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Predictive Value of Exercise Blood Pressure Changes for Orthostatic Hypotension in Patients With Parkinson's Disease

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Background and Purpose Orthostatic hypotension (OH) is common in patients with Parkinson's disease (PD). Early recognition OH is required with sensitive assessments. The purpose of this study was to determine whether blood pressure (BP) changes during exercise can predict the occurrence of OH in PD.

Methods This prospective cohort study included 80 consecutive patients with PD. All patients agreed to participate in a baseline evaluation and cardiopulmonary exercise test (CPET). According to the initial active standing test (AST), those without OH (PD-nonOH) at baseline had their AST results followed up for 6 months. The main outcome was defined as whether patients without OH at baseline would develop OH after 6 months. Logistic regression analysis was applied to identify the relevant variables. A nomogram was constructed based on clinical features and identified variables. The concordance index (C-index) and area under the receiver operating characteristic curve (AUC) were used to evaluate the accuracy and predictive ability of the nomogram, respectively.

Results CPET results indicated that peak load, peak heart rate, heart rate recovery at 1 min, and systolic BP change (ΔSBP) were lower in those with OH than in the PD-nonOH group ($p<0.05$) at baseline. Logistic regression analysis indicated that peak load and ΔSBP during CPET had significant effects on OH ($p<0.05$). Age, sex, peak load, and ΔSBP were used to construct the nomogram model (C-index=0.761). The prediction model had an AUC of 0.782 (95% confidence interval=0.649–0.889) and a specificity and sensitivity of 70.0% and 81.8%, respectively.

Conclusions This study has identified predictive factors for OH development in patients with PD. CPET could be used as a complementary examination to identify patients at a high risk of OH.

Keywords Parkinson's disease; orthostatic hypotension; cardiopulmonary exercise test; exercise blood pressure.

INTRODUCTION

Parkinson's disease (PD) is an age-related neurodegenerative disorder with various motor and nonmotor symptoms.[1] Cardiovascular autonomic dysfunction is a nonmotor manifestation in PD that requires early detection. Orthostatic hypotension (OH) is among the most common cardiovascular autonomic dysfunctions in PD from an early stage[2,3] whose reported prevalence has ranged from 9.6% to 64.9%.[4] Recent findings highlight the significance of aging, disease severity, drug consumption, and hypertension as risk factors for OH development.[5] Timely OH diagnosis is important because its presence may reflect the early pathology of autonomic nervous system (ANS) dysfunction. Active standing test (AST) or the head-up tilt test (HUTT), ^{123}I-metaiodobenzylguanide (MIBG) cardiac scintigraphy, 24-hour ambulatory blood pressure (BP) monitoring (ABPM), and autonomic dysfunction test are

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well-established tools for assessing ANS,[6-8] but there have been few sensitive assessments of autonomic dysfunction and OH in PD.[2,9] The cardiopulmonary exercise test (CPET) can comprehensively evaluate cardiopulmonary fitness level during exercise,[10] and has become an adaptive and mature technique for screening myocardial ischemia in coronary heart disease and can predict hypertension incidence based on the BP response to exercise.[11,12] Studies have found that increases in BP are smaller in patients with PD than in controls, suggesting that parasympathetic and sympathetic dysfunction can be assessed using CPET.[13,14] The HUTT is a sensitive method for detecting OH because it does not cause leg muscle contraction.[15] However, the arteriole dilation and reduced systemic vascular resistance during exercise, which was suspected to reinforce sympathetic nerve damage and lead to insufficient compensatory vasoconstriction, increase the sensitivity in detecting OH.[16]

The purpose of this study was to determine whether BP changes during exercise can predict OH occurrence in PD. CPET might be a more sensitive method for evaluating cardiac autonomic dysfunction in PD.

METHODS

Subjects

This prospective cohort study consecutively enrolled 80 patients with PD (35 males and 45 females) at Beijing Rehabilitation Hospital from June 2020 to November 2020 (Multidisciplinary Rehabilitation Registration Study on Parkinson's disease, ethics approval number 2020bkky010, ChiCTR2000033768), and each patient signed an informed-consent form.

The inclusion criteria were 1) meeting the clinical diagnostic criteria for PD, 2) Hoehn and Yahr (H-Y) stage 1 to 3, 3) Mini Mental State Examination score ≥24, 4) informed of the need for and risks of the examination, and 5) CPET assessment could be completed safely.

