

## ORIGINAL RESEARCH



# Correlation between serum uric acid, homocysteine and cystatin C levels and Parkinson's disease

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## Abstract

### Background

Parkinson's disease (PD) is a progressive neurodegenerative disorder associated with metabolic abnormalities. Serum biomarkers such as uric acid (UA), homocysteine (Hcy), and cystatin C (Cys-C) may be involved in its pathogenesis and progression.

### Objective

To evaluate the associations between serum UA, Hcy, and Cys-C levels and disease duration, severity, and cognitive function in patients with PD.

### Methods

From January 2023 to December 2024, sixty patients diagnosed with PD and sixty age- and sex-matched healthy controls were enrolled. PD patients were further stratified by disease duration (<5 years vs.  $\geq 5$  years), Hoehn and Yahr (H&Y) stage (mild vs. moderate-to-severe), and Montreal Cognitive Assessment (MoCA) score (normal cognition vs. cognitive impairment). Serum levels of UA, Hcy, and Cys-C were compared among groups, and Pearson correlation analysis was performed to examine their relationships with disease duration, H&Y stage, and MoCA score.

### Results

Compared with healthy controls, PD patients exhibited significantly higher serum Hcy and Cys-C levels and lower UA levels (all  $P < 0.01$ ). Patients with longer disease duration, higher H&Y stage, or cognitive impairment showed elevated Hcy and Cys-C levels and reduced UA levels ( $P < 0.01$  for all comparisons). Pearson correlation analysis revealed that UA was negatively correlated with disease duration ( $r = -0.757$ ,  $P < 0.001$ ), H&Y stage ( $r = -0.869$ ,  $P < 0.001$ ), and MoCA score ( $r = -0.606$ ,  $P < 0.001$ ), while Hcy and Cys-C were positively correlated with these indicators (all  $P < 0.01$ ).

### Conclusion

Elevated serum Hcy and Cys-C and reduced UA levels are closely associated with PD progression and cognitive decline. These biomarkers may serve as valuable indicators for monitoring disease severity and guiding clinical management.

**Keywords:** Parkinson's disease, serum uric acid, homocysteine, cystatin C, Hoehn and Yahr, cognitive function, disease duration

## Introduction

Parkinson's disease (PD) ranks as the 2<sup>nd</sup> most prevalent progressive neurodegenerative condition following Alzheimer's disease, majorly affecting individuals in middle and advanced age groups<sup>1</sup>. The core pathological hallmarks of PD include the extensive presence of Lewy bodies, composed primarily of  $\alpha$ -synuclein, and the significant depletion of dopaminergic neurons in the substantia nigra<sup>2</sup>. The clinical manifestations of PD encompass a series of motor and non-motor symptoms<sup>3</sup>. The former is mainly manifested as muscle rigidity, bradykinesia, abnormal posture and gait, and often accompanied by static tremor<sup>4</sup>. The latter can also appear sensory dysfunction, depression, anxiety, sleep disorders, cognitive dysfunction and other symptoms<sup>5</sup>. Currently, there are over 4 million individuals worldwide living with PD. With the ongoing aging of the global population, projections manifest that the number of PD patients will surge to approximately 15 million by 2050, with China accounting for more than half of this total<sup>6</sup>. The onset of PD is relatively insidious and the progression is slow, and patients are usually in the middle and late stages when diagnosed<sup>7</sup>. Therefore, the search for the risk biomarkers of

PD has been concerned by most researchers.

