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ORIGINAL RESEARCH

Nonlinear Relationship Between Homocysteine and Mild Cognitive Impairment in Early Parkinson's Disease: A Cross-Sectional Study

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Background: Cognitive impairment, a prevalent non-motor symptom in advanced Parkinson's disease (PD), has been associated with hyperhomocysteinemia, an important risk factor for PD progression and cognitive decline in PD. However, evidence regarding the association between homocysteine (Hcy) and cognitive function during early PD remains insufficient. Therefore, this study aims to examine the correlation between Hcy levels and cognitive function in the early stage of PD.

Methods: The study included 218 individuals in the early stages of PD who were consecutively admitted to the Suining Central Hospital Neurology Department. All the individuals completed the Parkinson's Disease Cognitive Rating Scale (PD-CDR). The Unified Parkinson's Disease Rating Scale part III (UPDRS-III) was employed for measuring the severity of motor symptoms, while the Hoehn-Yahr scale was used to measure the clinical symptom stage. Fasting venous blood samples were also drawn to measure the Hcy concentration, red blood cell folate, and vitamin B12.

Results: In this cross-sectional study, 47 (21.5%) patients with PD showed cognitive dysfunction. The serum Hcy levels were significantly higher in the cognitive impairment PD (PDCI) group compared with the cognitive normal PD group (P<0.001). The Generalized Additive Model (GAM) analysis revealed a nonlinear relationship between Hcy and the risk of PDCI. Multiple logistic regression analyses demonstrated a positive relationship between elevated Hcy and the risk of PDCI in the fully adjusted model ([OR]:3.1, 95% CI, 1.1–8.5, P=0.028). Segmented linear regression analysis showed that when Hcy levels were above 17.7 umol/l, the risk of PDCI increased by 1.6 times for every 1 unit elevated in Hcy (95% CI:1.1–2.2, P=0.008).

Conclusion: This study revealed a nonlinear positive correlation between the risk of PDCI and elevated serum Hcy levels in early PD patients, suggesting hyperhomocysteinemia as one of the treatable factors for cognitive impairment in the early stages of PD.

Keywords: homocysteine, early Parkinson's disease, cognitive impairment, relationship

Introduction

Parkinson's disease dementia (PDD) is a widely recognized non-motor symptom in the advanced stages of PD, the cumulative incidence of PDD in PD patients suffering for more than 10 years is 75%.[1] It encompasses a spectrum of cognitive impairments across domains, including memory, attention, executive functioning, and visuospatial abilities. These cognitive impairments significantly affect social functioning and overall quality of life for individuals coping with PD. The pre-dementia stage comprises subjective cognitive impairment and mild cognitive impairment (MCI)[2], MCI not only serves as a significant risk factor for the development of early PDD,[3] but it is also recognized as a favorable stage for cognitive intervention therapy. However, it is often overlooked by clinicians, thereby resulting in missed opportunities for proactive interventions. According to a recent meta-analysis, the prevalence of MCI in PD patients is up to 40%.[4] Previous studies showed that around 20–40% of patients newly diagnosed with PD present with MCI.[5,6] Discrepancies in reported prevalence rates may arise from the diverse of assessment tools employed.[7] In conclusion, early diagnosis and intervention for MCI are crucial for preventing and minimizing its progression to PDD, suggesting an urgent need for exploring treatable risk factors.

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Elevated plasma Hcy levels may serve as a significant potential risk factor for PD-MCI. They have been observed not only in the general elderly population with cognitive impairment,[8] but also associated with conditions such as vascular cognitive impairment and Alzheimer's disease.[9,10] Recently, Fan et al have extensively reviewed the association of Hcy with the development and progression of PD.[11] The use of levodopa (L-dopa) has been found to elevate Hcy plasma levels,[12] therefore, it can potentially pose a risk for PDCI. However, the existing studies reporting on the relationship between Hcy levels and PDCI present contradictory findings. Several reports have documented a decline in cognitive function among PD patients with hyperhomocysteinemia.[13–18] As early as 2004, O'Suilleabhain et al conducted a study on a group of PD patients with a mean duration of 3.6 years, the results revealed that PD patients with coexisting hyperhomocysteinemia exhibited poorer cognitive function.[18] Recently, a large-scale study indicated that elevated Hcy are a risk factor for cognitive impairment in PD.[15] Moreover, a long-term observational study also suggests that Hcy may serve as a suitable biomarker for predicting early cognitive decline in PD.[16] However, contrasting results have also been reported. Camicioli et al did not find association between Hcy levels and cognitive function in a sample of 50 non-demented elderly PD patients.[19] Similarly, Rodriguez-Oroz et al did not discover a direct relationship between plasma Hcy and cognitive impairment or dementia in 89 PD patients with a disease duration more than 10 years.[20] The discrepancies may be related to differences in study design, sample sizes, or cognitive measurement methodologies. Furthermore, clinicians have not paid significant attention to investigating the cognitive function of individuals in the early stages of PD, and the existing body of knowledge in this area remains insufficiently explored. Therefore, exploring the cognitive function in early PD patients and its association with Hcy levels is of great clinical significance.