The exclusion criteria were 1) other possible causes of OH, such as concomitant severe diabetes, stroke, chronic kidney disease, or cardiogenic disease, 2) other comorbidities and complications affecting CPET results, such as coronary artery disease, 3) history of recent surgical procedures, or 4) refusal or otherwise unable to complete the test as instructed due to leg or joint disease.

Clinical assessments

General information

We collected the age, sex, medication, disease duration, family history, medical history, education level, and heart rate variability (HRV) of the subjects.

Baseline assessment

The H-Y stage and Movement Disorder Society Unified Parkinson's Disease Rating Scale part III (MDS-UPDRS-III) score were used to assess the severity of disease and motor dysfunction in patients with PD. H-Y stages were used to classify the disease into five stages: 1–2.5 and 3–5 for early and intermediate-to-late stages, respectively.[17] The MDS-UPDRS-III is the motor symptom examination that assesses PD-related symptoms in terms of gait, facial expression, speech, bilateral tremor, bilateral tonicity, bilateral hand/upper and lower limb dexterity, and postural balance function with a score of 0–4 for each aspect, giving a total score of 0–108. Higher scores indicate more-severe motor impairment.[18] The levodopa equivalent dose (LED) was calculated to assess the efficacy of different anti-PD medications in patients using the following drug-equivalence formula: 100-mg levodopa=1-mg pramipexole=1-mg rasagiline=5-mg ropinirole=10-mg selegiline=100-mg amantadine (1 tablet)=100-mg piribedil. Combined with the catechol-O-methyltransferase inhibitor entacapone, the total amount was calculated at 1.33 times the dose of levodopa.[19]

AST

BP measurement was performed using a manual sphygmomanometer after resting in the supine position for 5 min in a quiet environment. We first measured BP in the supine position, and then measured it at 1 min, 3 min, and 5 min after moving to the upright position with the cuff on the same arm.[20] OH was defined as a decrease in systolic BP (SBP) of at least 20 mm Hg or a decrease in diastolic BP (DBP) of at least 10 mm Hg after standing up from the supine position for either 1, 3, or 5 min in accordance with the definition and diagnostic criteria of OH in the consensus statement of the American Academy of Neurology.[20]

CPET

The ramp continuous incremental test was performed using the Quark PFT ergo system from COSMED Italy. There were four sequential phases[21]: 1) patients were sedentary on the bike for 3 min, 2) they were instructed to maintain a uniform speed of 60 rev/min without resistance for 3 min as a warm up, 3) individualized incremental rates were set according to age and sex, starting from no load and a load increasing at 10 W/min, and patients were encouraged to maintain the speed of 55–65 rev/min and stopped when maximum exercise tolerance was reached and restriction symptoms developed within 6–10 min, and 4) patients sat and rested for 5 min during the recovery period and gradually returned to a steady state.[11]

The following main parameters were measured in the test.[10] First, heart rate (HR) was automatically measured at the end of each load level. Second, SBP and DBP were measured dur-

ing the last minute of each level. For every 3.5 mL/(kg·min) increase in VO_2, BP rises by approximately 10 mm Hg; ΔSBP and ΔDBP are the difference between the maximum SBP and maximum DBP and the BP at the beginning of the warm-up phase, respectively. Third, the maximum VO_2 mostly evaluates the ability of the body to utilize oxygen during aerobic exercise. Fourth, anaerobic threshold is the turning point from anaerobic exercise to aerobic metabolism. Fifth, the oxygen pulse (VO_2/HR) represents the ratio of VO_2 per heart beat to HR per unit time, and is an effective indicator of cardiovascular efficiency. Sixth, the metabolic equivalent (MET) is calculated as 1 MET=VO_2×3.5 mL/(kg·min). Seventh, carbon dioxide ventilation equivalent and its slope reflect the ventilation efficiency. Eighth, HR recovery at 1 min (HRR) is the difference between after 1 min at the end of exercise and the maximum HR during exercise. Ninth, the presence of T-wave changes on the electrocardiogram during exercise often indicates the possibility of myocardial ischemia and provides a reference for differential disease diagnosis.[22]

Follow-up

After excluding patients who experienced OH at baseline, the remaining individuals were followed up for 6 months at the outpatient clinic or through telephone consultations. Because some patients were unable to go back to the clinic for follow-up examinations, they were introduced to their local hospital to undergo examinations and reported their evaluation results by telephone.

The flow chart of the study is shown in Fig. 1.

