly outperformed either biomarker alone. By combining a peripheral vascular marker (CIMT) with a direct neuroimaging indicator of cerebral small vessel disease (PWMHs), it captured the critical interaction between systemic and central vascular pathology underlying cognitive impairment in PD. Given the routine clinical availability of carotid ultrasound and brain MRI, this approach offered a potential strategy for early identification of at-risk individuals. This paved the way for targeted interventions to delay or prevent cognitive decline in PD. However, the clinical application of this model requires further validation in longitudinal settings and external cohorts, with formal assessment of calibration and reliability.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Aarsland D, Batzu L, Halliday GM, et al. Parkinson disease-associated cognitive impairment. *Nat Rev Dis Primers*. 2021;7(1):47. doi:10.1038/s41572-021-00280-3
2. Baiano C, Barone P, Trojano L, et al. Prevalence and clinical aspects of mild cognitive impairment in Parkinson's disease: a meta-analysis. *Mov Disord*. 2020;35(1):45–54. doi:10.1002/mds.27902
3. Liu H, Deng B, Xie F, et al. The influence of white matter hyperintensity on cognitive impairment in Parkinson's disease. *Ann Clin Transl Neurol*. 2021;8(9):1917–1934. doi:10.1002/acn3.51429
4. Pedersen KF, Larsen JP, Tysnes OB, et al. Natural course of mild cognitive impairment in Parkinson disease: a 5-year population-based study. *Neurology*. 2017;88(8):767–774. doi:10.1212/WNL.0000000000003634
5. Biundo R, Weis L, Antonini A. Cognitive decline in Parkinson's disease: the complex picture. *NPJ Parkinsons Dis*. 2016;2:16018. doi:10.1038/npjparkd.2016.18
6. Posada IJ, Benito-León J, Louis ED, et al. Mortality from Parkinson's disease: a population-based prospective study (NEDICES). *Mov Disord*. 2011;26(14):2522–2529. doi:10.1002/mds.23921
7. Benito-Rodríguez CM, Bermejo-Pareja F, Berbel Á, et al. Twenty-three-year mortality in Parkinson's disease: a population-based prospective study (NEDICES). *J Clin Med*. 2025;14(2):498. doi:10.3390/jcm14020498

8. De Anda-Duran I, Alonso CF, Libon DJ, et al. Carotid intima-media thickness and midlife cognitive function: impact of race and social disparities in the Bogalusa Heart Study. *Neurology*. 2022;98(18):e1828–e1836. doi:10.1212/WNL.0000000000200155
9. Yan LY, He QF, Lu MY, et al. Association between carotid plaque and Parkinson's disease. *Ann Transl Med*. 2019;7(5):94. doi:10.21037/atm.2019.01.68
10. Peng L, Xu Y, Qiao T, et al. Study on the correlation between carotid intima-media thickness and cognitive impairment in Parkinson's disease. *J Nanjing Med Univ*. 2025;45(3):389–395.
11. Prins ND, Scheltens P. White matter hyperintensities, cognitive impairment and dementia: an update. *Nat Rev Neurol*. 2015;11(3):157–165. doi:10.1038/nrneurol.2015.10
12. Zhang Z, Li S, Wang S. Application of periventricular white matter hyperintensities combined with homocysteine into predicting mild cognitive impairment in Parkinson's disease. *Int J Gen Med*. 2023;16:785–792. doi:10.2147/IJGM.S399307
13. Huang X, Wen MC, Ng SY, et al. Periventricular white matter hyperintensity burden and cognitive impairment in early Parkinson's disease. *Eur J Neurol*. 2020;27(6):959–966. doi:10.1111/ene.14192
14. Mak E, Dwyer MG, Ramasamy DP, et al. White matter hyperintensities and mild cognitive impairment in Parkinson's disease. *J Neuroimaging*. 2015;25(5):754–760. doi:10.1111/jon.12230
15. Zhao W, Cheng B, Zhu T, et al. Effects of white matter hyperintensity on cognitive function in PD patients: a meta-analysis. *Front Neurol*. 2023;14:1203311. doi:10.3389/fneur.2023.1203311