This study aims to examine the cognitive function of patients with early-stage PD and investigates the potential association between elevated Hcy levels and cognitive decline in these patients. Additionally, for the first time, this study analyzes the dose-response relationship between HCY levels and the risk of cognitive impairment in early PD, the innovative statistical approach of the current study represents a pivotal advancement in resolving ambiguities and enhancing the comprehension of the progression of cognitive impairment in PD.

Methods

Patients and Clinical Assessments

Patients Selection

A total of 218 hospitalized patients diagnosed with PD were consecutively recruited between March 2021 and March 2023 from the Department of Neurology at Suining Central Hospital. All enrolled patients completed a standardized diagnostic process, including inquiries into basic medical history, collection of demographic data (age, gender, years of education, and body mass index), review of past medical history (blood pressure, diabetes mellitus), neurological physical examination, standardized assessments of PD motor symptoms, evaluation of neuropsychological scales, brain MRI, and various laboratory tests. All participants met the Movement Disorder Society (MDS) Clinical Diagnostic Criteria for PD,[21] with an onset of less than 3 years before enrollment be defined as early PD.

Clinical Assessments

The severity of motor symptoms was assessed using UPDRS-III, while the stage of clinical symptoms was determined based on the Hoehn-Yahr scale. Comprehensive cognitive function was evaluated using the Parkinson's Disease Cognitive Rating Scale (PD-CRS), which has a total score of 134. The diagnostic cutoffs were set at 80.5 for PD-MCI and 73.5 for PDD.[22] PD-CRS is a specialized cognitive screening tool that has been repeatedly validated in clinical research studies in multiple countries for assessing cognitive function in PD patients with excellent sensitivity and specificity.[23] The diagnosis of cognitive impairment was based on the recommendations of the MDS.[24]

Inclusion and Exclusion Criteria

The exclusion criteria were as follows: 1. Secondary parkinsonism associated with specific causes, such as infections, medication-induced, poisoning, cerebral arteriosclerosis, and trauma. 2. Parkinsonism accompanied by other neurodegenerative diseases (specifically multiple system atrophy, progressive supranuclear palsy, and dementia with Lewy bodies). 3. Presence of significant memory or cognitive decline preceding the onset of PD symptoms, as reported by

both the patient and/or family members. 4. Significant intracranial lesions detected on brain MRI. 5. Unable to cooperate in completing the clinical scale assessment and blood sample collection. 6. Recent or current use of medications, such as antiepileptic drugs and certain chemotherapy drugs that can impact blood Hcy levels or the presence of thyroid dysfunction or renal insufficiency that affects Hcy metabolism. Peripheral venous blood samples were collected from all enrolled subjects within 24 hours after admission for the analysis of Hcy, vitamin B12, and red blood cell folate concentrations. This study was designed and carried out following the Declaration of Helsinki. Furthermore, the study was reviewed and approved by the Institutional Ethics Review Committee of Suining Central Hospital (approval number 202003025) and informed consent was obtained from all participants.

