


## RESEARCH ARTICLE

# Effect of diabetes control status on the progression of Parkinson's disease: A prospective study

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## Abstract

**Objective:** To evaluate whether the control status of type 2 diabetes mellitus (DM) influences the progression of Parkinson's disease (PD). **Methods:** We conducted a prospective cohort study from March 2009 to August 2020. Patients at baseline were categorized into DM and non-DM groups, and those with DM were further classified into the well and poorly controlled DM groups based on the 7.0% of glycated hemoglobin (HbA1C) levels. Multivariate Cox proportional hazards regression models were used to explore the predictors for PD-related outcomes by hazard ratios (HRs) and 95% confidence intervals (CIs). **Results:** Of the 379 patients enrolled, 49 (12.9%) had DM, and 22 of DM (44.9%) were poorly controlled. The adjusted HRs were 2.060 (95% CI 1.165–3.641) for United Rating Scale (UPDRS) III score increased  $\geq 14$  in the poorly controlled-DM group, and 1.066 (95% CI 0.572–1.986) in the well-controlled DM group, relative to the non-DM group ( $p$  trend = 0.025), after adjusting for sex, age, age of onset, body mass index, and UPDRS III and Montreal Cognitive Assessment (MoCA) scores at baseline. The adjusted HRs were 2.079 (95% CI 1.212–3.566) for reaching Hoehn & Yahr stage  $\geq 3$  in the poorly controlled DM group, and 0.879 (95% CI 0.413–1.871) in the well-controlled DM group, compared with the non-DM group ( $p$  trend = 0.021). Time to death or time to MoCA 3-point decrease were not significantly different among the three groups. **Interpretation:** Poorly controlled DM is an independent risk factor contributing to motor progression in PD. Our study highlights the importance of adequate control of diabetes in PD.

## Introduction

The association between Parkinson's disease (PD) and type 2 diabetes mellitus (DM) has been disclosed in recent years. The two conditions often coexist,<sup>1</sup> and impaired glucose tolerance is frequently observed in patients with PD.<sup>1,2</sup>

DM is associated with an increased risk of suffering from PD. Pooled evidence based on population-based cohort studies suggests that patients with DM have an average 38% higher risk of developing PD.<sup>3</sup> Furthermore, DM in PD patients is associated with more severe motor disability, less response to dopaminergic drugs,<sup>1,4</sup> more severe axial motor symptoms,<sup>5</sup> and cognitive impairment.<sup>6,7</sup> A case-control study<sup>8</sup> also observed that patients

with comorbid DM developed motor complications on average 12 months earlier in PD, independent of medications or other disease-related factors.

To date, the effect of DM on the progression of PD is still largely unknown. In the older normal population, DM is reported as a risk factor for progression of parkinsonism-like signs.<sup>9</sup> In PD, although some researchers have studied the prognostic value of early onset of DM, they mainly defined DM by the measurement of fasting and postprandial blood glucose. Compared with blood glucose, glycated hemoglobin (HbA1C) is a more stable index that can reflect the cumulative glycemic history of the preceding 2 to 3 months. HbA1C provides a reliable measure of chronic hyperglycemia and relates well to the risk of developing long-term diabetes complications.

Elevated HbA1C levels have been reported as an independent risk factor for the prognosis of neurodegenerative disorders such as amyotrophic lateral sclerosis.<sup>10</sup> However, the association between HbA1C levels and disease progression in PD remains unknown. Therefore, in the present study, we aimed to examine the impact of HbA1C levels on motor deterioration, cognitive decline, and survival in a cohort of Chinese PD patients.

## Patients and methods

### Standard protocol approvals, registrations, and patient consents

The current study was permitted by the Ethics Committee of Sichuan University West China Hospital. All participants provided written informed consent.

### Study participants

Initially, 4518 PD patients who met the Unified Kingdom PD Society Brain Bank clinical diagnostic criteria for PD<sup>11</sup> were seen and registered in the Department of Neurology, Sichuan University West China Hospital, between March 2009 and August 2019 (Figure 1). The clinical diagnosis of PD was also determined by the MDS version of clinical diagnostic criteria for PD<sup>12</sup> before we performed the statistical analysis.

Participants were invited to follow-up ( $n = 492$ ) if they 1) had Hoehn and Yahr (H&Y) stage  $<3$  and assessed UPDRS III at off-medication, 2) were older than 40 years, 3) had a PD duration of  $<3$  years, 4) reported no motor complications, dementia, stroke, and myocardial infarction, and 5) performed blood test for screening diabetes. All participants were followed up at least once (range 1-10), with an interval of at least one year. During follow-up, 24 patients withdrew informed consent, 37 lost contact, and 52 had broken data. Finally, the remaining 379 patients were included for data analysis (Figure 1).

### Definition of DM

Type 2 DM was defined as a past medical history of DM with or without the use of hypoglycemic agents, or serum HbA1C levels of  $\geq 6.5\%$  (48 mmol/mol) at the time of PD enrollment according to the WHO suggestion.<sup>13</sup> Past medical history data were obtained from patients and their relatives or extracted by patients' medical records, when available. The serum HbA1C levels were examined in the clinical laboratory of Sichuan University West China Hospital. Enrolled participants were classified as patients with and without DM

(DM group vs. non-DM group). Patients with poorly controlled DM were defined as serum HbA1c levels of  $\geq 7.0\%$  (53 mmol/mol).<sup>14</sup> On the contrary, patients with serum HbA1c levels of  $<7.0\%$  were classified into the well-controlled DM group.