The precise pathogenesis of PD remains incompletely understood. However, it is currently postulated that PD is linked to the degeneration of dopaminergic neurons. This neuronal damage is thought to be influenced by a multitude of factors, containing genetics, environmental exposures, as well as oxidative stress<sup>8</sup>. Uric acid (UA) serves as the final metabolite of purine compounds, primarily existing in the form of urate in cells or cellular fluids, and as an important antioxidant, UA can reduce the oxidative damage of dopaminergic neurons in substantia nigra by clearing free radicals in the body, down-regulating the level of oxidative stress and thus achieving protective effect<sup>9</sup>. Homocysteine (Hcy), an intermediate product of amino acid metabolism, can promote the decline of dopaminergic neurons in the substantia nigra by promoting their apoptosis and exacerbating catecholamine hydroxylation. This, in turn, leads to damage to dopaminergic neurons and is recognized as a risk element for PD progression<sup>10</sup>. Cystatin C (Cys-C), an repressor of cathepsins, is synthesized by the body's nucleated cells and is ubiquitous in all nucleated cells and bodily fluids<sup>11</sup>. Cys-C is not only a laboratory indicator with

high sensitivity in evaluating renal function, but also may be linked to many neurological diseases<sup>12</sup>. At present, many studies have pointed out that serum UA, Cys-C as well as Hcy levels are linked to PD<sup>13-15</sup>. However, the link between serum UA, Cys-C along with Hcy levels and whether PD is combined with cognitive impairment, disease duration along with severity of disease remains inconclusive.

The intention of this study was to assess the link between PD and serum UA, Hcy along with Cys-C levels. Additionally, it sought to understand the links between these serum biomarker levels and factors such as the coexistence of cognitive impairment, the duration of PD, and its severity. Such investigation aims to elucidate the relationships between PD and the levels of UA, Hcy, and Cys-C in serum, thereby offering supportive evidence for potential underlying mechanisms in the pathogenesis of PD.

**Data and methods**

*General data*

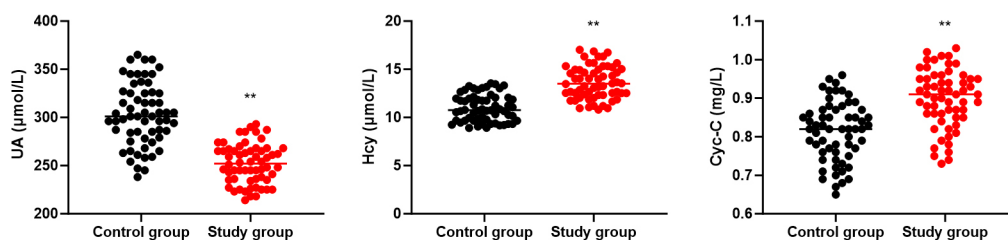
**Table 1 Clinical efficacy in 2 groups**

Groups	Cases	CR	PR	SD	PD	ORR	CBR
Control group	51	10	21	10	10	31 (60.78%)	41 (80.39%)
Study group	51	20	22	7	2	42 (82.35%)	49 (96.08%)
$\chi^2$						5.83	6.04
P						0.01	0.01

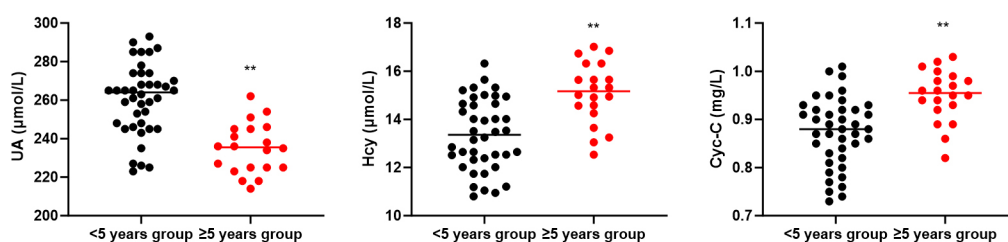
Sixty PD patients who were hospitalized in our hospital from January 2023 to December 2024 were chosen as the study group. Inclusion criteria: (1) The patient was diagnosed by a specialist and met the Parkinson's Association criteria for PD diagnosis; (2) Patients or family members were informed of this study and signed consent forms. Exclusion criteria: (1) Secondary Parkinson's syndrome, neurodegenerative diseases other than PD, dementia (non-PD), cerebrovascular history, and brain trauma; (2) Malignant tumors, blood diseases, acute and chronic infections, heart, liver and renal insufficiency; (3) In the past 3 months, the patient had taken drugs that may affect serum UA, Hcy and Cys-C levels.