Statistical Analysis

All data analyses were performed using Empower-Stats software (X&Y Solutions, Inc., Boston, MA) and the R statistical software package (http://www.R-project.org, The R Foundation). Continuous variables were shown as mean ± standard deviation (SD) or median (range). Categorical variables were displayed as numbers and proportions. The Mann–Whitney *U*-test was employed to compare differences in continuous variables that exhibited a non-normally distributed or non-homogeneous normal distribution. The Student's *t*-test was used for homogeneous normal distribution variables, while categorical variables were analyzed by the chi-square test. Three logistic regression models were employed to investigate the association between HCY levels and PD-CI risk. Model 1 did not account for any confounding variables, while Model 2 adjusted for age and gender. Model 3 included additional adjustments for the Hoehn-Yahr stage; UPDRS-III score; years of EDUCATION; vitamin B12, red blood cell folate; hypertension; diabetes mellitus; body mass index; and month of levodopa treatment. Generalized additive models were used to visually represent the trends between the HCY and risk for PD-CI. A recursive method was used to find the inflection point in the non-linear relationship between HCY and PDCI risk. $P<0.05$ was used to determine statistical significance.

Results

Characteristics of the PDCI and non-PDCI Groups

In this cross-sectional survey study, only 9 cases (4%) did not receive levodopa treatment, 47 (21.5%) out of the 218 early PD patients were identified as having PDCI. Among these, 46 cases met the diagnostic criteria for MCI based on a PD-CRS score falling within the range of 73.5 to 80.5. One case with a PD-CRS score of 72.5 met the criteria for PDD. A PD-CRS score of 80.5 was used as the cut-off value to divide the study population into the PDCI group and the non-PDCI group. The differences in demographic and clinical characteristics between the two compared groups are presented in Table 1. The difference in age between the two groups was significant, with the PDCI group showing a mean age of 75.2 ±8.3 years and the non-PDCI group having a mean age of 69.6 ±8.3 years ($p < 0.001$). The PDCI group had a significantly higher number of males than females ($p = 0.046$). Additionally, the PDCI group had significantly higher UPDRS-III scores, Hoehn-Yahr stages, and duration of levodopa use compared to the non-PDCI group. However, no significant differences were found in factors such as years of education, body mass index, and the presence of hypertension or diabetes between the two groups. In the laboratory examination, the PDCI group exhibited significantly higher levels of Hcy ($p<0.001$) and vitamin B12 ($p=0.006$). However, no significant differences were observed in red cell folate.

In this study, the difference between two groups categorized by HCY levels was also investigated: the normal group (≤20 μmol/L) and the elevated group (>20 μmol/L). The patients in the elevated HCY group exhibited lower levels of vitamin B12 (315.0 (116.2–496.5) VS 471.5 (283.0–670.2), $P = 0.002$), a longer duration of levodopa use (12.4 ±5.3 vs 10.0 ± 6.0, $P = 0.028$), higher Hoehn-Yahr stages (2.5 ±0.7 VS 2.2 ±0.9, $P = 0.039$), and a higher prevalence of diabetes ($P = 0.026$) (Table 2). Further investigation into the association between Hcy and PDCI risk was conducted to fully control for these variables, as well as common factors (body mass index, red blood cell folate, education level, etc.) known to affect plasma HCY concentration and cognitive function.

Table 1 Characteristics of Patients in Non-PDCI and PDCI Groups (n = 218)

	Non-PDCI Group	PDCI Group	P-value
N	171	47	
Age, mean (SD), years	69.6 ± 8.3	75.2 ± 8.3	<0.001
Gender, n (%)			0.046
Male	81 (47.4%)	30 (63.8%)	
Female	90 (52.6%)	17 (36.2%)	
HP, n (%)			0.204
Yes	84 (49.1%)	28 (59.6%)	
No	87 (50.9%)	19 (40.4%)	
DM, n (%)			0.326
Yes	56 (32.7%)	19 (40.4%)	
No	115 (67.3%)	28 (59.6%)	
MDS-UPDRS III	25.9 ± 8.9	30.2 ± 9.6	0.004
Hoehn & Yahr score	2.1 ± 0.9	2.5 ± 0.7	0.004
Education, years	8.9 ± 4.6	8.0 ± 4.1	0.225
BMI, mean (SD), kg/m^2	23.1 ± 4.7	23.2 ± 2.5	0.877
Levodopa use, month	10.0 ± 6.0	12.0 ± 5.5	0.037
Hcy, mean (SD), μmol/L	14.1 ± 4.3	19.7 ± 8.5	<0.001
Vitamin B12, median (range), pg/mL	469.0 (283.0–670.5)	362.0 (130.0–515.5)	0.006
Red cell folate, median (range), ng/mL	184.0 (163.0–346.0)	220.0 (136.5–552.0)	0.938

Abbreviations: HP, hypertension; DM, diabetes mellitus; MDS UPDRS III, Movement Disorders Society Unified Parkinson's Disease Rating Scale Part III; BMI, body mass index; Hcy, Homocysteine.

