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Value of blood biomarkers in the diagnosis of Parkinson's disease: a case-control study from Xinjiang

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Abstract

Objective Based on the data of Parkinson's disease patients in Xinjiang, China, to explore the clinical application value of blood biomarkers in diagnosing Parkinson's disease patients.

Methods The research subjects were patients with Parkinson's disease who were diagnosed and hospitalized at the Second Affiliated Hospital of Xinjiang Medical University between January 2021 and January 2023 and those who underwent health check-ups at the hospital, 243 and 249 cases were included, respectively, and those who underwent health check-ups were used as a healthy control group of the Parkinson's disease patient group.

Results Significant differences in age, systolic blood pressure, cystatin C, and uric acid distributions were found between healthy controls and Parkinson's patients ($P < 0.05$), and multivariate analysis showed that there was a correlation between body mass index, uric acid, and Parkinson's disease ($P < 0.05$), and that those who were overweight or obese, and those who had a low level of uric acid, had a greater probability of suffering from Parkinson's disease ($B > 0$). There were significant differences in gender, cystatin C, and urea between Parkinson's patients with a disease duration of < 5 years and those with a disease duration of ≥ 5 years ($P < 0.05$). In multivariate analysis, there was a correlation between gender and duration of Parkinson's disease ($P < 0.05$), and the duration of the disease was greater in male patients than in females.

Conclusion Uric acid combined with body mass index is informative for early screening of Parkinson's disease.

Keywords Parkinson's disease, Blood biomarkers, Diagnosis, Uric acid

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Introduction

Parkinson's disease (PD) is a common neurodegenerative disease, the incidence of which is second only to Alzheimer's disease [1]. Parkinson's disease usually develops in the middle-aged and elderly population, and is mainly manifested by symptoms such as muscle stiffness, tremor, and bradykinesia, etc. The pathophysiological mechanisms of PD are complex, involving a variety of mechanisms such as inflammation, oxidative stress, mitochondrial dysfunction, aberrant protein aggregation, and over-activation of N -methyl-D -aspartate receptors, and it has a significant clinical heterogeneity [2]. Currently, PD is diagnosed mainly by observation of clinical symptoms and signs, combined with imaging and laboratory tests [3]. However, the diagnostic accuracy of early PD and differential diagnosis with atypical PD still needs to be improved [4].

In recent years, with the development of medical technology, the research on the mechanism of neurodegenerative diseases has become increasingly in-depth, and more and more studies have shown that serological indexes play an important role in the diagnosis and progression of Parkinson's disease, which involves a number of aspects such as homocysteine, uric acid, creatinine and cystatin C. Uric acid is an intracellular antioxidant that plays an important role in reducing oxidative stress and cellular damage. Studies have shown that increasing uric acid levels may be helpful in the prevention and treatment of Parkinson's disease, as uric acid protects by scavenging free radicals from the body, down-regulating the level of oxidative stress, and reducing oxidative damage to nigrostriatal dopaminergic neurons [5–6]. In addition, creatinine and cystatin C are indicators closely related to renal function, and their levels can reflect glomerular filtration rate. In neurodegenerative diseases, impairment of renal function may affect the levels of these indicators, which in turn affects disease progression and prognosis. Studies have shown that cystatin C, a protease inhibitor, is involved in the process of degenerative diseases [7], and plays an important role in the protection and repair of nerve cells. As a reliable biomarker, blood biomarkers can largely reflect the physiological and pathological states in patients and provide important clues for the pathogenesis and treatment of Parkinson's disease.

The aim of this study is to explore the relationship between blood biomarkers and the diagnosis and progression of Parkinson's disease, so that we can better understand the pathogenesis of Parkinson's disease, predict the severity of the disease, and provide a scientific basis for targeted intervention of the disease.