Statistical analysis

Statistical analysis was performed using SPSS (version 23.0; IBM Corp., Armonk, NY, USA) and R (version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria) software. Clinical characteristics were compared between groups using the independent-sample *t*-test for normally distributed data and the Mann-Whitney U-test was used for nonnormally distributed data, and the measures at baseline were expressed as mean±standard deviation values or as medians and interquartile ranges. Variables with the ability to predict OH occurrence in patients with PD were screened using logistic regression analysis. A nomogram was constructed using the identified variables, age, and sex to predict OH occurrence. The receiver operating characteristic (ROC) curve and concordance index (C-index) were generated to assess the predictive ability of the model. A larger area under the ROC curve (AUC) indicates that the model has a better classification ability.[23] $p<0.05$ was considered significant.

RESULTS

Clinical characteristics of the subjects

Demographic information, disease duration, and H-Y stage at baseline are listed in Table 1. There were 17 cases (21.3%) with OH (PD-OH group) (6 females and 11 males) and 63 (78.7%) without OH (PD-nonOH group) (39 females and 24

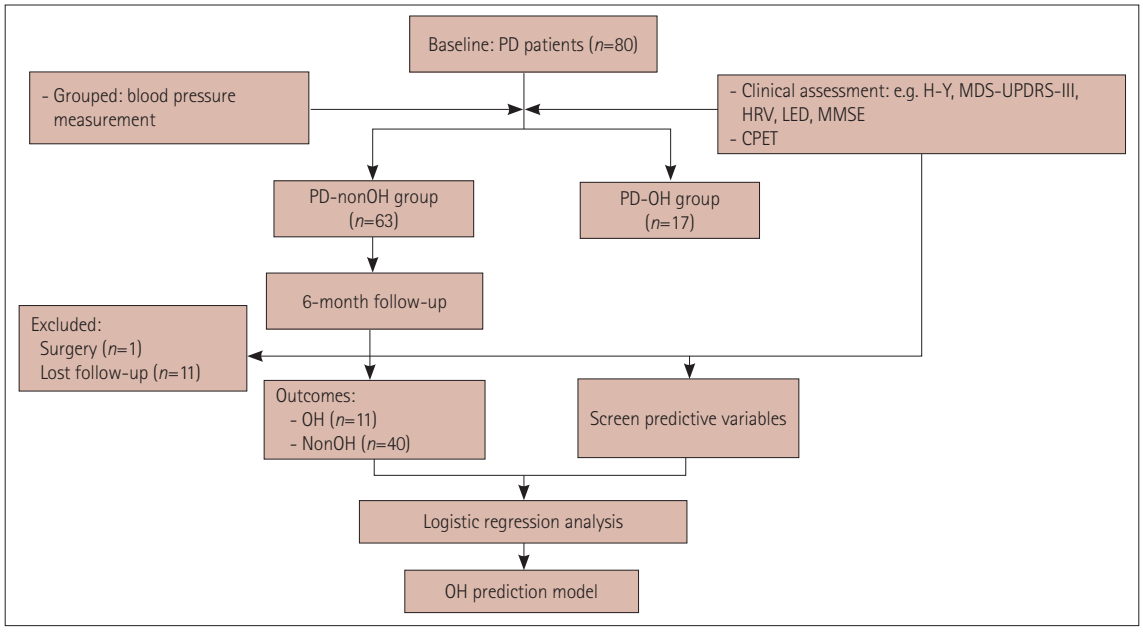

Fig. 1. Flow chart of constructing the prediction model. CPET, cardiopulmonary exercise test; HRV, heart rate variability; H-Y, Hoehn and Yahr; LED, levodopa equivalent dose; MDS-UPDRS-III, Movement Disorder Society Unified Parkinson's Disease Rating Scale part III; MMSE, Mini Mental State Examination; OH, orthostatic hypotension; PD, Parkinson's disease; PD-nonOH, patients without OH; PD-OH, patients with OH.