During the same period, 60 healthy volunteers were selected for physical examination in the outpatient department of our hospital, and their age and gender matched the control group.

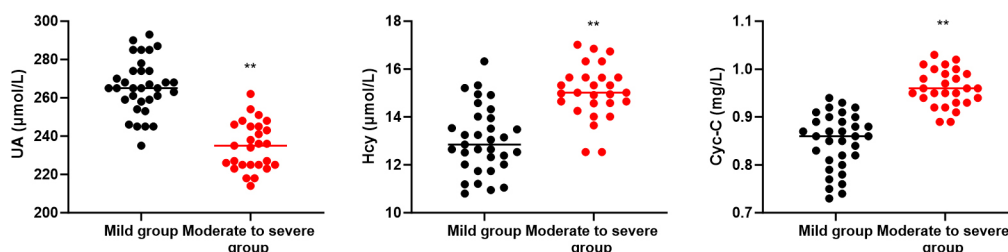
Exclusion criteria: (1) Previous history of neurodegenerative diseases, cerebrovascular disease, dementia, brain trauma;



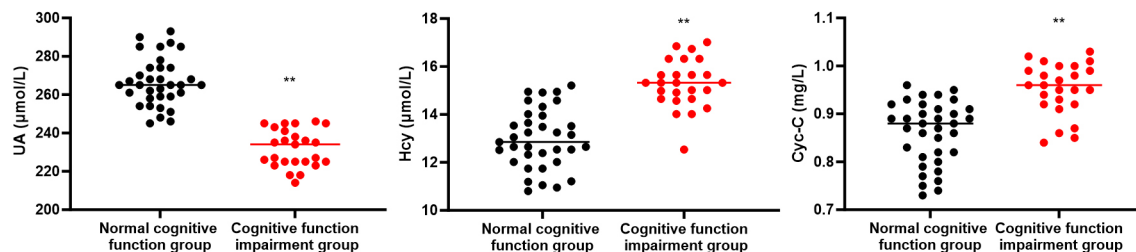
**Figure 1 Serum UA, Hcy and Cys-C levels in 2 groups. \*\*P<0.01.**



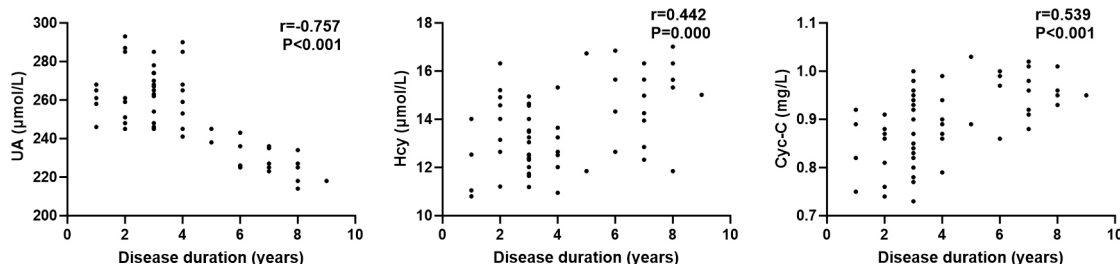
**Figure 2 Serum UA, Hcy and Cys-C levels of PD patients in <5 years group and ≥5 years group. \*\*P<0.01**