Table 2 Characteristics of the Study Population Grouped by Hcy

	Normal Hcy	Elevated Hcy	P-value
N	180	38	
Age, mean (SD), years	70.5 ± 8.6	72.5 ± 8.4	0.187
Gender, n (%)			0.192
Male	88 (48.9%)	23 (60.5%)	
Female	92 (51.1%)	15 (39.5%)	
HP, n (%)			0.110
Yes	88 (48.9%)	24 (63.2%)	
No	92 (51.1%)	14 (36.8%)	
DM, n (%)			0.026
Yes	56 (31.1%)	19 (50.0%)	
No	124 (68.9%)	19 (50.0%)	
MDS-UPDRS III	26.5 ± 9.0	28.5 ± 10.2	0.213
Hoehn & Yahr score	2.2 ± 0.9	2.5 ± 0.7	0.039
Education, years	8.8 ± 4.5	7.9 ± 4.5	0.281
BMI, mean (SD), kg/m^2	23.2 ± 4.3	22.9 ± 4.6	0.690
Levodopa use, month	10.0 ± 6.0	12.4 ± 5.3	0.028
PD-CRS score	100.3 ± 17.1	93.7 ± 20.9	0.038
Vitamin B12, median (range), pg/mL	471.5 (283.0–670.2)	315.0 (116.2–496.5)	0.002
Red cell folate, median (range), ng/mL	186.5 (163.0–404.2)	174.0 (145.0–346.5)	0.146

Abbreviation: PD-CRS, Parkinson's Disease Cognitive Rating Scale.

Association Between Hcy and PDCI

Binary logistic regression was initially employed to analyze the effect of each variable on PDCI. As depicted in Figure 1: age, UPDRS-III scores, Hcy, vitamin B12 and red cell folate were identified as significant risk factors for early PDCI (P<0.05). Similarly, three logistic regression models were employed to adjust for various variables and further investigate the