Table 1. Comparisons between PD-OH and PD-nonOH groups

Variable	PD-OH (*n*=17)	PD-nonOH (*n*=63)	*p*
Age (yr)	66 (12)	60 (8)	<0.001*
Sex (*n*)			0.260
Female	6	39	
Male	11	24	
Disease duration (months)	90 (84)	72 (63)	0.567
BMI (kg/m^2)	25.4 (1.8)	23.7 (3.5)	0.061
Hoehn & Yahr stage (*n*)			0.781
Total	2.0 (0.5)	2.0 (1.0)	
Stage 1–1.5	1	5	
Stage 2	9	30	
Stage 2.5	4	12	
Stage 3	3	16	
MDS-UPDRS-III (scores)	32 (22)	30.5 (17)	0.400
LED (mg/d)	547 (446.7)	500 (296.8)	0.120
Peak load (W)	85 (34)	82.5 (38)	0.948
MET (mL/kg/min)	4 (1.3)	4 (1.8)	0.390
FVC (% of predicted)	93.04 (10.37)	98.27 (18.12)	0.417
Peak HR (bpm)	100 (26)	120 (33)	0.002*
HR max/pred (%)	85 (14.5)	95 (15.0)	0.051
Peak VE (L/min)†	31.90±11.19	27.19±9.01	0.076
Peak VO_2 (mL/min)	1250.0 (367)	1210.5 (408)	0.553
VO_2 %pred	82.5 (26)	84.0 (24)	0.920
Peak VO_2/kg max (mL/min/kg)	17.35 (14.2)	19.95 (6.4)	0.228
Peak VO_2/HR (mL/beat)	12.6 (2.4)	10.2 (4.2)	0.041*
Peak VE/VCO_2	28.25 (6.2)	27.55 (5.1)	0.176
OUES	1781.5 (522.5)	1686.5 (598.3)	0.350
HRR 1 min (bpm)	2 (6)	11 (15)	0.074
$petO_2$ max (mm Hg)†	111.29±4.79	111.47±5.05	0.894
$petCO_2$ max (mm Hg)†	38.70±3.80	39.09±3.83	0.574
Peak SBP (mm Hg)	142 (44)	153 (43)	0.054
Peak DBP (mm Hg)	89 (35)	92 (27)	0.452
ΔSBP (mm Hg)	23 (24)	40 (25)	0.005*
ΔDBP (mm Hg)	7 (20)	13 (26)	0.513
Quiet SBP (mm Hg)	100 (26)	120 (21)	0.133
Quiet DBP (mm Hg)	64 (20)	74 (14)	0.990
SDNN (ms)	133.5 (37)	146.5 (62)	0.263
SDNN index	45 (80)	52 (40)	0.197
SDANN (ms)	118 (57)	129 (63)	0.406

*p<0.05 statistically significant; †The above variables in the analysis, except for $petO_2$, $petCO_2$, and peak VE, which used independent *t*-tests; other variables used Mann-Whitney U test.
BMI, body mass index; DBP, diastolic blood pressure; FVC, forced vital capacity; HR, heart rate; HRR, heart rate recovery; LED, levodopa equivalent dose; MDS-UPDRS-III, Movement Disorder Society Unified Parkinson's Disease Rating Scale part III; MET, metabolic equivalent; OH, orthostatic hypotension; OUES, oxygen uptake efficiency slope; PD, Parkinson's disease; PD-nonOH, patients without OH; PD-OH, patients with OH; $petCO_2$, partial pressure of end-tidal carbon dioxide; $petO_2$, partial pressure of oxygen in end-tidal gas; SBP, systolic blood pressure; SDANN, standard deviation of the average normal to normal RR intervals; SDNN, standard deviation of normal to normal RR intervals; VCO_2, carbon dioxide production; VE, minute ventilation; VO_2, oxygen uptake; VO_2/kg, kilogram oxygen uptake; VO_2 %pred, peak oxygen uptake as a percentage of predicted value; ΔSBP, SBP changes; ΔDBP, DBP changes.

males). Age, disease duration, BMI, MDS-UPDRS-III, and LED were compared between the two groups using the Mann-Whitney U-test. At baseline, patients in the PD-OH group were older than those without OH, while other parameters did not differ significantly between the groups. Chi-square tests were used to compare sex proportions, which did not differ significantly. Follow-ups were performed on 63 cases, of which 51 had a complete follow-up. The OH incidence was 21.6% (11/51) after 6 months of follow-up.

Comparison of CPET parameters

SBP and DBP did not differ significantly between the groups before the third CPET phase, while SBP increased in both groups after the exercise was loaded. Peak load, peak HR, HRR, and ΔSBP were lower in the PD-OH than in the PD-nonOH group, but VO_2/HR was significantly higher in the PD-OH group; all of these differences were statistically significant (p<0.05) (Table 1).