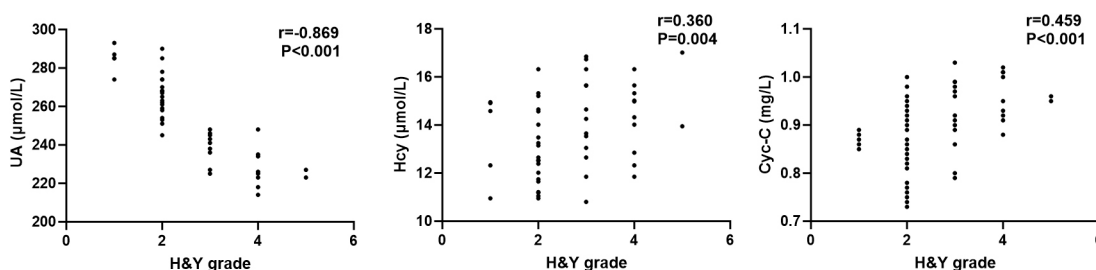
**Figure 3 Serum UA, Hcy and Cys-C levels of PD patients in mild group and moderate to severe group. \*\*P<0.01.**



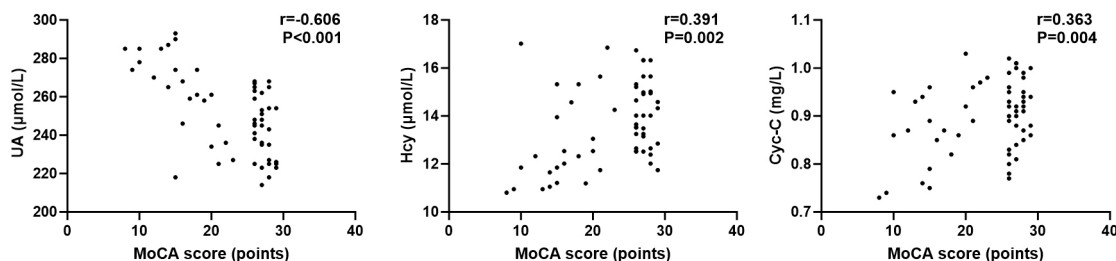
**Figure 4 Serum UA, Hcy and Cys-C levels of PD patients in normal cognitive function group and cognitive function impairment group. \*\*P<0.01.**



**Figure 5 Link between serum UA, Hcy and Cys-C levels and disease duration in PD patients.**



**Figure 6 Link between serum UA, Hcy and Cys-C levels and H&Y in PD patients.**



**Figure 7 Link between serum UA, Hcy and Cys-C levels and MoCA score in PD patients.**

(2) Malignant tumors, blood diseases, acute and chronic infections, heart, liver and renal insufficiency; (3) In the past 3 months, the healthy volunteer had taken drugs that may affect serum UA, Hcy and Cys-C levels.

This study was approved by the hospital Ethics Committee and met the ethical standards of the Declaration of Helsinki.

**Methods**

**Collection of baseline information**

Detailed medical history and physical examination were conducted for all subjects, and gender, age, history of smoking, drinking, hypertension and diabetes of each subject were recorded.

**Grouping of PD patients**

According to the varying durations of their illness, PD patients were categorized into two groups: one with less than 5 years’ duration (consisting of 40 cases) and the other with 5 years or more (comprising 20 cases).

Based on the Hoehn and Yahr (H&Y) grading criteria (16), Integrative Therapies and Translational Insights

PD patients were categorized into two groups: the mild group (H&Y≤2, consisting of 33 cases) and the moderate to severe group (H&Y>2, comprising 27 cases).

Utilizing Montreal Cognitive Assessment (MoCA), the cognitive function of the enrolled patients was assessed (17). The content assessment index included 8 aspects, including visuospatial structure, executive function, calculation, attention and concentration, memory, language, abstract thinking and orientation, with together 30 points. When the MoCA scale score was ≥26, the cognitive function was normal group, and when the MoCA scale score was < 26, the cognitive function was disabled group. If the level of education was less than 12 years, an additional point was added to correct for educational bias. According to the scores, the patients were categorized into two groups: the normal cognitive function group (35 cases) and the cognitive impairment group (25 cases).