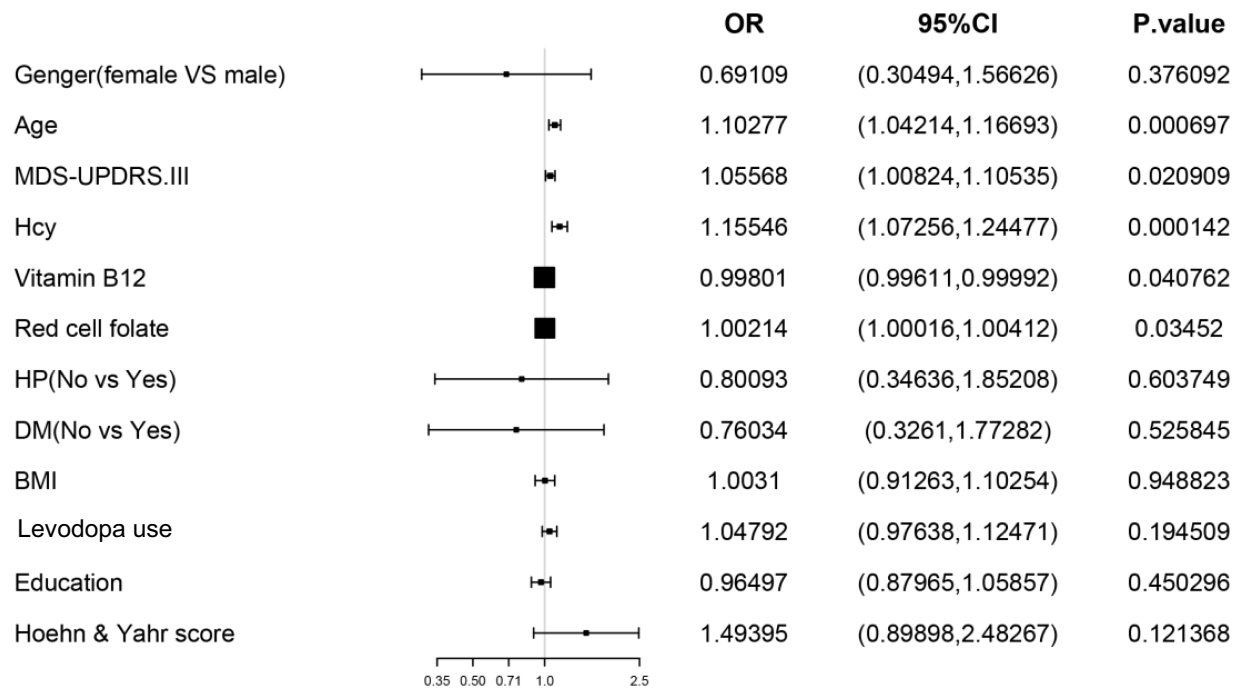

Figure 1 A forest plot displays the results of the binary logistic regression between each variable and the PDCI.

association between Hcy and PDCI. The initial analysis without adjustments revealed a positive correlation between Hcy levels and an elevated risk of PDCI. Specifically, the high Hcy group exhibited a 3.5-fold greater risk of cognitive impairment in comparison to the low Hcy group for every 1 μmol/L increase in Hcy levels (P = 0.004), even after adjusting for age and sex, this positive correlation persisted (Table 3). After comprehensively accounting for potential confounding factors, including age, gender, UPDRS-III scores, Hoehn-Yahr stages, years of education, and duration of levodopa use, the fully adjusted models exhibited a consistent trend (Table 3). Moreover, the results from the smooth curve fitting analysis based on the generalized additive model revealed a significant non-linear relationship, as illustrated in Figure 2. This indicates a marked increase in the risk of PDCI associated with elevated Hcy levels, even after adjusting for all confounding factors. Moreover, the application of a segmented linear regression model identified an inflection point at an Hcy level of 17.7 μmol/L, indicating a significant rise in the risk of PDCI in the non-linear relationship. When Hcy levels exceeded 17.7 μmol/L, the incidence of PDCI increased by 50% for every 1-unit increase in HCY (OR: 1.5, 95% CI: 1.2, 1.8, p<0.001) (Table 4).

Table 3 Multivariate Logistic Regression for the Association Between Hcy and PDCI

	Model 1 OR (95% CI)	P-value	Model 2 OR (95% CI)	P-value	Model 3 OR (95% CI)	P-value
HCY	1.2 (1.1, 1.2)	<0.001	1.2 (1.1, 1.2)	<0.001	1.2 (1.1, 1.2)	<0.001
HCY tertile						
Low	Ref		Ref		Ref	
Middle	1.7 (0.7, 4.3)	0.244	1.5 (0.6, 3.8)	0.418	1.6 (0.6, 4.6)	0.363
High	3.5 (1.5, 8.2)	0.004	3.3 (1.4, 8.0)	0.009	3.1 (1.1, 8.5)	0.028
P for trend	1.9 (1.2, 2.9)	0.003	1.9 (1.2, 2.9)	0.006	1.8 (1.1, 2.9)	0.026

Notes: Model 1: adjust for None. Model 2: adjusted for Age and Gender. Model 3: adjust for Age; Gender; MDS-UPDRS III; Education; Hoehn & Yahr score; Vitamin B12; Red cell folate; HP; DM; BMI; Levodopa use.