Variables associated with OH in PD

According to the risk factors for OH reported in the literature combined with the information we collected, logistic regression analysis was performed to evaluate the independent variables for predicting OH with statistical significance (p<0.2): peak load, peak SBP, peak DBP, and ΔSBP were added to the regression analysis (Table 2).

The above-mentioned screened parameters were included in the logistic regression analysis to further screen for variables. Peak load (odds ratio [OR]=1.024, 95% confidence interval [CI]=1.001–1.048, p=0.037) and ΔSBP (OR=0.954, 95% CI=0.918–0.992, p=0.018) were associated with OH occurrence after 6 months of follow-up (Table 3). Peak load and ΔSBP therefore had independent predictive value.

Construction of OH prediction model

A nomogram was constructed using four variables (age, sex, peak load, and ΔSBP) to evaluate OH risk, and its C-index was 0.761 (p=0.001) (Fig. 2). Each variable was evaluated using a score from 0 to 100, with a total score ranging from 0 to 160, which was used to identify the predicted probability of OH. The AUC for the nomogram prediction model was 0.782 (95% CI=0.649–0.889), which verified the accuracy of the nomogram (Fig. 3). The sensitivity and specificity of the prediction model were 81.8% and 70.0%, respectively.

DISCUSSION

This prospective study found that peak load and ΔSBP during exercise had significant effects on OH as measured by CPET, and offers insight into identifying patients at a high risk of OH.

We adopted the recommended diagnostic criteria, including initial OH and delayed OH (DOH).[24] The presence of DOH suggests mild impairment or early sympathetic failure, and over time about half of patients with PD develop OH, and these patients with DOH may have an even worse prognosis.[25] DOH might therefore be more suitable to use as a di-

Table 2. Results of the preliminary screening variables of the logistic regression analysis

Variable	B	SE	Wald	OR value	95% CI	*p*
General information						
Age (yr)	-0.001	0.040	0.000	0.999	0.923–1.081	0.983
BMI (kg/m^2)	-0.024	0.117	0.042	0.976	0.777–1.227	0.837
Disease duration (months)	-0.001	0.006	0.010	0.999	0.998–1.011	0.920
Hoehn & Yahr stage	0.184	0.692	0.071	1.202	0.310–4.662	0.790
MDS-UPDRS-III (scores)	0.025	0.030	0.675	1.025	0.966–1.087	0.411
LED (mg/d)	0.000	0.001	0.049	1.000	0.998–1.003	0.825
SDANN (ms)	0.002	0.009	0.043	1.002	0.984–1.020	0.836
SDNN index	0.001	0.009	0.005	1.001	0.983–1.018	0.943
SDNN (ms)	0.003	0.007	0.134	1.003	0.989–1.017	0.714
CPET variable						
Peak load (W)	0.014	0.009	2.303	1.014	0.996–1.032	0.129*
MET (mL/kg/min)	-0.008	0.225	0.001	1.008	0.649–1.566	0.971
FVC (% of predicted)	-0.007	0.060	0.015	0.993	0.883–1.116	0.902
MVV (l)	0.003	0.011	0.059	1.003	0.981–1.024	0.808
OUES	0.000	0.001	0.001	1.000	0.998–1.002	0.976
Peak HR (bpm)	-0.013	0.011	1.467	0.987	0.967–1.008	0.226
Peak VE (L/min)	0.013	0.041	0.103	1.013	0.935–1.907	0.748
Peak VO_2 (mL/min)	0.001	0.001	0.406	1.001	0.999–1.002	0.524
Peak VO_2/kg (mL/min/kg)	-0.002	0.059	0.001	0.969	0.998–1.121	0.969
Peak VE/VO_2	-0.011	0.029	0.156	0.989	0.935–1.046	0.693
$\Delta VO_2/\Delta$work-rate slope	0.119	0.109	1.190	1.126	0.910–1.395	0.275
Peak VO_2/HR (mL/beat)	0.014	0.078	0.034	1.014	0.871–1.182	0.854
Peak VE/VCO_2	-0.086	0.103	0.699	0.403	0.890–1.335	0.403
VE/VCO_2 slope	-0.018	0.043	0.163	0.983	0.902–1.070	0.687
HRR 1 min (bpm)	0.013	0.019	0.439	1.013	0.975–1.052	0.508
$petO_2$ max (mm Hg)	-0.002	0.065	0.001	0.998	0.878–1.134	0.972
$petCO_2$ max (mm Hg)	-0.065	0.088	0.554	0.937	0.788–1.113	0.457
Peak SBP (mm Hg)	-0.032	0.014	5.392	0.968	0.943–0.995	0.020*
Peak DBP (mm Hg)	-0.032	0.020	2.555	0.968	0.931–1.007	0.110*
ΔSBP (mm Hg)	-0.033	0.017	3.861	0.968	0.937–1.000	0.049*
ΔDBP (mm Hg)	-0.011	0.020	0.283	0.989	0.951–1.029	0.595