### Clinical assessments

At baseline, a standardized assessment for all patients was completed by trained neurologists in our movement disorder center. Demographic and clinical data including sex, age, height, body mass index (BMI), age of onset, disease duration, years of schooling, and therapeutic schedule were collected. The levodopa equivalent daily dosage (LEDD) was calculated using previously published criteria.<sup>15</sup>

The Unified PD Rating Scale (UPDRS) part III<sup>16</sup> and H&Y stage<sup>17</sup> were applied to evaluate the motor severity. During follow-up, patients were asked to withhold their antiparkinsonian medications for at least 12h before motor assessment. For patients who were not assessed at off medication state ( $n = 82$ , 21.6%), we estimated an off-score by adding the difference value of the study population's mean off-score and mean on-score to the patient's on-score.<sup>18</sup>

The Chinese version of the Non-Motor Symptoms Scale (NMSS)<sup>19</sup> was used to assess the non-motor symptoms (NMS). Cognitive function was assessed by the Montreal Cognitive Assessment (MoCA)<sup>20</sup> and the Frontal Assessment Battery (FAB),<sup>21</sup> with lower scores indicating poor cognition. The depressive symptom was assessed by the Hamilton Depression Rating Scale (HDRS) (24 items),<sup>22</sup> and the anxious symptom was assessed by the Hamilton Anxiety Rating Scale (HARS).<sup>23</sup>

### Clinical endpoints

#### Survival

Continuous survival surveillance was performed by an active annual follow-up for patients and their family members until August 1, 2020, which indicated approximately 11 years after our study began (2009) and 14 years after the patients were firstly diagnosed (2006). Time to death was defined as the interval in years from the onset of PD to the follow-up visits in which the patients had either the PD-related (33/51, 64.7%) or non-PD-related (18/51, 35.3%) death.

#### Motor decline

An increase of 2.5-5.2 points in the UPDRS III was considered a clinically significant difference.<sup>24</sup> In this study,