Materials and methods

Study subjects

This is a retrospective case-control study of patients with Parkinson's disease who were seen and hospitalized at the Second Affiliated Hospital of Xinjiang Medical University between January 2021 and January 2023, and those who underwent health check-ups at the hospital, with those who underwent health check-ups being used as a healthy control group for the Parkinson's disease patient group. The hospital is the Xinjiang Clinical Medical Research Centre for Neurological Diseases, and patients come from various prefectures in Xinjiang. The study was approved by the Ethics Committee of the Second Affiliated Hospital of Xinjiang Medical University, conducted in accordance with the 1964 Helsinki Declaration or comparable standards.

Inclusion criteria for patients with Parkinson's disease: All study subjects met the diagnostic criteria for primary Parkinson's disease [8]. Patients with atypical Parkinson's (e.g., multiple system atrophy or progressive supranuclear palsy), severe heart disease, renal disease, liver disease, hematological disease, cancer, and infectious or inflammatory diseases were excluded, and 243 patients with Parkinson's disease were finally included.

Inclusion criteria for the healthy control group: Healthy medical check-up patients with non-Parkinson's disease, non-Parkinsonian superimposed syndrome, no neurodegenerative diseases, no inflammatory diseases and no relevant family history who underwent medical check-up at our hospital's medical check-up center during the same period. Health examiners who matched the gender and age of the Parkinson's disease patient group (approximate 1:1 match) were screened from our hospital's medical health screening system, and 249 cases were finally included.

Data collection

The basic information of all the study subjects was collected through the hospital information system, including height, weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, course of disease, smoking and alcohol consumption, presence of diabetes mellitus. Blood samples were drawn from the study subjects, avoiding high protein diet for 1 day before blood sampling, 3 ml of blood from the median elbow vein was drawn on an empty stomach on the day of blood sampling, anticoagulated with heparin, centrifuged within 1 h after blood sampling, and the blood samples were measured by the Co-has 8000 automatic biochemistry analyzer for the corresponding indexes including cystatin C, uric acid, urea, and creatinine indexes within 24 h. Body mass index (BMI) = weight (kg)/height (m)2, $BMI < 18.5$ for weight wasting, $18.5 \le BMI \le 23.9$ for normal weight, $BMI \ge 24.0$ for overweight and obesity.

To ensure the accuracy of the patient's disease assessment and consistency between assessors, the Unified Parkinson's Disease Rating Scale (UPDRS 3.0) [9] and Hoehn & Yahr (H-Y) staging [10], published in 1987, were used to assess the severity and staging of Parkinson's disease in patients 24 h after cessation of anti-Parkinson's disease medication (or 72 h for anti-Parkinson's extended-release medication). Early stage of Parkinson's disease is referred to as H-Y stage 1 to 2, and middle to late stage is referred to as H-Y stage 3 to 5.

Statistical processing

Excel software was used for data entry and collation, and SPSS 26.0 statistical software was used for statistical analysis. Quantitative data were described using mean and standard deviation $\left(\bar{x} \pm s\right)$ when they met the normality test, and median (M) and interquartile spacing (P_{25}~P_{75}) if they did not; qualitative data were statistically described using frequency counts and percentages (%). Comparisons of quantitative data between healthy individuals and Parkinson's patients as well as between H-Y quartiles were performed using the t test or Mann-Whitney U test, and comparisons of qualitative data were performed using the χ^2 test. Indicators with P<0.1 in the univariate analysis were included in the logistic regression for multivariate analysis. In the study, the area under the curve (AUC) was obtained by drawing the receiver operating characteristic (ROC) curve, and the diagnostic value of the indexes was determined by using the AUC value, which took the value of [0, 1], and the larger the value, the greater the diagnostic value. The test level was $\alpha = 0.05$.