*We considered $p<0.2$ as statistically significant screening.
BMI, body mass index; CI, confidence interval; CPET, cardiopulmonary exercise test; DBP, diastolic blood pressure; FVC, forced vital capacity; HR, heart rate; HRR, heart rate recovery; LED, levodopa equivalent dose; MDS-UPDRS-III, Movement Disorder Society Unified Parkinson's Disease Rating Scale part III; MET, metabolic equivalent; MVV, maximum minute ventilation; OH, orthostatic hypotension; OR, odds ratio; OUES, oxygen uptake efficiency slope; $petCO_2$ partial pressure of endtidal carbon dioxide; $petO_2$, partial pressure of oxygen in end-tidal gas; SBP, systolic blood pressure; SDANN, standard deviation of the average normal to normal RR intervals; SDNN, standard deviation of normal to normal RR intervals; SE, standard error; VCO_2, carbon dioxide production; VE, minute ventilation; VO_2, oxygen uptake; VO_2/kg, kilogram oxygen uptake; ΔDBP, DBP changes; ΔSBP, SBP changes; $\Delta VO_2/\Delta$work-rate slope, oxygen uptake to work rate slope.

Table 3. Logistic regression analysis for the occurrence of OH in patients with Parkinson's disease

Variable	B	Standard error	Wald	OR value	95% CI	*p*
Peak load	0.024	0.012	4.335	1.024	1.001–1.048	0.037
ΔSBP	-0.047	0.020	5.616	0.954	0.918–0.992	0.018
Constants	-1.718	1.090	2.486			0.001

CI, confidential interval; OH, orthostatic hypotension; OR, odds ratio; ΔSBP, systolic blood pressure changes.