**Collection of blood samples and detection of serum UA, Hcy and Cys-C levels**

About 5 mL of fasting venous blood was acquired from all subjects at admission and physical examination, placed in an anticoagulant tube, left at room temperature for 1 h, centrifuged (rotational speed 3500 r/min, time 10 min, radius 8 cm), and serum was separated. Automatic biochemical analyzer was used to determine serum UA, Hcy and Cys-C levels.

### **Statistical analysis**

GraphPad Prism 10 statistical software was utilized for analyzing the data. Statistical information was presented as proportions (%) and analyzed using the  $\chi^2$  test. The measurement data followed a normal distribution and were exhibited as mean  $\pm$  standard deviation ( $\bar{x} \pm s$ ), with analysis conducted through an independent-samples t-test. Personal correlation method was employed for analyzing the link between serum UA, Hcy and Cys-C levels and H&Y, disease duration and MoCA score of PD patients.  $P < 0.05$  meant the difference was statistically significant.

## **Results**

### **Baseline information of patients in 2 groups**

No significant differences were seen between 2 groups in terms of age, gender, as well as history of smoking, alcohol consumption, hypertension, or diabetes ( $P > 0.05$ , Table 1).

### **Serum UA, Hcy and Cys-C levels in 2 groups**

Compared with healthy controls, PD patients exhibited significantly elevated serum Cys-C and Hcy levels ( $P < 0.01$ ), whereas their serum UA levels were notably lower ( $P < 0.01$ , Figure 1).

### **Serum UA, Hcy and Cys-C levels of PD patients in <5 years group and $\geq 5$ years group**

When compared to the group with disease duration  $< 5$  years, the group with a disease duration of 5 years or more showed significantly higher serum Cys-C and Hcy levels ( $P < 0.01$ ), whereas their serum UA levels were markedly lower ( $P < 0.01$ , Figure 2).

Serum UA, Hcy and Cys-C levels of PD patients in mild group and moderate to severe Relative to the mild group, the moderate to severe group exhibited significantly higher serum Cys-C and Hcy levels ( $P < 0.01$ ), whereas their serum UA levels were notably lower ( $P < 0.01$ , Figure 3).

Serum UA, Hcy and Cys-C levels of PD patients in normal cognitive function group and cognitive function impairment group

When relative to the normal cognitive function group, the cognitive impairment group demonstrated significantly elevated serum Cys-C and Hcy levels ( $P < 0.01$ ). Conversely, their serum UA levels were markedly lower ( $P < 0.01$ , Figure 4).

### **Link between serum UA, Hcy and Cys-C levels and disease duration in PD patients**

Pearson correlation analysis revealed a negative link between UA and disease duration ( $r = -0.757$ ,  $P < 0.001$ ), whereas Hcy and Cys-C exhibited positive correlations with disease duration ( $r = 0.442$ ,  $P = 0.000$  and  $r = 0.539$ ,  $P < 0.001$ ), as manifested in Figure 5.

### **Link between serum UA, Hcy and Cys-C levels and H&Y in PD patients**

Pearson correlation analysis revealed a negative link between UA and H&Y grade ( $r = -0.869$ ,  $P < 0.001$ ), whereas Hcy Integrative Therapies and Translational Insights

and Cys-C exhibited positive correlations with H&Y grade ( $r = 0.360$ ,  $P = 0.004$  and  $r = 0.459$ ,  $P < 0.001$ ), as revealed in Figure 6.

### **Link between serum UA, Hcy and Cys-C levels and MoCA score in PD patients**

Pearson correlation analysis revealed a negative link between UA and MoCA score ( $r = -0.606$ ,  $P < 0.001$ ), whereas Hcy and Cys-C exhibited positive correlations with MoCA score ( $r = 0.391$ ,  $P = 0.002$  and  $r = 0.363$ ,  $P = 0.004$ ), as revealed in Figure 7.