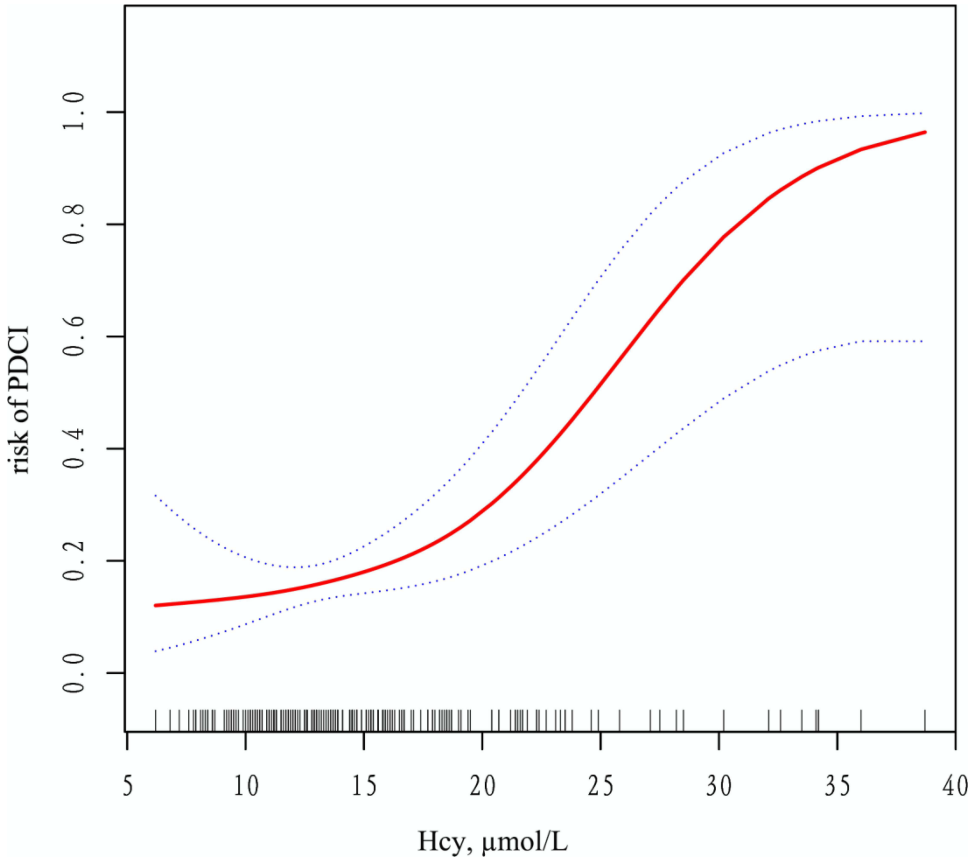

Figure 2 Nonlinear relationship between Hcy and risk of PDCI in early PD.

Discussion

While the cognitive impairment in PD has gained widespread recognition among clinicians, the cognitive status of patients with early-stage PD is often overlooked. In this study, the preliminary investigation revealed that approximately 21% of patients with early PD have cognitive impairment. Furthermore, elevated serum Hcy levels were found associated with an increased risk of cognitive impairment in early PD. This finding aligns with previous data, and importantly, this study is the first to present a nonlinear relationship between Hcy levels and MCI in early PD.

PDCI is typically observed during the middle and later stages of the disease.[25] Nonetheless, studies have reported that around 20–40% of newly diagnosed PD patients exhibit MCI.[5,6] According to the Norwegian ParkWest Study report, patients with MCI at early-stage of PD had a significantly higher risk of progression to dementia during follow-up compared to those without MCI, with a relative risk of 39.2 (95% CI, 5.2–296.5, $P < 0.001$).[3] Thus, exploring the modifiable factors associated with cognitive impairment in early-stage PD is crucial from a clinical perspective. Data from previous research has indicated that laboratory-based risk factors, such as reduced serum uric acid levels, elevated Hcy concentrations, decreased glomerular filtration rate, elevated triglyceride levels, and increased serum 25(OH)D levels, are correlated with cognitive impairment in PD.[15,16,26–30] However, there are disparities among these findings,

Table 4 The Results of Segmented Linear Regression Model

Inflection Point of Hcy	Effect Size (OR)	95% CI	P-value
< 17.7 (K1)	1	(0.8, 1.2)	0.696
> 17.7 (K2)	1.5	(1.2, 1.8)	<0.001
P for log likelihood ratio test			0.005

Note: The adjustments are same to Model 3.

particularly concerning Hcy, as few studies failed to find an association between Hcy and cognitive decline with PD.[17,19] These disparities may stem from differences in the comprehensiveness of cognitive assessments or the sample size. This study reaffirms the positive correlation between Hcy and PDCI, and for the first time, examines their association using a dose-response relationship. At an Hcy level cutoff of 17.7 μmol/L, a significant increase in the risk of early PDCI occurrence was noted.