Result

Value of blood biomarkers in the diagnosis of Parkinson's disease

Description and comparison of variables between healthy controls and patients with Parkinson's disease

There were 249 healthy controls, 118 males (48.8%), with a mean age of 64 years, and 243 Parkinson's patients, 124 males (51.2%), with a mean age of 65 years, in the study subjects. There were differences in the distribution of *age*, *systolic blood pressure*, *cystatin C*, *and uric acid* between healthy controls and Parkinson's patients ($P<0.05$), with age and SBP of Parkinson's patients being greater than that of healthy controls, and cystatin C, and uric acid being less than that of healthy controls; and between healthy controls and Parkinson's patients in terms of gender, BMI, DBP, heart rate, creatinine, alcohol consumption and smoking, and the presence of hypertension, diabetes mellitus, hyperlipidemia, renal disease, and atrial fibrillation were not significantly different ($P>0.05$), see Table 1.

Multivariate logistic regression analysis of Parkinson's disease diagnostic indicators

BMI, heart rate, SBP, cystatin C, and uric acid ($P<0.1$) were included in logistic regression for multivariate analysis of diagnostic indicators of Parkinson's disease, there was a correlation between BMI, uric acid and diagnosis of Parkinson's disease ($P<0.05$), and the probability of

Table 1 Comparison of variables between healthy controls and patients with Parkinson's disease M(P25 ~ P75) / n(%)

Variables	Healthy controls	Parkinson's patients	z /χ^2 value	*P* value
Age: ≥65 years	118(47.4)	114(46.9)	0.011	0.916
Gender: male	118(47.4)	124(51.0)	0.652	0.420
BMI			5.073	0.079
Normal	100(40.2)	74(30.5)		
Wasting	9(3.6)	10(4.1)		
Overweight or obesity	140(56.2)	159(65.4)		
SBP (mmHg)	127(117 ~ 138)	130(121 ~ 138)	-2.199	0.028
DBP (mmHg)	75(68 ~ 81)	76(70 ~ 83)	-1.549	0.121
Heart rate (beats/min)	73(65 ~ 82.5)	76(69 ~ 83)	-1.875	0.061
Alcohol: yes	27(10.8)	27(11.1)	0.009	0.924
Smoking: yes	30(12.0)	30(12.3)	0.010	0.920
Hypertension: yes	77(30.9)	76(31.3)	0.007	0.933
Diabetes mellitus: yes	28(11.2)	28(11.5)	0.009	0.923
Hyperlipidemia: yes	5(2.0)	5(2.1)	0.002	0.969
Kidney disease: yes	1(0.4)	1(0.4)	< 0.001	0.986
Atrial fibrillation: yes	8(3.2)	8(3.3)	0.002	0.960
Cystatin C	0.98(0.835 ~ 1.21)	0.92(0.79 ~ 1.12)	-2.244	0.025
Urea	5.22(4.185 ~ 6.76)	5.23(4.315 ~ 6.33)	-0.827	0.408
Uric acid	310(253 ~ 374)	285(229.5 ~ 337.25)	-3.912	< 0.001
Creatinine	67(56 ~ 83.4)	67(56 ~ 77)	-0.882	0.378

Table 2 Multivariate logistic regression analysis of diagnostic indicators in patients with Parkinson's disease

Variables	B value	95% CI	Standard error	Wald	*P* value	OR value
Body mass index (reference: 18.5–23.9 kg/m^2)						
Wasting	0.369	0.537 ~ 3.891	0.505	0.533	0.465	1.446
Overweight or obesity	0.583	1.191 ~ 2.693	0.208	7.846	0.005	1.791
Heart rate (beats/min)	-0.003	0.984 ~ 1.010	0.007	0.272	0.602	0.997
SBP	0.007	0.996 ~ 1.018	0.006	1.456	0.228	1.007
Cystatin C	-0.123	0.477 ~ 1.639	0.315	0.152	0.696	0.884
Uric acid	-0.004	0.993 ~ 0.998	0.001	14.875	< 0.001	0.996
Constant	0.349	—	1.001	0.122	0.727	1.418