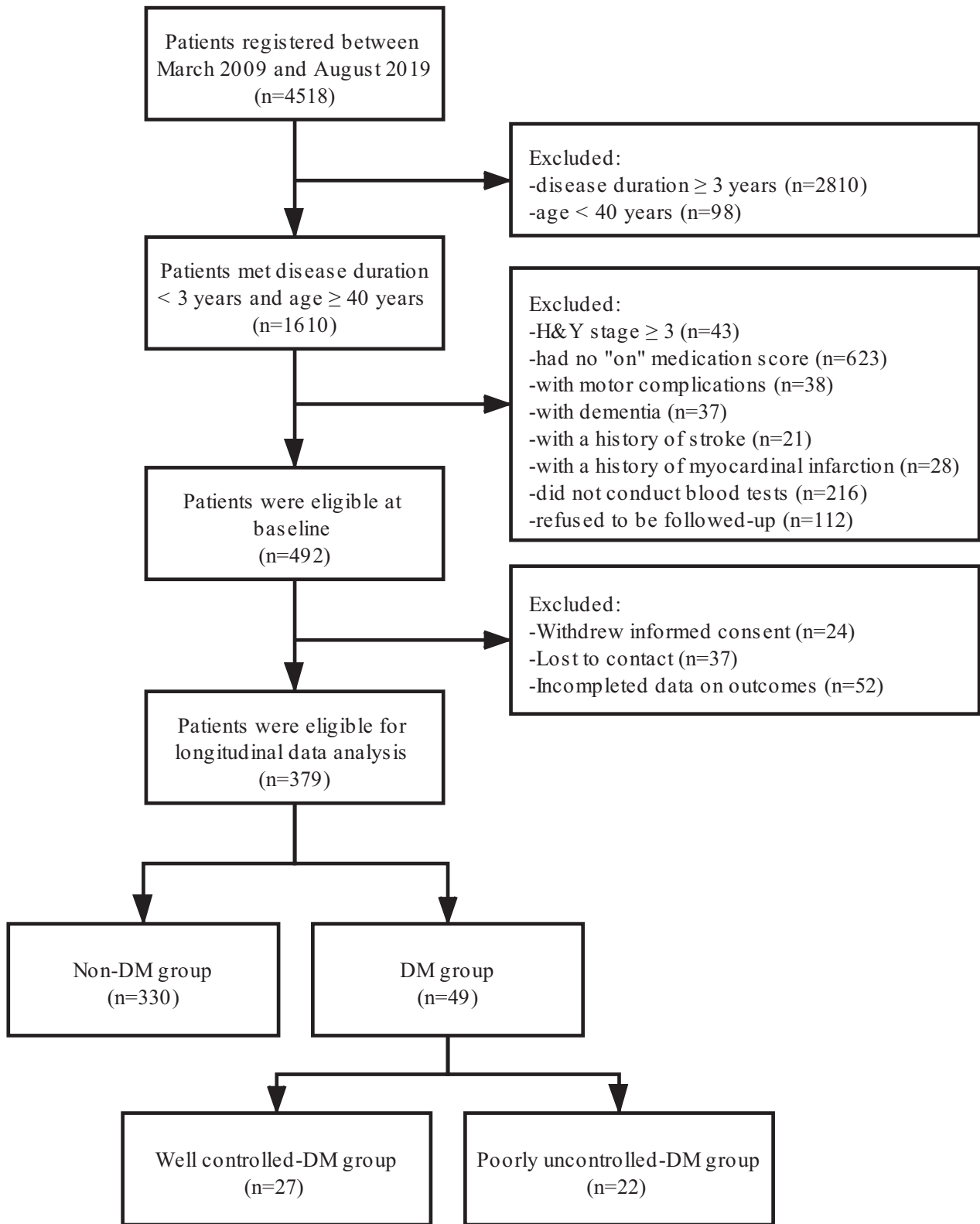


Figure 1. A flow diagram of the study population.

we defined fast motor progression as an at least 14-point increase in the UPDRS III (mean 3.5-point per year) based on the mean follow-up period of  $4.0 \pm 2.4$  years. Time to such event was defined as the interval in years from baseline to the time in which a 14-point increase was first monitored. Conversion to H&Y stage  $\geq 3$  was set as an additional outcome of motor progression. Time to reach such a milestone was defined as the interval in years from the onset of PD to the time in which the patient firstly scored  $\geq 3$  in the H&Y stage.

### Cognitive decline

Cognitive decline was defined as a  $>3$ -point decrease in the MoCA. Time to cognitive decline was defined as the interval in years from baseline to the time in which a 3-point decrease was first recorded.

### Statistical analyses

Frequencies and descriptive statistics were used to summarize the clinical characteristics of samples. Baseline data were reported as percentages for categorical variables and mean  $\pm$  standard deviation (SD) for continuous variables.

The Student's *t*-test and Chi-square test were performed to compare the continuous and categorical variables between DM and non-DM groups, respectively. For overall comparisons among non-DM, well-controlled DM, and poorly controlled DM groups, analysis of variance (ANOVA) was used. Once statistical significance was detected in overall comparisons, pairwise comparisons were further conducted using the Student *t*-test or Chi-square test. The Bonferroni correction method was used to adjust the *p* values and exclude the potential false-positive rate incurred by multiple comparisons. In this method,  $p < 0.0167$  ( $0.05/3$ ) were considered as significantly different.

The Kaplan-Meier survival curves were plotted and the log-rank tests were used. The univariate and multivariate Cox proportional hazards models were used to estimate the hazard ratios (HRs) and examine 95% confidence intervals (CIs). In the multivariate model, sex, age, age of onset, BMI, and UPDRS III and MoCA scores at baseline were adjusted.

Statistical analyses were executed by SPSS version 22.0 and R version 4.0.2 and *p* values  $< 0.05$  (two-tailed) were set as statistically significant.

### Data availability

Data are available upon request to the corresponding authors.

## Results

### Baseline data

A total of 379 patients (214 men and 165 women) were included in the study. At baseline, 49 (12.9%) of the cohort had DM, and 22 (44.9%) of DM were poorly controlled. Among the 49 patients with DM, 43 (87.8%) were previously diagnosed and 6 (12.2%) were newly diagnosed at enrollment based on blood HbA1C levels  $\geq 6.5\%$ . Of the six PD patients with newly diagnosed DM, 2 (33.3%) were poorly controlled.

The mean age of the included patients at enrollment was  $62.1 \pm 11.0$  years, with mean age of onset of  $60.5 \pm 11.0$  years and mean disease duration of  $1.6 \pm 0.8$  years. At baseline, the mean UPDRS III score was  $25.9 \pm 11.1$ , and the mean LEDD was  $210.7 \pm 204.7$  mg/d.

### Comparisons of baseline characteristics between groups

At baseline, patients in DM group were significantly older ( $p < 0.001$ ), with older age of onset ( $p < 0.001$ ), higher BMI ( $p = 0.017$ ), and lower FAB ( $p = 0.019$ ) and MoCA ( $p = 0.029$ ) scores than those in non-DM group (Table 1). The overall comparisons indicated that age ( $p < 0.001$ ), age of onset ( $p < 0.001$ ), BMI ( $p = 0.044$ ), FAB score ( $p = 0.015$ ), and MoCA score ( $p = 0.004$ ) were significantly different among non-DM, well-controlled DM, and poorly controlled DM groups (Table 1). The subsequent pairwise comparisons indicated that patients with poorly controlled DM had significantly older age ( $p = 0.010$ ), older age of onset ( $p = 0.009$ ), and lower FAB ( $p = 0.015$ ) and MoCA ( $p = 0.004$ ) scores than those without DM, and patients with well-controlled DM had significantly younger age ( $p = 0.008$ ) and age of onset ( $p = 0.019$ ) than those without DM (Table 1). The baseline characteristics between patients with poorly and well-controlled DM were not significantly different (Table 1).