## **Discussion**

Currently, despite the precise pathogenic mechanism of PD remaining elusive, studies have confirmed the implication of  $\alpha$ -synuclein misfolding and aggregation, mitochondrial dysfunction, oxidative stress, neuroinflammation, as well as other factors in the onset and progression of PD<sup>18</sup>.

UA, a product of purine metabolism, is a natural antioxidant that can effectively scavenge active nitrogen and oxygen free radicals<sup>19</sup>. The role of UA in neuronal protection by inhibiting oxidative stress has been confirmed in many studies<sup>20</sup>. Currently, accumulating evidence suggests that PD patients exhibit low serum UA levels, which are linked to an elevated risk of PD development. Higher UA levels have been shown to help prevent the onset of PD and exert a protective effect<sup>21</sup>. A meta-analysis exploring the correlation between UA and PD revealed that individuals with PD exhibited lower UA levels relative to the control group, with a noticeable decline in serum UA levels as the progression of PD advanced<sup>22</sup>. In addition, domestic and foreign studies have further manifested a link between lower UA levels and some clinical features of PD, such as postural instability, depression, and cognitive impairment<sup>23,24</sup>.

Hcy serves as a crucial intermediate in the metabolic process of methionine<sup>25</sup>. Current evidence has indicated a strong link between elevated Hcy levels and PD progression, suggesting that high Hcy could be a primary risk factor for developing PD<sup>26</sup>. Research has illuminated that the mechanisms underlying PD, when driven by increased Hcy levels, encompass diverse pathways, including the induction of apoptosis, oxidative stress, mitochondrial malfunction, and DNA damage within nerve cells<sup>27</sup>.

Cys-C is a class of cathepsin inhibitors, which can cause dopaminergic neuron damage by mediating inflammatory factors<sup>28</sup>. The increase of serum Cys-C can promote the release of inflammatory mediators, cause a large number of glial cells to accumulate, produce more inflammatory mediators, and cause changes in the properties of substantia nigra dopamine neurons<sup>29</sup>. The decrease of dopaminergic neurons is related to the impaired neurological function in PD patients<sup>30</sup>. Once the sub-cortical function is impaired, it will cause the impairment of visual space, attention, memory, executive ability and other functions, and then lead to cognitive dysfunction in PD patients<sup>31</sup>.

Our study revealed that, in contrast to healthy controls, PD patients exhibited significantly elevated serum Cys-C and Hcy levels, while their serum UA levels were notably declined. This finding aligns with a meta-analysis conducted by Wen et al., which indicated serum UA levels were markedly decreased in PD patients and further diminished as the disease advances<sup>32</sup>. Additionally Perinán et al. reported that increased Hcy levels in PD patients constitute a risk factor for cognitive decline<sup>33</sup>. Dong et al. Also proposed that PD

patients displayed significantly higher serum Cys-C levels compared to healthy controls<sup>34</sup>.

Furthermore, our study delved into the serum UA, Cys-C along with Hcy levels in PD patients stratified by disease duration. These findings revealed that, in contrast to the group suffering a disease duration <5 years, the serum Cys-C and Hcy levels were significantly elevated in the group suffering a disease duration of 5 years or more. Conversely, the serum UA level was notably declined in the latter group. Additional Pearson correlation analysis further confirmed that UA levels were inversely linked to disease duration, whereas Hcy and Cys-C levels were positively linked to disease duration. Similarly, Andreadou et al. demonstrated a strong and significant inverse link between UA with disease duration in PD patients<sup>35</sup>. Losy et al. reported a significant positive link between increased serum Hcy levels and both elevated duration of PD and advanced disease stages<sup>36</sup>.