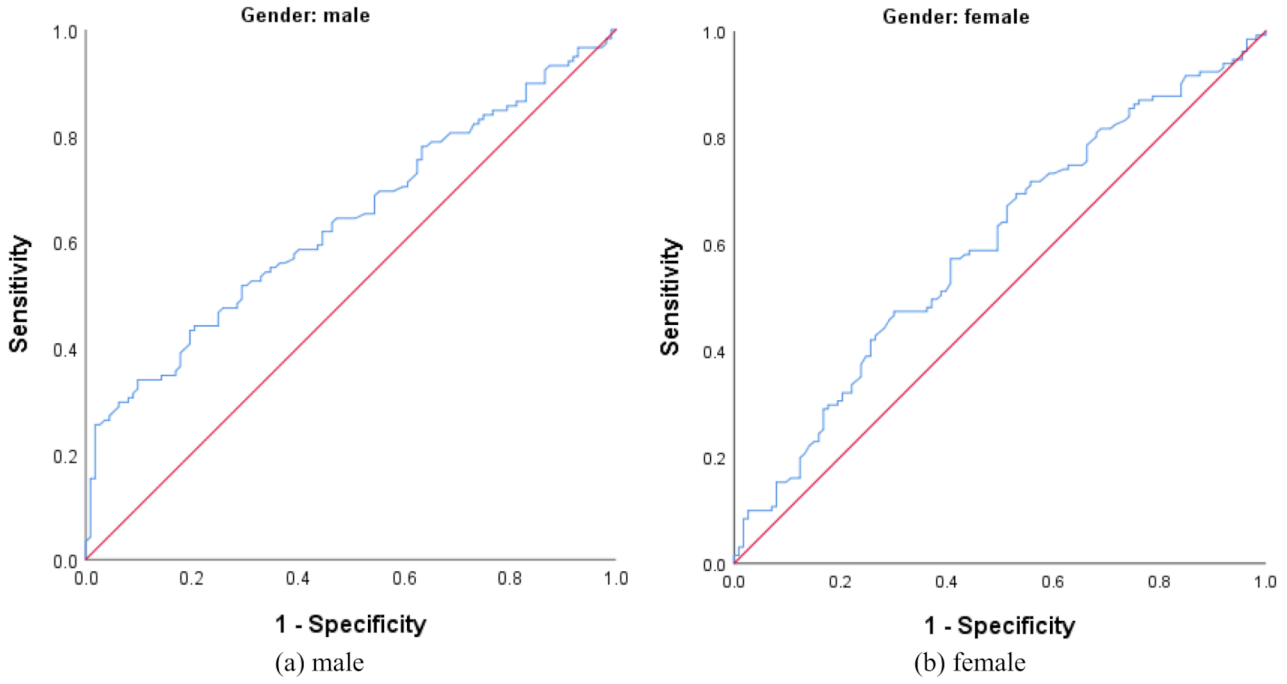

Fig. 1 ROC curves of patients with Parkinson's disease diagnosed by uric acid

Parkinson's disease was greater for those with overweight or obesity, and with a low level of uric acid ($B > 0$), see Table 2.

Diagnostic value of uric acid in Parkinson's disease

Since the normal criteria for uric acid differed by gender, the analysis was performed by gender: in male patients, the AUC value of uric acid in diagnosing Parkinson's disease and its 95% CI were 0.636 (0.565 ~ 0.708), the cut-off value was 385.50, the sensitivity was 90.2%, and the specificity was 33.9%; in female patients, the AUC value of uric acid in diagnosing Parkinson's disease and its 95% CI of 0.595 (0.524–0.666), cut-off value of 294.50, sensitivity of 69.9% and specificity of 47.3%, as shown in Fig. 1. Further combined with uric acid and BMI to diagnose Parkinson's disease, in male patients, the AUC value and its 95% CI were 0.659 (0.589 ~ 0.730), with a sensitivity of 91.1% and a specificity of 39.0%; in female patients, the AUC value and its 95% CI were 0.615 (0.545 ~ 0.685), with a sensitivity of 78.8% and a specificity of 41.2%, see Fig. 2.