### Clinical outcomes

Of the 379 patients, 51 died (13.5%), with a mean time to death or censoring of  $6.2 \pm 2.5$  years. For participants with follow-up data on motor assessments, 154 (40.6%) reported an increase of  $\geq 14$ -point in the UPDRS III after mean  $4.0 \pm 2.4$  years of follow-up, and 118 (31.1%) reached the H&Y stage  $\geq 3$  after mean disease duration of  $5.3 \pm 2.3$  years. In addition, 133 (35.1%) patients had a decrease of  $>3$ -point in the MoCA after mean of  $4.0 \pm 2.4$  years of follow-up. The mean increased scores

**Table 1.** Comparisons of baseline characteristics between PD patients with and without DM.

	Without DM (N = 330)	With DM			p value				
		Total (N = 49)	Well controlled (N = 27)	Poorly controlled (N = 22)	p1	p2	p3	p4	p5
Sex, male	185(56.1%)	29(59.2%)	14(51.9%)	15(68.2%)	0.681	0.476	0.672	0.266	0.247
Age	61.2 ± 11.0	68.0 ± 9.0	67.7 ± 8.5	68.3 ± 9.7	<0.001*	<0.001*	0.008*	0.010*	1.000
Age of PD onset	59.6 ± 11.0	66.2 ± 9.0	65.9 ± 8.6	66.7 ± 9.5	<0.001*	<0.001*	0.019*	0.009*	1.000
PD duration	1.6 ± 0.8	1.7 ± 0.8	1.9 ± 0.9	1.6 ± 0.8	0.454	0.296	0.483	1.000	0.514
Education	9.9 ± 4.4	9.9 ± 4.6	11.0 ± 4.3	8.5 ± 4.6	0.925	0.685	0.478	0.143	0.044
BMI	22.8 ± 3.0	23.8 ± 2.7	24.1 ± 2.7	23.5 ± 2.6	0.017*	0.044	0.066	0.739	1.000
UPDRS III	25.7 ± 11.0	27.6 ± 12.2	26.0 ± 12.6	29.6 ± 11.7	0.254	0.274	1.000	0.323	0.768
H&Y	2.0 ± 0.4	2.0 ± 0.4	2.0 ± 0.5	2.0 ± 0.5	0.837	0.926	1.000	1.000	1.000
LEDD	210.7 ± 205.4	210.7 ± 201.4	190.7 ± 198.1	232.1 ± 212.0	0.999	0.752	1.000	1.000	1.000
Levodopa	182(55.2%)	30(61.2%)	15(55.6%)	15(55.6%)	0.424	0.491	0.968	0.233	0.367
Dopamine agonist	98(29.7%)	11(22.5%)	7(25.9%)	4(18.2%)	0.296	0.485	0.679	0.249	0.518
Pramipexole	52(15.8%)	6(12.2%)	4(14.8%)	2(9.1%)					
Piribedil	41(12.4%)	4(8.2%)	2(7.4%)	2(9.1%)					
Ropinirole	3(0.9%)	1(2.0%)	1(3.7%)	0					
Rotigotine	2(0.6%)	0	0	0					
Hypoglycemic agents	0	29(59.2%)	18(66.7%)	11(50.0%)	-	-	-	-	0.238
FAB	15.6 ± 2.5	14.7 ± 3.0	15.3 ± 3.2	14.1 ± 2.8	0.019*	0.016*	1.000	0.015*	0.291
MoCA	23.9 ± 4.5	22.2 ± 5.3	23.4 ± 5.1	20.6 ± 5.2	0.029*	0.005*	1.000	0.004*	0.110
HDRS	9.4 ± 8.0	10.0 ± 7.7	10.4 ± 9.5	9.4 ± 4.8	0.607	0.790	1.000	1.000	1.000
HARS	6.9 ± 6.0	7.3 ± 6.9	7.8 ± 8.2	6.8 ± 5.0	0.676	0.780	1.000	1.000	1.000
NMSS	34.9 ± 29.9	40.6 ± 35.9	41.8 ± 42.1	39.2 ± 29.1	0.224	0.457	1.000	0.706	1.000

PD, Parkinson's disease; DM, diabetes mellitus; BMI, body mass index; UPDRS, Unified Parkinson's disease Rating Scale; H&Y stage, Hoehn and Yahr stage; LEDD, Levodopa Equivalent Daily Doses; FAB, Frontal Assessment Battery; MoCA, Montreal Cognitive Assessment; HDRS, Hamilton Depression Rating Scale; HARS, Hamilton Anxiety Rating Scale; NMSS, Non-Motor Symptoms Scale.

p1: DM group vs. non-DM group.

p2: non-DM group vs. well-controlled DM group vs. poorly controlled DM group.

p3: non-DM group vs. well-controlled DM group.

p4: non-DM group vs. poorly controlled DM group.

p5: well-controlled DM group vs. poorly controlled DM group.

\*Significant difference.

in the UPDRS III and MoCA were  $8.5 \pm 10.5$  and  $0.9 \pm 3.2$ , respectively.

Among the 49 patients with DM, 29 (59.2%) were under treatment of hypoglycemic agents at baseline and the number increased to 41 (83.7%) during follow-up. Eighteen (36.7%) patients with DM had both baseline and follow-up tests on HbA1C. Of the 18 patients with DM, 9 (50%) were poorly controlled at baseline, and 2 of them (22.2%) were controlled during follow-up; 9 (50%) patients were well controlled at baseline, and 2 of them lost to control during follow-up.