To delve deeper into the link between serum levels of UA, Hcy, along with Cys-C and the extent of disease severity in PD patients, we conducted an H&Y staging assessment across our patient cohort. Our study revealed that, in contrast to the mild disease group, the moderate to severe disease group exhibited significantly elevated serum Cys-C and Hcy levels, whereas their serum UA levels were notably decreased. Furthermore, a Pearson correlation analysis demonstrated a negative association between UA and the H&Y grade, contrasting with the positive correlations observed between Hcy, Cys-C, and the H&Y grade. Our findings align with previous research, such as Sun et al., who reported a significant inverse relationship between UA levels and H&Y scales in PD patients<sup>37</sup>. Similarly, Quan et al. conducted a systematic review and meta-analysis, reinforcing a positive link between Hcy levels and the H&Y stage in PD patients<sup>38</sup>. Additionally, Lu et al. proposed that Cys-C, an inflammatory marker, could serve as an objective predictor of PD symptom severity<sup>39</sup>.

Moreover, our research endeavor evaluated the serum concentrations of UA, Cys-C along with Hcy in PD patients stratified into those with normal cognitive function and those with cognitive impairment. These findings revealed that, in contrast to the normal cognitive function group, the cognitive impairment group presented notably elevated serum Cys-C and Hcy levels, along with a marked decrease in serum UA levels. Concurrently, Pearson correlation analysis manifested a negative association between UA and MoCA scores, whereas Hcy and Cys-C demonstrated a positive correlation with MoCA scores. Likewise, Zhai et al. observed a significant inverse link between MoCA scores and UA among PD patients, alongside a positive correlation between MoCA scores and UA<sup>40</sup>. Furthermore, Xie et al. conducted a meta-analysis, affirming the connection between Hcy and cognitive decline in PD patients<sup>41</sup>.

Our study has several limitations. Firstly, our study is a cross-sectional design, which can only establish correlations rather than causation. Longitudinal studies are needed to further clarify the causal relationships between these biomarkers and the progression of PD. Secondly, although we have made efforts to match the control group with the PD patients in terms of basic demographic characteristics, there may still be other unmeasured confounding factors. For instance, lifestyle factors such as diet, exercise habits, and smoking status could potentially influence the serum levels of these biomarkers. Patients with different dietary patterns may have varying

intakes of purine-containing foods, which could affect UA levels. Similarly, exercise has been shown to have an impact on oxidative stress and inflammatory markers, potentially influencing Hcy and Cys-C levels. Thirdly, the sample size of our study, while sufficient for the current analysis, may limit the generalizability of our findings. A larger-scale study involving a more diverse population, including patients from different ethnic backgrounds and geographical regions, would be beneficial to confirm the robustness of our results. Fourthly, the assessment of cognitive function in our study mainly relied on the MoCA score. Although MoCA is a widely used and validated tool, it may not capture all aspects of cognitive impairment in PD patients. Other cognitive assessment methods, such as a more comprehensive neuropsychological battery, could provide a more in-depth understanding of the relationship between these biomarkers and cognitive function.

To summarize, the serum concentrations of Cys-C and Hcy exhibit a strong correlation with the duration, severity, and cognitive status of PD patients. In a clinical setting, alterations in the serum levels of UA, Hcy, as well as Cys-C can potentially forecast the course of PD and offer valuable insights for therapeutic interventions.

## Declarations

### *Ethics approval and consent to participate*

This study was approved by the Ethics Committee of Huaibei People's Hospital, (Approval No. LS-2020-06). Written informed consent was obtained from all participants or their legal guardians prior to enrolment.

### Consent for publication

Not applicable.

### Availability of data and materials

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

### Competing interests

The authors declare that they have no competing interests.

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### Authors' contributions

Liming Zhang and Cheng Yu conceived and designed the study. Zhuo Chen and Xiaoli Liang acquired clinical data and performed laboratory measurements. Hui Huang supervised the study, verified the underlying data, and performed/overseen the statistical analyses. Liming Zhang, Cheng Yu, and Zhuo Chen drafted the manuscript. Xiaoli Liang and Hui Huang critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript and agree to be accountable for all aspects of the work.

### Acknowledgements

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