Value of blood biomarkers in the severity of Parkinson's disease

Among the 243 Parkinson's patients, 142 (59.2%) were in early Parkinson's disease, 98 (40.8%) in middle and late Parkinson's disease. There was no significant difference in age, BMI, SBP, DBP, heart rate, alcohol consumption and smoking, hypertension, diabetes, hyperlipidemia, nephropathy, atrial fibrillation, cystatin C, urea, uric acid and creatinine distribution between early and middle and late Parkinson's patients ($P > 0.05$), see Table 3.

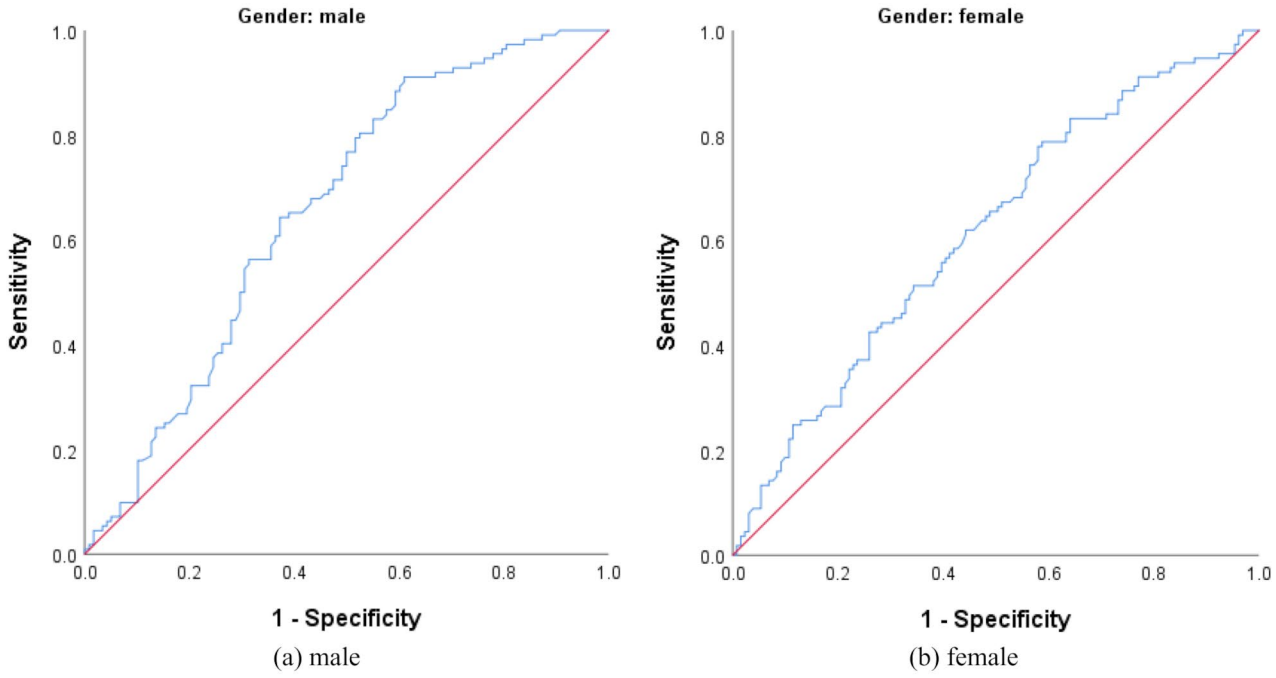

Fig. 2 ROC curves of patients with Parkinson's disease diagnosed by combined uric acid and BMI

Table 3 Comparison of characteristics of Parkinson's patients with different H-Y stages M(P25 ~ P75)/ $\bar{x} \pm s$ / n(%)