### Diabetes and the progression of PD

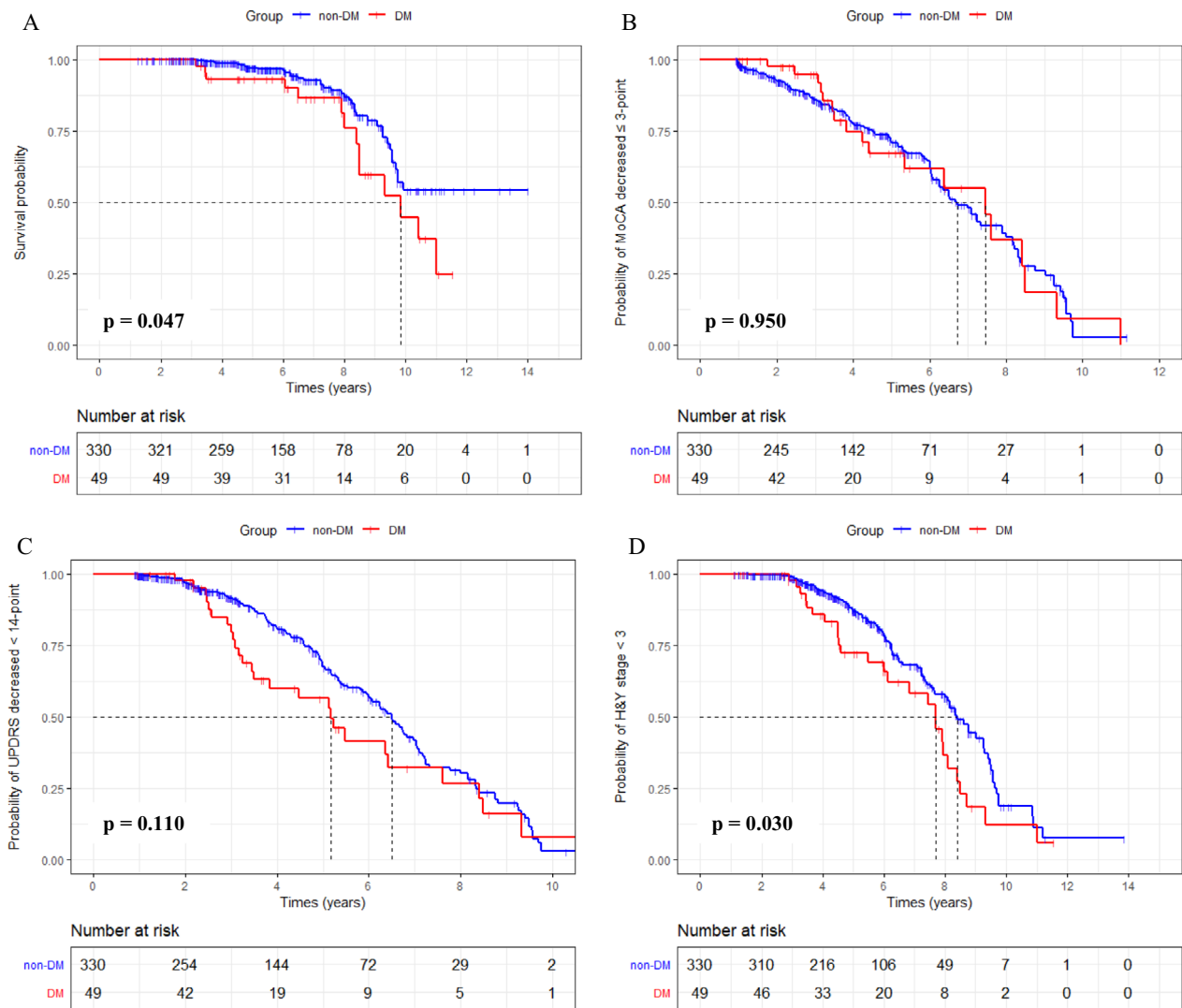
Kaplan-Meier curves indicated that patients with DM showed a significantly shorter survival time ( $p = 0.047$ ) and faster time to reach H&Y stage  $\geq 3$  ( $p = 0.030$ ) than those without DM (Figure 2). The multivariable Cox model indicated that DM had no association with the PD

outcomes after adjusting sex, age, age of onset, BMI, and UPDRS III and MoCA scores at baseline (Table 2).

### Diabetes control status and the progression of PD

Kaplan-Meier curves indicated that time to death and time to H&Y stage 3 were significantly different among the three groups ( $p = 0.007$  and  $p < 0.001$ , respectively) (Figure 3). No significant differences were observed in time to UPDRS III  $\geq 14$ -point increase or time to MoCA  $> 3$ -point decrease (Figure 3).

