Vascular, inflammatory and metabolic risk factors in relation to dementia in Parkinson's disease patients with type 2 diabetes mellitus

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ABSTRACT

**There are limited data on vascular, inflammatory, metabolic risk factors of dementia in Parkinson's disease (PD) with type 2 diabetes mellitus (DM) (PD-DM). In a study of 928 subjects comprising of 215 PD with DM (including 31 PD-DM with dementia, PD-DMD), 341 PD without DM (including 31 PD with dementia, PDD) and 372 DM without PD (including 35 DM with dementia, DMD) patients, we investigated if vascular, inflammatory, metabolic, and magnetic resonance imaging (MRI) markers were associated with dementia in PD-DM. Lower fasting blood glucose (FBG<5mmol/L, OR=4.380; 95%CI: 1.748-10.975; p=0.002), higher homocysteine (HCY>15μmol/L, OR=3.131; 95%CI: 1.243-7.888; p=0.015) and hyperlipidemia (OR=3.075; 95%CI: 1.142-8.277; p=0.026), increased age (OR=1.043; 95%CI: 1.003-1.084; p=0.034) were the most significant risk factors in PDD patients. Lower low-density lipoprotein cholesterol (LDL-C<2mmol/L, OR=4.499; 95%CI: 1.568-12.909; p=0.005) and higher fibrinogen (>4g/L, OR=4.066; 95%CI: 1.467-11.274; p=0.007) were the most significant risk factors in PD-DMD patients. The area under the curve (AUC) for fibrinogen and LDL-C was 0.717 (P=0.001), with a sensitivity of 80.0% for the prediction of PD-DMD.
In summary, we identified several factors including LDL-C and fibrinogen as significant risk factors for PD-DMD and these may have prognostic and treatment implications.**

INTRODUCTION

Patients with type 2 diabetes mellitus (DM) may have a higher risk of developing Parkinson's disease (PD) [1]. Patients with comorbid PD and DM (PD-DM) are commonly encountered in clinical practice. Cognitive dysfunction in this group of patients may contribute to the underlying neurodegenerative process and impact on quality of life [2, 3]. Vascular, inflammatory and metabolic derangements can potentially modulate the underlying pathophysiologic processes in PD [4–7]. In fact, glucose metabolism abnormalities (including insulin resistance) have been observed in 50-80% of patients with PD [8–10]. PD-DM patients have been previously associated with cognitive decline or dementia [11, 12]. The mechanism of dementia in PD-DM (PD-DMD) patients has yet to be elucidated.

Several lines of evidence suggested that altered blood glucose could lead to cognitive impairment in old age [13], and patients with PD-DM are more prone to develop cognitive impairment than patients with PD but without DM [14]. In addition, various vascular, inflammatory [15, 16] and metabolic markers, including cystatin C (Cys C), homocysteine (HCY), low-density lipoprotein (LDL-C), neutrophils, lymphocytes, white matter lesions (WMLs) and subcortical arteriosclerotic encephalopathy (SAE), have been shown to be associated with dementia in PD and DM [12, 17, 18]. It is possible that vascular, inflammatory and metabolic risk factors in PD can modulate underlying neurodegeneration particularly in the presence of diabetes and dementia [19–21]. However, among these risk factors, which risk factors could be mostly associated with dementia and if these risk factors could be potential prognostic clinical variables to facilitate the early prediction of PD-DMD patients have not been reported and need to be further explored.

To address these gaps in knowledge, we conducted a large cohort study to examine the relationship between vascular, inflammatory, metabolic risk factors and dementia in PD-DM patients. We also identified the potential and most significant risk factors for PD-DMD, with the aim of validating the potential prognostic clinical variables to facilitate the early prediction of PD-DMD patients.