Variables	H-Y staging		$t/z/\chi^2$ value	*P* value
	Early (H-Y < 3)	Middle and late stage (H-Y ≥ 3)		
Age: ≥65 years	63(44.4)	49(50.0)	0.739	0.390
Gender: male	63(44.4)	60(61.2)	6.596	0.010
BMI			0.363	0.834
Normal	44(31.0)	30(30.6)		
Wasting	5(3.5)	5(5.1)		
Overweight or obesity	93(65.5)	63(64.3)		
SBP (mmHg)	130.18 ± 15.98	132.23 ± 16.01	-0.977	0.330
DBP (mmHg)	75(69 ~ 81)	77(70 ~ 85)	-1.802	0.072
Heart rate (beats/min)	76.55 ± 11.13	76.61 ± 14.13	-0.039	0.969
Alcohol: yes	13(9.2)	14(14.3)	1.529	0.216
Smoking: yes	14(9.9)	15(15.3)	1.619	0.203
Hypertension: yes	44(31.0)	30(30.6)	0.004	0.951
Diabetes mellitus: yes	16(11.3)	12(12.2)	0.054	0.817
Hyperlipidemia: yes	4(2.8)	1(1.0)	0.917	0.338
Kidney disease: yes	0(0.0)	1(1.0)	1.455	0.228
Atrial fibrillation: yes	4(2.8)	4(4.1)	0.288	0.592
Cystatin C	0.90(0.78 ~ 1.11)	0.93(0.79 ~ 1.15)	-0.760	0.447
Urea	5.23(4.35 ~ 6.54)	5.11(4.23 ~ 6.31)	-0.581	0.561
Uric acid	276.50(237.50 ~ 336.75)	286.50(209.75 ~ 341.25)	-0.467	0.640
Creatinine	66.00(55.85 ~ 77.00)	69.00(56.50 ~ 78.50)	-1.196	0.232

Value of blood biomarkers in the course of Parkinson's disease

Description and comparison of variables among patients with Parkinson's disease in different courses

Among the 243 Parkinson's patients, 147 patients (64.2%) had a course of < 5 years and 82 patients (35.8%) had a course of ≥ 5 years. There were significant differences in gender, cystatin C, and urea distribution between patients with Parkinson's disease of < 5 years and those with disease of ≥ 5 years ($P < 0.05$), and the proportion of

Table 4 Comparison of characteristics of Parkinson's patients with different course of disease M(P25～P75)/ $\bar{x} \pm s$ / n(%)

Variables	Course of disease (years)		$t/z/\chi^2$ value	*P* value
	< 5	≥ 5		
Age: ≥65 years	69(46.9)	39(47.6)	0.008	0.928
Gender: male	62(42.2)	51(62.2)	8.439	0.004
BMI				
Normal	44(29.9)	24(29.3)	0.084	0.959
Wasting	6(4.1)	4(4.9)		
Overweight or obesity	97(66.0)	54(65.9)		
SBP (mmHg)	130.00(120.00～137.00)	130.00(121.00～137.25)	-0.097	0.923
DBP (mmHg)	76.00(70.00～83.00)	75.00(68.75～80.25)	-1.302	0.193
Heart rate (beats/min)	75(69.00～83.00)	77.00(68.00～85.00)	-0.712	0.477
Alcohol: yes	18(12.2)	8(9.8)	0.324	0.569
Smoking: yes	18(12.2)	11(13.4)	0.065	0.799
Hypertension: yes	47(32.0)	27(32.9)	0.022	0.882
Diabetes mellitus: yes	19(12.9)	8(9.8)	0.508	0.476
Hyperlipidemia: yes	4(2.7)	1(1.2)	0.556	0.456
Kidney disease: yes	0(0.0)	1(1.2)	1.801	0.180
Atrial fibrillation: yes	5(3.4)	3(3.7)	0.010	0.919
Cystatin C	0.95 ± 0.29	1.05 ± 0.35	-2.197	0.029
Urea	5.01(4.23～6.17)	5.54(4.44～6.46)	-2.316	0.021
Uric acid	284.09 ± 77.82	288.99 ± 85.93	-0.438	0.662
Creatinine	66.00(56.00～76.00)	69.00(58.00～78.00)	-0.932	0.352
H-Y staging (≥ 3)	52(35.6)	39(48.8)	3.706	0.054

Table 5 Multivariate logistic regression analysis of course in patients with Parkinson's disease

Variables	B value	95% CI	Standard error	Wald	*P* value	OR value
Gender (reference: female)	0.731	1.145～3.766	0.304	5.786	0.016	2.076
Cystatin C	0.677	0.727～5.325	0.508	1.775	0.183	1.968
Urea	0.069	0.900～1.275	0.089	0.596	0.440	1.071
H-Y staging (reference: <3)	0.483	0.896～2.935	0.303	2.552	0.110	1.622
Constant	-2.245	—	0.601	13.961	< 0.001	0.106

males, as well as the levels of cystatin C and urea, were higher in patients with disease of ≥ 5 years than in those with disease of < 5 years, as shown in Table 4.