In the multivariable Cox model, the adjusted HRs were 2.060 (95% CI 1.165-3.641,  $p = 0.013$ ) for UPDRS III  $\geq 14$ -point increase in the poorly controlled DM group, and 1.066 (95% 0.572-1.986,  $p = 0.841$ ) in the well-controlled DM group, relative to the non-DM group ( $p$  trend = 0.025), after adjustment of sex, age, age of onset, BMI, and UPDRS III and MoCA scores at baseline



**Figure 2.** Kaplan-Meier curve for each clinical outcome between DM and non-DM groups. (A) Patients with DM had a significantly shorter survival time than those without DM ( $p = 0.047$ ). (B) Time to MoCA decreased  $\geq 3$ -point was not significantly different between PD patients with and without DM ( $p = 0.950$ ). (C) Time to UPDRS III increased  $\geq 14$ -point was not significantly different between PD patients with and without DM ( $p = 0.110$ ). (D) Patients with DM had a significantly faster time to H&Y stage  $\geq 3$  than those without DM ( $p = 0.030$ ).

(Table 2). The adjusted HRs were 2.079 (95% CI 1.212-3.566,  $p = 0.008$ ) for H&Y stage  $\geq 3$  in patients with poorly controlled DM, and 0.879 (95% CI 0.413-1.871,  $p = 0.737$ ) in patients with well-controlled DM, compared with patients without DM ( $p$  trend = 0.021). In contrast, time to death and time to MoCA  $> 3$ -point decrease were not significantly different among the three groups.

## Discussion

To the best of our knowledge, this is the first study to evaluate the effects of diabetes control status on PD

progression in a cohort of Chinese patients. We observed that the risk of motor progression, as assessed by UPDRS III and H&Y stage, was double in individuals with poorly controlled DM compared with those without DM, but had no differences between the two populations. However, the risk for mortality and cognitive decline was not different between patients with well or poorly controlled DM and those without DM.

The association between DM and motor severity in PD has been disclosed by several observational and case-control studies<sup>1,5</sup> in which reported pre-existing DM by medical record or fast blood glucose test. The fast blood glucose test only reflects the transient glucose levels and

**Table 2.** Hazard ratios (HRs) and 95% confidence intervals (CIs) for each clinical outcome in PD.

	Univariate		Multivariate	
	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value
Without DM vs. With DM				
Death	1.852 (0.998-3.435)	0.051	0.960 (0.480-1.919)	0.908
UPDRS-III increased $\geq$ 14-point	1.396 (0.919-2.121)	0.118	1.464 (0.944-2.274)	0.089
H&Y stage converted to $\geq$ 3	1.613 (1.041-2.500)	0.033*	1.475 (0.929-2.342)	0.099
MoCA decreased >3-point	0.977 (0.592-1.610)	0.926	0.949 (0.563-1.600)	0.845
Without DM vs. Well-controlled DM vs. Poorly controlled DM				
Death			<i>p</i> for trend = 0.754	
Without DM vs. Well-controlled DM	0.973 (0.346-2.737)	0.985	0.617 (0.206-1.845)	0.388
Without DM vs. Poorly controlled DM	3.180 (1.615-6.273)	0.003*	1.247 (0.565-2.752)	0.584
UPDRS-III increased $\geq$ 14-point			<i>p</i> trend = 0.025*	
Without DM vs. Well-controlled DM	1.035 (0.568-1.886)	0.911	1.066 (0.572-1.986)	0.841
Without DM vs. Poorly controlled DM	1.915 (1.117-3.283)	0.018*	2.060 (1.165-3.641)	0.013*
H&Y stage converted to $\geq$			<i>p</i> trend = 0.021*	
Without DM vs. Well-controlled DM	0.849 (0.408-1.767)	0.661	0.879 (0.413-1.871)	0.737
Without DM vs. Poorly controlled DM	2.629 (1.575-4.387)	<0.001*	2.079 (1.212-3.566)	0.008*
MoCA decreased >3-point			<i>p</i> trend = 0.959	
Without DM vs. Well-controlled DM	0.817 (0.410-1.626)	0.564	0.810 (0.396-1.657)	0.564
Without DM vs. Poorly controlled DM	1.205 (0.610-2.382)	0.591	1.137 (0.558-2.315)	0.724

PD, Parkinson's disease; DM, diabetes mellitus; UPDRS, Unified Parkinson's disease Rating Scale; H&Y stage, Hoehn and Yahr stage; MoCA, Montreal Cognitive Assessment; HR, hazard ratio.

In the multivariate model, sex, age, age of onset, BMI, UPDRS III score, and MoCA score at baseline were adjusted.