Hcy, a thio-containing amino acid produced through the demethylation of methionine, is an essential byproduct of metabolic processes occurring in different human body tissues. Elevated plasma Hcy is not only a well-established risk factor for cardiovascular disease but also a significant factor in cognitive impairment, supported by extensive clinical evidence.[31,32] Beyond its association with PDCI, there is clear evidence supporting its involvement in both the motor symptoms and the progression of PD.[11,16] From a molecular biology perspective, Hcy can induce nerve cell apoptosis by promoting energy consumption and damaging DNA chains.[33] Under physiological conditions, Hcy undergoes methylation to form methionine, a process in which folic acid and vitamin B12 play roles in maintaining low Hcy levels. Therefore, deficiencies in folic acid and/or vitamin B12, coupled with excessive accumulation of Hcy, can impede methionine metabolism, resulting in reduced cytosine methylation in DNA and subsequent DNA chain breakage.[34] In this study, a significant difference in the plasma concentration of vitamin B12 was observed between the PDCI group and the non-PDCI group. This difference may partially explain the higher levels of Hcy in the PDCI group, potentially indicating insufficient intake of this vitamin in the PDCI group. Many Studies have demonstrated that increased Hcy levels in the body lead to nerve cell apoptosis, oxidative stress, mitochondrial malfunction, and neuronal DNA damage, which contribute to the onset and progression of PD.[11] Moreover, Hcy can activate NMDA receptors and increase the excitotoxic effects of glutamate resulting in neuronal degeneration.[35] High Hcy levels enhance the sensitivity of the nervous system to methylation processes of toxic substances within the brain, exerting a direct toxic effect on neurons. They can also affect cerebral microcirculation through endothelial damage, resulting in inadequate brain perfusion and cognitive impairment in PD.[36,37] Data from a clinical study have shown that interventions aimed at lowering Hcy levels can effectively arrest cognitive decline in patients with non-PD-related MCI,[38,39] thereby further underscoring the association between elevated Hcy levels and the development of cognitive impairment.[38]

This study is notable for its novel use of a dose-response relationship to investigate the association between Hcy levels and PDCI. It provided a specific and quantitative understanding of the risk prediction of PDCI based on Hcy levels. However, it is important to note that this was a cross-sectional observational study conducted among PD patients, without a matched control group observation based on age and gender. While this study utilized various regression models to adjust for the effects of confounding variables, a more comprehensive comparison of data between the control and case groups could offer an improved understanding of the results. Second, The results of this study are based on a single-center with a relatively small sample size and a lack of consideration for the impact of depression and anxiety states on cognitive function,[40,41] therefore, caution is required when extrapolating the findings to a wider patient population affected by PD. Third, Hcy levels in this study were measured on the second day of hospitalization after fasting. As homocysteine levels may fluctuate at different time points, relying on a single test result may lack stability in interpreting the results. According to a previous long-term observational study,[16] plasma Hcy levels would significantly increase over time in both the PD group and the healthy control group. Given the elevated homocysteine levels are a known risk factor for cardiovascular and cerebrovascular diseases, long-term follow-up studies may pose potential health risks to the patients. Therefore, further cross-sectional studies can be conducted in the short term (maybe within one week of hospitalization) to complete 2–3 measurements of Hcy levels to enhance its accuracy. Conducting longitudinal studies may allow for randomized interventional trials targeting Hcy reduction in PD patients with cognitive impairment. This approach could offer deeper insights into the association of Hcy with PDCI.

In conclusion, this study provides initial evidence of the relationship between quantitative Hcy levels and early PDCI risk, suggested Hcy levels is significantly associated with cognitive decline in early PD. Additionally, a Hcy level cutoff of 17.7 μmol/L, associated with a significant increase in the probability of early cognitive impairment occurrence, was identified for the first time. More comprehensive cross-sectional and longitudinal intervention studies, involving larger cohorts, are required to validate these findings and elucidate the potential causal relationship between increased Hcy levels and cognitive decline in Early-stage PD.

Data Sharing Statement

The data sets utilized and analyzed in the current study are available upon reasonable request from the corresponding author.

Ethical Statements and Declarations

The study was reviewed and approved by the Institutional Ethics Review Committee of Suining Central Hospital (approval number 202003025) and informed consent was obtained from all participants. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author Contributions

All authors contributed significantly to the reported work, including conception, study design, data acquisition, analysis, interpretation, drafting, revising, and critical review of the article. They approved the final version for publication, and agreed on the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

Disclosure

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