Description and comparison of variables among patients with Parkinson's disease in different courses

Gender, cystatin C, urea, and H-Y staging were included in logistic regression for multivariate analysis of the course of Parkinson's disease, and there was a correlation between gender and the course of Parkinson's disease ($P < 0.05$), which was greater in males than in females, as shown in Table 5.

Discussion

Parkinson's disease is a chronic progressive neurodegenerative disease, and current diagnosis relies on clinical symptoms and neuroimaging, but these methods have limitations. Blood biomarkers are biomarkers in the serum that reflect disease onset, progression, and treatment efficacy. Recent studies have shown that some specific blood biomarkers have high potential in the diagnosis, differential diagnosis and prediction of disease progression in Parkinson's disease. This study analyses the value of some blood biomarkers in the diagnosis and progression of Parkinson's disease based on the information of Parkinson's patients in a large neurological diagnostic and treatment hospital in Xinjiang.

The results of the study showed that the levels of cystatin C and uric acid in Parkinson's patients were smaller than those in healthy controls, and further multivariate analysis yielded a correlation between BMI, uric acid and the diagnosis of Parkinson's patients, and that those who were overweight or obese and had low uric acid had a greater risk of developing Parkinson's disease. Further analysis using the ROC curve combined with BMI and uric acid yielded an AUC value of 0.659 for men and 0.615 for women, which is of some reference value in the screening process for Parkinson's disease. Currently, relevant studies have found a correlation between overweight or obesity and many progressive and aging-related neurodegenerative diseases, such as Parkinson's disease and Alzheimer's disease [11, 12]. Researchers

believe that obesity may lead to physiological changes such as inflammatory responses and oxidative stress [13], which increase the risk of nerve cell damage and death, and thus increase the likelihood of developing Parkinson's disease. In addition, being overweight or obese may further increase the risk of developing Parkinson's disease by affecting the function of the dopamine system in the brain [14]. Dopamine is the primary neurotransmitter in Parkinson's disease [15] and is critical for functions such as motor control and emotion regulation. Being overweight or obese may interfere with the normal functioning of the dopamine system, thereby exacerbating the development of Parkinson's disease. It has been found that blood uric acid levels in patients with Parkinson's disease are significantly lower than those in healthy controls [16, 17], and high uric acid levels may reduce the incidence of Parkinson's disease and delay its progression [18, 19]. Uric acid is the end product of human purine metabolism, which has the effect of lowering the level of oxidative stress, and this mechanism is thought to play an important role in the pathogenesis of Parkinson's disease, and high uric acid may have a neuroprotective effect [18]. Chen et al. [20] also found that uric acid has a protective effect on oxidative stress-induced dopaminergic neuron damage through the experiments of Parkinson's animal, suggesting that uric acid is a potential neuroprotective agent. However, the levels of serum uric acid have shown robust and strong associations with the future risk of cardiovascular disease [21]. The relation between uric acid and cardiovascular disease is observed not only with frank hyperuricemia (defined as more than 6 mg per deciliter [360 μmol per liter] in women and more than 7 mg per deciliter [420 μmol per liter] in men) but also with uric acid levels considered to be in the normal to high range (> 5.2 to 5.5 mg per deciliter [310 to 330 μmol per liter]) [22–24]. Therefore, although uric acid has a protective effect against Parkinson's disease, considering its impact on cardiovascular disease, further research is still needed to determine the ideal control range of uric acid levels to achieve a balance between Parkinson's disease risk and cardiovascular disease risk.