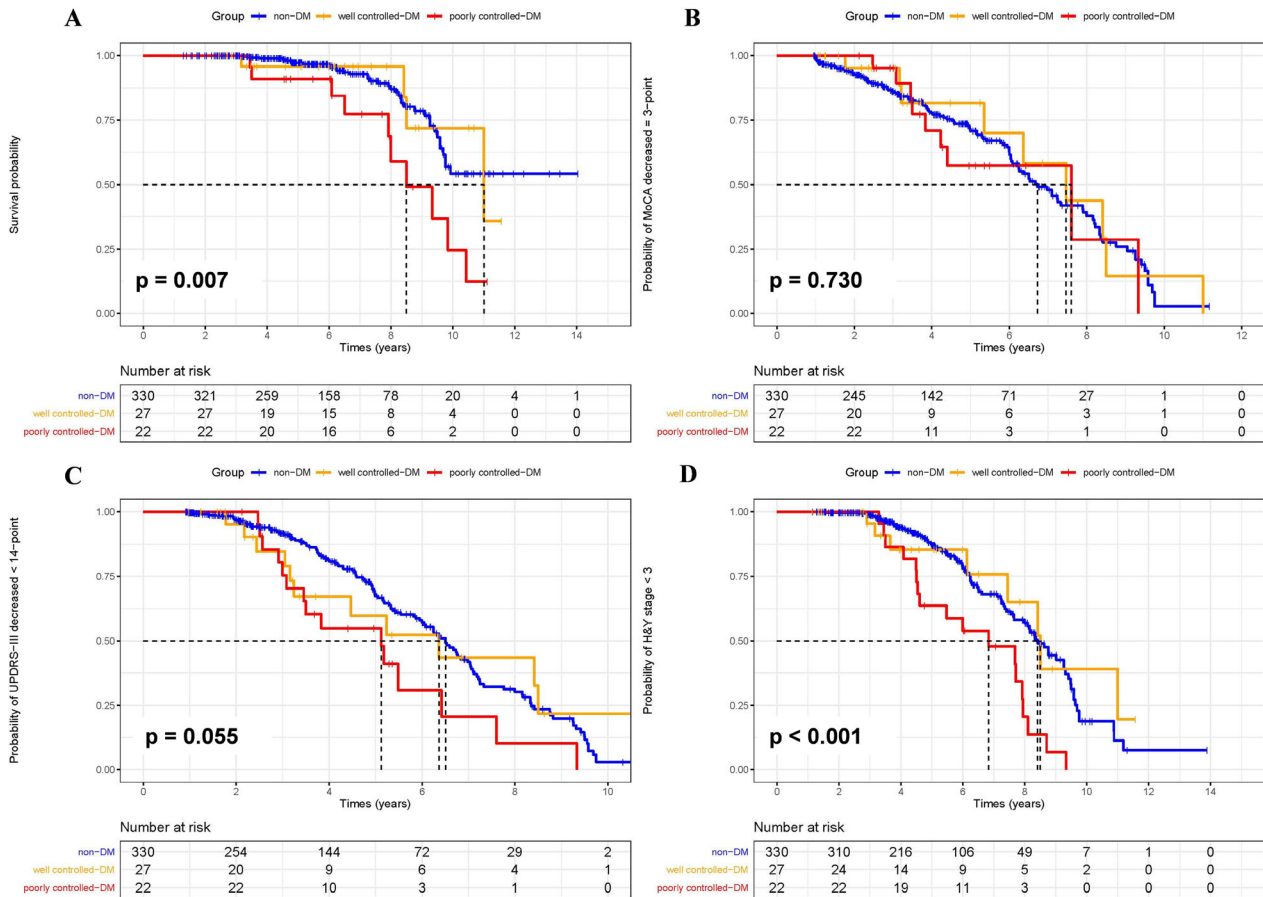
\*Significant difference.

probably changes in a short period, which is not suitable to select as a predictor. However, HbA1C in blood can provide evidence about an individual's average blood glucose levels for a long period, which has been recommended as a standard of testing and monitoring DM.<sup>25</sup> There is a direct association between HbA1C and insulin resistance, and insulin resistance has been considered as a possible pathway to link PD and DM. Insulin resistance is associated with mitochondrial dysfunction, a potential way to contribute to DM, rather than the involvement of the pathogenesis of DM [30]. Therefore, in the current study, we used HbA1C as a biomarker to monitor disease progression.

Although no association between the coexistent DM and motor progression was observed in our cohort, we found that poor control status of DM is associated with faster disease progression in patients with PD. In addition, we found that there is no difference between patients with well controlled DM and those without DM. The majority of patients (77.8%) still had poor blood glucose control at the time of follow-up, which also supports the finding that the uncontrolled status of DM is associated with faster disease progression. Therefore, we think that only poor control status plays a role in accelerating the motor progression of PD. Our finding emphasizes the importance of adequate control of diabetes, especially in monitoring serum HbA1C levels, in patients with PD.

One explanation for the association between DM and motor progression in PD is that diabetes is a risk factor for cerebrovascular and cardiovascular conditions which can contribute to parkinsonian-like signs.<sup>26,27</sup> However, in the current study, we still observed an association between poor control status of DM and motor progression after excluding patients with stroke, myocardial infarction, suggesting that diabetes influences motor progression probably through some other mechanisms. A retrospective cohort study<sup>28</sup> using 18F-FP-CIT PET imaging found that the coexistent DM in PD had a significant adverse effect on decreased striatal dopamine transporter availability. Similarly, a prospective cohort study<sup>7</sup> demonstrated that patients with DM had lower striatal dopamine transporter binding and accelerated motor deterioration, supporting the notion of an acceleration in the disease process. In addition, PD and DM are reported to share common biologically plausible cellular mechanisms. The insulin receptor is one of the core targets in substantia nigra neurons, which can be regulated by hyperglycemia to suppress substantia nigra dopaminergic neuronal firing and to decrease dopamine turnover.<sup>29</sup>

Two previous studies<sup>4,30</sup> found that the pre-existing DM was associated with a faster cognitive decline. Our results did not support the above finding. The different ways to define cognitive decline between previous studies