16. Wu H, Hong H, Wu C, et al. Regional white matter hyperintensity volume in Parkinson's disease and associations with the motor signs. *Ann Clin Transl Neurol*. 2023;10(9):1502–1512. doi:10.1002/acn3.51839
17. Carvalho de Abreu DC, Pieruccini-Faria F, Son S, et al. Is white matter hyperintensity burden associated with cognitive and motor impairment in patients with Parkinson's disease? A systematic review and meta-analysis. *Neurosci Biobehav Rev*. 2024;161:105677. doi:10.1016/j.neubiorev.2024.105677
18. Litvan I, Bhatia KP, Burn DJ, et al; Movement Disorders Society Scientific Issues Committee. Movement Disorders Society Scientific Issues Committee report: SIC Task Force appraisal of clinical diagnostic criteria for Parkinsonian disorders. *Mov Disord*. 2003;18(5):467–486. doi:10.1002/mds.10459
19. Litvan I, Agid Y, Calne D, et al. Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop. *Neurology*. 1996;47(1):1–9. doi:10.1212/wnl.47.1.1
20. Gilman S, Low P, Quinn N, et al; American Autonomic Society and American Academy of Neurology. Consensus statement on the diagnosis of multiple system atrophy. *Clin Auton Res*. 1998;8(6):359–362. doi:10.1007/BF02309628
21. Ashburner J, Friston KJ. Unified segmentation. *Neuroimage*. 2005;26(3):839–851. doi:10.1016/j.neuroimage.2005.02.018
22. Lu Y, Zhu Y, Ma Y, et al. Association of subclinical atherosclerosis and cognitive decline: a community-based cross-sectional study. *BMJ Open*. 2022;12(5):e059024. doi:10.1136/bmjopen-2021-059024
23. Xie B, Shi X, Xing Y, et al. Association between atherosclerosis and Alzheimer's disease: a systematic review and meta-analysis. *Brain Behav*. 2020;10(4):e01601. doi:10.1002/brb3.1601
24. Lin F, Pa J, Karim R, et al. Subclinical carotid artery atherosclerosis and cognitive function in older adults. *Alzheimers Res Ther*. 2022;14(1):63. doi:10.1186/s13195-022-00997-7
25. Baradaran H, Demissie S, Himali JJ, et al. The progression of carotid atherosclerosis and imaging markers of dementia. *Alzheimers Dement*. 2020;6(1):e12015. doi:10.1002/trc2.12015
26. Kouzuki M, Nagano M, Suzuki T, et al. Cerebrospinal fluid biomarkers of Alzheimer's disease are associated with carotid plaque score and hemodynamics in intra- and extra-cranial arteries on ultrasonography. *J Clin Neurosci*. 2018;49:32–36. doi:10.1016/j.jocn.2017.12.006
27. Amidfar M, Askari G, Kim YK. Association of metabolic dysfunction with cognitive decline and Alzheimer's disease: a review of metabolomic evidence. *Prog Neuropsychopharmacol Biol Psychiatry*. 2024;128:110848. doi:10.1016/j.pnpbp.2023.110848
28. Wang W, Gottesman RF, Meyer ML, et al. Carotid intima-media thickness and amyloid-β deposition: the ARIC-PET Study. *J Alzheimers Dis*. 2022;88(1):17–22. doi:10.3233/JAD-215671
29. Wardlaw JM, Smith C, Dichgans M. Small vessel disease: mechanisms and clinical implications. *Lancet Neurol*. 2019;18(7):684–696. doi:10.1016/S1474-4422(19)30079-1
30. Saeed U, Compagnone J, Aviv RI, et al. Imaging biomarkers in Parkinson's disease and Parkinsonian syndromes: current and emerging concepts. *Transl Neurodegener*. 2017;6:8. doi:10.1186/s40035-017-0076-6
31. Stein JH, Korcarz CE, Hurst RT, et al; American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. *J Am Soc Echocardiogr*. 2008;21(2):93–111; quiz 189–190. doi:10.1016/j.echo.2007.11.011
32. Brumm MC, Siderowf A, Simuni T, et al; Parkinson's Progression Markers Initiative. Parkinson's progression markers initiative: a milestone-based strategy to monitor Parkinson's disease progression. *J Parkinsons Dis*. 2023;13(6):899–916. doi:10.3233/JPD-223433