In this study, we found that the level of cystatin C in Parkinson's disease patients was significantly lower than that in the control group, and with the prolongation of the disease duration in Parkinson's disease patients, the serum cystatin level showed a trend of gradual increase, which is consistent with the findings of Ye Ming et al. [25] and Xiong et al. [26]. Serum cystatin is widely present in the body fluids and tissues of all mammals, and plays a variety of biological roles in the human body, and is associated with normal tissue cell proliferation and growth, inflammatory response, tumor metastasis, and neurodegenerative diseases [27], and the detection of cystatin C levels in specific tissues and body fluids is of great significance in searching for markers of disease, and in studying the progression of the disease and the effects of treatment. Some studies suggest that the elevated serum cystatin levels in Parkinson's disease patients may be related to its protective role in neurodegenerative diseases: 1) the state of oxidative stress in the body can cause the continuous expression of intracranial tissue proteases, resulting in the damage and death of dopamine neurons, which contributes to the progression of Parkinson's disease; whereas, cystatin C can play a role similar to that of protease inhibitors under the state of oxidative stress in the body and protect against the cell damage caused by intracranial tissue proteases. tissue protease-induced cell damage. ② Cystatin C not only induces autophagy (a major degradation pathway of misfolded or unfolded proteins and the ubiquitin-proteasome pathway [28]), degrades α-synaptic nuclear proteins and inhibits their aggregation, but also regulates angiogenesis through vascular endothelial growth factor and promotes neuronal survival [7]. (iii) A study found that human serum cystatin partially reversed damage to midbrain dopaminergic neurons and promoted dopaminergic neuron regeneration in rat fetuses exposed to 6-hydroxydopa [26]. Therefore, increasing cystatin C levels may be helpful in reducing dopaminergic neuron damage and improving disease prognosis.

With the clinical application of modern biological indicator detection technology, the research on early biological markers of Parkinson's disease has made more significant progress in recent years [29], but still faces great challenges. At present, the diagnostic value of biological markers is very limited.

The present study has some limitations, the first is that we did not consider the effect of drugs on serological markers, and we cannot be sure whether the abnormalities of cystatin C and uric acid are the result of drug use. In addition, we did not consider the effect of genetics on Parkinson's disease, and we did not investigate whether the Parkinson's disease patients in this study were caused by family genetics. We hope that next time we will consider more comprehensively the factors that cause Parkinson's disease and the factors that affect the progression of Parkinson's disease.

Conclusions

Blood biomarkers have some clinical applications in the diagnosis of Parkinson's disease, among which, there is a correlation between uric acid, body mass index and the diagnosis of Parkinson's disease, and uric acid combined with body mass index has a reference value for the diagnosis of Parkinson's disease; and there is a correlation between cystatin C and the diagnosis of Parkinson's disease and the course of the disease.

Abbreviations

AUC	Area under the curve
BMI	Body mass index
PD	Parkinson's disease
ROC	Receiver operating characteristic
SBP	Systolic blood pressure, DBP: Diastolic blood pressure

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Author contributions
Rurui Wei and Yan Zhang: conceptualization, formal analysis, investigation, funding acquisition, methodology, visualization, writing– original draft, writing– review and editing; Peishan Li, Abudula Aisha, Hanati Nuerlanbieke and Aliyaer Niyazi: conceptualization, resources; Yang Yuan and Qinfen Wu: project administration, resources, supervision; Mingqin Cao: conceptualization; project administration; review and editing. All authors have read and agreed to the published version of the manuscript.

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Data availability
The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Declarations

Ethics approval and consent to participate
The study was approved by the Ethics Committee of the Second Affiliated Hospital of Xinjiang Medical University, all methods were carried out in accordance with relevant guidelines and regulations. The Ethics Committee of the Second Affiliated Hospital of Xinjiang Medical University waived the need for informed consent.

Consent to publish
Not applicable.

Competing interests
The authors declare no competing interests.

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