**Figure 3.** Kaplan-Meier curve for each clinical outcome among non-DM, well controlled-DM, and poorly controlled-DM groups at baseline. (A) Survival time was significantly different among the three groups ( $p = 0.007$ ). Pairwise comparisons: non-DM group vs. poorly controlled DM group ( $p = 0.002$ ); non-DM group vs. well controlled-DM group ( $p = 0.980$ ); and poorly controlled-DM group vs. well-controlled DM group ( $p = 0.049$ ). (B) Time to reach MoCA decreased >3-point was not significantly different among the three groups ( $p = 0.730$ ). Pairwise comparisons: non-DM group vs. poorly controlled DM group ( $p = 0.570$ ); non-DM group vs. well-controlled DM group ( $p = 0.570$ ); and poorly controlled-DM group vs. well controlled-DM group ( $p = 0.650$ ). (C) Time to UPDRS III  $\geq 14$ -point increase was not significantly different among the three groups ( $p = 0.055$ ). Pairwise comparisons: non-DM group vs. poorly controlled-DM group ( $p = 0.013$ ); non-DM group vs. well-controlled DM group ( $p = 0.900$ ); and poorly controlled DM group vs. well-controlled DM group ( $p = 0.300$ ). (D) Time to H&Y stage 3 was significantly different among the three groups ( $p < 0.001$ ). Pairwise comparisons: non-DM group vs. poorly controlled DM group ( $p < 0.001$ ), non-DM group vs. well-controlled DM group ( $p = 0.660$ ), and poorly controlled DM group vs. well-controlled DM group ( $p = 0.023$ ).

and our research may contribute to such a discrepancy. Previous studies used the annual score decline in Mini-Mental Status Examination (MMSE)<sup>4</sup> or self-reported cognitive decline<sup>30</sup> as clinical milestones. In the current study, we used a >3-point in the MoCA to define the cognitive decline. A more sensitive cognitive assessment scale with a defined cut-off value in the future will help to verify this issue. Moreover no association between DM and mortality in our cohort is likely due to the result that our follow-up period was too short to obtain such an endpoint. In addition, the cause of death in some patients was not related to PD (18/51, 35.3%), which may have a potential interference on our results. Further stratified longitudinal studies will assist in clarifying this issue.

Some limitations should be pointed out. First, although several confounding factors were adjusted, some potential unmeasured confounders, such as diabetes duration, will still interfere with our results. Second, the sample of DM in our cohort is relatively small, which limited the stratification analysis by the conversion of diabetes control status. Third, all the participants were solely recruited through a tertiary referral center in west China, which contributes to our results may not be generalized to other populations. Fourth, the relatively short observation of disease progression for some patients is not sufficient to conclude the impact of HbA1C on long-term outcomes.

In conclusion, poorly controlled diabetes is an independent risk factor contributing to motor progression in PD.



Our study highlights the importance of adequate control of diabetes in PD patients.

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## Conflict of Interest

The authors (ORW, WQQ, HYB, ZLY, LKC, LJY, JZ, SW, CB, and SHF) declare that they have no conflict of interest.

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### Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1.** Hazard ratios (HRs) and 95% confidence intervals (CIs) for each clinical outcome based on age and BMI in PD.

### Appendix 1: Authors.

Name	Location	Contribution
Ruwei Ou, MD&PhD	Department of Neurology, Laboratory of Neurodegenerative Disorders, National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University, Chengdu, Sichuan, China	Conceived and designed the study, acquired the data, performed the analysis, and drafted the manuscript.
Qianqian Wei, MD&PhD	Department of Neurology, Laboratory of Neurodegenerative Disorders, National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University, Chengdu, Sichuan, China	Acquired the data and performed the analysis.
Yanbing Hou, MD&PhD	Department of Neurology, Laboratory of Neurodegenerative Disorders, National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University, Chengdu, Sichuan, China	Acquired the data and performed the analysis.

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### Appendix 1 . Continued.

Name	Location	Contribution
Lingyu Zhang, MD	Department of Neurology, Laboratory of Neurodegenerative Disorders, National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University, Chengdu, Sichuan, China	Acquired the data and performed the analysis.
Kuncheng Liu, MD	Department of Neurology, Laboratory of Neurodegenerative Disorders, National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University, Chengdu, Sichuan, China	Acquired the data and performed the analysis.
Junyu Lin, MM	Department of Neurology, Laboratory of Neurodegenerative Disorders, National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University, Chengdu, Sichuan, China	Acquired the data and performed the analysis.
Zheng Jiang, MM	Department of Neurology, Laboratory of Neurodegenerative Disorders, National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University, Chengdu, Sichuan, China	Acquired the data and performed the analysis.
Wei Song, MD&PhD	Department of Neurology, Laboratory of Neurodegenerative Disorders, National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University, Chengdu, Sichuan, China	Acquired the data and performed the analysis.
Bei Cao, MD	Department of Neurology, Laboratory of Neurodegenerative Disorders, National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University, Chengdu, Sichuan, China	Acquired the data and performed the analysis.

(Continued)

**Appendix 1** . Continued.

Name	Location	Contribution
Huifang Shang*, MD	Department of Neurology, Laboratory of Neurodegenerative Disorders, National	Conceived and designed the study, and edited the manuscript.

(Continued)

**Appendix 1** . Continued.

Name	Location	Contribution
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