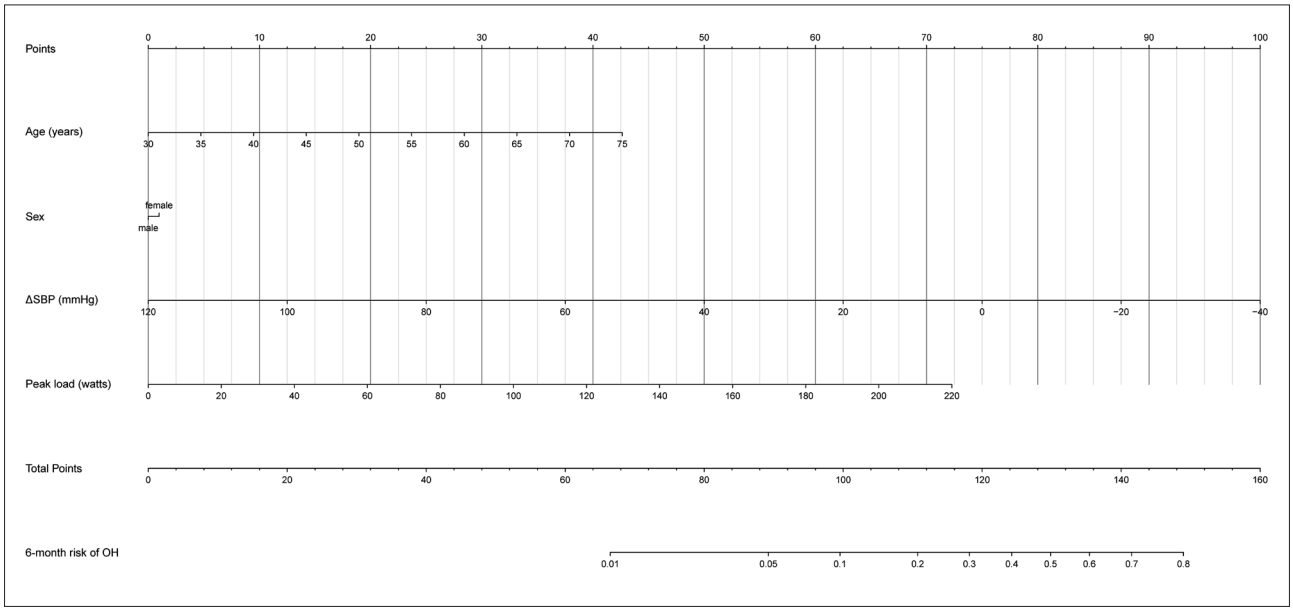

Fig. 2. The nomogram for predicting OH in Parkinson's disease based on the logistic regression analysis results. Points were assigned for age, sex, peak load, and ΔSBP by drawing a line upward from the corresponding values to the point line. The sum of these four points, plotted on the "total points" line, corresponds to the estimated risk of OH occurrence at 6 months. OH, orthostatic hypotension; ΔSBP, systolic blood pressure changes.

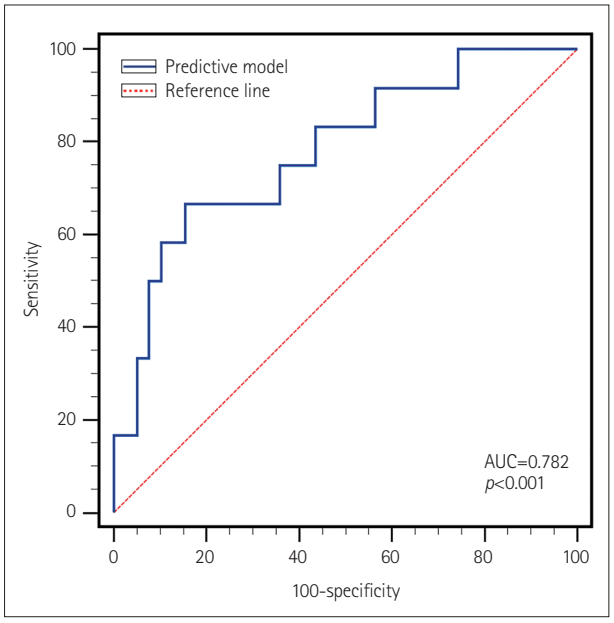

Fig. 3. AUC for the nomogram. AUC, area under the receiver operating characteristic curve.

agnostic criterion for evaluating BP changes in patients with PD in the standing position within 5 min,[24] thus reducing the rate of missed diagnoses. At baseline, there were 17 cases (21.3%) with OH, most of which were standard and DOH. After 6 months, 11 patients (21.6%) had developed OH. The OH prevalence ranged from 9.6% to 64.9% in previous studies due to different demographics and evaluation methods, corresponding to the early stage of most patients with PD in our study.[4] Cardiovascular autonomic dysfunction might be too mild to be detected in supine and standing tests, so the incidence of symptomatic OH would be relatively low. More importantly, some patients with OH did not complain about severe orthostatic symptoms in their daily life, so follow-ups are required to track BP changes.

In patients with PD, OH often reflects sympathetic denervation, which is associated with the loss of cardiac and extracardiac noradrenergic innervation and with arterial baroreceptor reflex dysfunction that especially manifest during standing and exercise.[25-27] OH incidence increases with age due to the degradation of BP regulation mechanisms and impaired sensitivity to external changes.[28] In the present study, the ages of the patients differed significantly between the groups at baseline. Moreover, decreased HRV is a signal that cardiac function has deviated from a healthy baseline, and this is very common in patients with PD.[7,9] The standard deviation of normal-to-normal RR interval (SDNN) and the SDNN index could also reflect ANS imbalance in patients with PD.[29,30] However, SDNN and the SDNN index did not differ significantly between the two groups at baseline. No correlation was found between HRV and OH risk, which may be due to the mild autonomic dysfunction in patients with early PD in our study. This indicates that patients with OH experience more-severe ANS dysfunction. HRV can be applied for detection[31] and to assess effects on exercise and rehabilitation outcomes.

The changes in cardiovascular response during exercise were associated with impaired ANS in patients with PD.[13,32] Considering that CPET has been widely used to diagnose

and manage cardiovascular disorders and other diseases,[10,22] it is also worth applying to patients with PD. It was particularly interesting that BP increased less in some of patients with PD than in people without PD during CPET examinations, which prompted us to speculate whether BP changes during CPET is more sensitive at reflecting potential OH in patients with PD. The HUTT is a sensitive method for identifying OH because it does not cause leg muscle contraction.[33] However, due to arteriole dilation and reduced systemic vascular resistance during exercise, which is suspected sensitivity to reflect sympathetic nerve damage and lead to insufficient compensatory vasoconstriction,[16] just like in postprandial hypotension.[34] We found that the BP values of PD-OH patients were significantly less elevated during exercise. Previous research has demonstrated that the peaks of SBP and DBP increase with age in both males and females, and they are consistently higher in males than in females up to the age of 70 years.[35] The increased BP response is thought to play a key role during exercise. Reduced cardiac output and decreased BP during exercise are used to diagnose and evaluate coronary heart disease.[12] A significant difference in the increase of SBP between patients with PD and controls was found previously, which has been suggested to be a manifestation of damaged cardiovascular response and a potential mechanism for impaired central nervous system control and sympathetic nerve dysfunction response.[36] In our study, the differences between BP changes in the PD-OH and PD-nonOH groups could explain the sympathetic dysfunction being more severe in patients with PD with OH. The maximum VO_2, MET, and VO_2 efficiency slope did not differ significantly between the two groups due to the small number of included patients with PD.

Moreover, among the CPET index, HR tends to increase linearly with exercise loading.[37] Individuals with better cardiovascular performance in CPET also have better HRR; that is, their HR decreases more rapidly during the recovery period after exercise. The American Heart Association defines this clearly as follows: abnormal HRR is an abnormal HR decline rate after exercise cessation, HR decline of <12 times per min or <22 times within 2 min.[38] The present study found that the HRR of patients with PD was lower than the criteria, and the rate of decline was slower in the PD-OH than the PD-nonOH group, indicating that the HR recovery ability was worse with OH in patients with PD. However, the mechanism is still not clear, with some suggesting it is related to increased sympathetic excitability and decreased parasympathetic excitability, and others suggesting it is related to abnormal vagal nerve activity.[14,39] A higher peak HR during exercise was found to increase the HRR change during recovery.[40] The physical fitness of subjects could therefore also affect their HRR. In our study, the abnormal peak HR and HRR seemed to be related to the reduced exercise load due to impaired ANS function.[41] This indicates that exercise intolerance in patients with PD may be explained by impaired responses to norepinephrine release from sympathetic nerves and mild exercise capacity impairment.[42] No previous prospective studies have assessed the relationship between CPET and OH in PD. CPET can yield new and useful information for capturing possible abnormal changes associated with OH.

In the logistic regression analysis, in order to avoid losing some important variables, the *p* value for inclusion in this study was relaxed to 0.20 when screening variables. To calculate the OH risk scores of patients with PD, we added two variables (sex and age) to the logistic regression analysis because they were the most basic variables in the data set that can also predict OH occurrence. A nomogram was used to visualize the regression results to identify the predicted probability of OH occurrence. The ROC curve also indicated that the accuracy of the predictive model is general. However, the model is not yet suitable for use in clinical work, and should currently only be used as a predictive reference in research before further validation through long-term follow-ups. According to our analysis, OH occurrence in patients with early-stage PD might not be easy to detect by examining autonomic nervous function. There have been a few investigations of the combination of these methods as preliminary evaluations, which provide ideas for combining early autonomic nerve examination with other methods to improve detection accuracy.[25,29]

There were several limitations in our study. First, although we strictly calculated the LED of each patient, we did not standardize the interval time between CPET and medication administration in patients. Second, we measured BP using AST instead of the HUTT for convenience during the follow-up. Because of the travel restrictions during the COVID-19 pandemic, some rural patients could not receive the HUTT from a local hospital. Meanwhile, the diagnostic criteria of OH in the consensus statement of the American Academy of Neurology and EFNS guidelines were also both recommended.[20] We chose AST as the evaluation method for OH, despite the HUTT being more sensitive and specific. Moreover, different measurement environments may reduce the accuracy of follow-up data. Third, due to the restriction of data collection, we did not include the BP response during the recovery period as a further investigation. Fourth, the relatively small sample could have adversely affected the sensitivity and specificity of the model. Fifth, we did not assess other autonomic parameters such as the Valsalva maneuver or sympathetic skin response. Therefore, the sample size needs to be expanded to improve the accuracy of the prediction model, and future studies should compare its sensitivity with the HUTT.

In conclusion, despite all the limitations addressed above,

the present results can still support our findings of the peak load and SBP change during exercise being factors that influence OH occurrence in patients with PD. These are potentially useful indexes for predicting OH occurrence in patients with PD.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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