RESULTS

Baseline demographics in PD, DM and PD-DM patients

The baseline demographics in PD, DM and PD-DM patients are summarized in Table 1 and Figure 1. A total of 928 patients comprising of 341 PD (31 PD with dementia, PDD), 372 DM (35 DM with dementia, DMD) and 215 PD-DM (31 PD with dementia, PD-DMD) patients were recruited (Fig 1). No significant difference in the proportion of dementia cases among PD, DM and PD-DM patients was noted (Table 1). The numbers of patients with PD-DMD and DMD over 70 years were greater than the number of patients without dementia (Table 1). Among all these patients with dementia, the numbers of PD-DMD patients over 70 years were significantly more than those of PDD and DMD patients (Supplementary Table 2). PD-DMD and PDD patients exhibited higher UPDRS and NMSS scores than patients without dementia; PD-DMD patients exhibited higher H&Y stages and more use of atorvastatin than patients without dementia (Table 1). Among all of these patients with dementia, PD-DMD patients exhibited higher MDS-UPDRS and NMSS scores than patients with PDD (Figure 2, Supplementary Table 2). PD-DMD and DMD patients exhibited more anxiety and depression than patients without dementia. DMD patients were more often male and exhibited more acarbose use but less insulin use than DM patients without dementia (p<0.05). However, there was no significant difference in the use of metformin between DM and PD-DM patients or in the use of L-Dopa and PD duration between PD and PD-DM patients with dementia and those without dementia (Table 1). We found no significant difference in MMSE, MoCA, or H&Y scores, the proportion of males, the presence of anxiety or depression, or the use of insulin and acarbose among the PDD, DMD and PD-DMD patients (Supplementary Table 2).

Vascular and inflammatory risk factors for dementia in PD, DM and PD-DM patients

The potential vascular and inflammatory risk factors for dementia in PD, DM and PD-DM patients are summarized in Table 2A. We found that PD-DMD and DMD patients exhibited higher plasma levels of fibrinogen (>4g/L) and neutrophils, and more brain infarctions, SAE and WMLs (Fazekas 2), but lower levels of LDL-C (<2mmol/L) and lymphocytes, than PD-DM and DM patients without dementia (p<0.05), whereas no significant differences were noted in PD patients. Among all patients with dementia, PD-DMD and DMD patients exhibited more brain infarctions but lower levels of LDL-C (<2mmol/L) than PDD patients; PD-DMD patients exhibited higher levels of neutrophils and fibrinogen (>4g/L) but lower levels of lymphocytes than PDD patients. PD-DMD patients exhibited more SAE than DMD patients; DMD patients exhibited higher levels of hs-CRP (>3mg/L) than PDD patients (p<0.05) (Supplementary Table 2, Figure 2). However, there was no significant difference in blood pressure, BMI, WBC, or the incidence of smoking history,

Table 1. Baseline demographics in PD, DM and PD-DM patients.

Clinical variables	PD(n=341)			DM(n=372)			PD-DM(n=215)		
	D (-) (n=310)	D (+) (n=31)	p*	D (-) (n=337)	D (+) (n=35)	p*	D (-) (n=184)	D (+) (n=31)	p*
Age, years	65.0(56.0,73.0)	69.0(59.0,79.0)	0.082	61.0(52.0,69.0)	68.0(57.0,74.0)	0.013	73.0(66.0,80.0)	79.0(72.0,84.0)	0.004
<55, n (%)	60(19.35)	3(9.68)	0.186	109(32.34)	7(20.00)	0.133	9(4.89)	0	0.364
55–70, n (%)	156(50.32)	16(51.61)	0.891	148(43.92)	14(40.00)	0.198	64(34.78)	5(16.13)	0.040
>70, n (%)	94(30.32)	12(38.71)	0.336	80(23.74)	14(40.00)	0.035	111(60.33)	26(83.87)	0.012
Male, n (%)	175(56.45)	18(58.06)	0.863	192(56.97)	27(77.14)	0.021	88(47.83)	16(51.61)	0.696
PD duration, month	48 (16.5,84)	60(24,84)	0.260	-	-	-	36(12,96)	36(12,72)	0.363
Use of drugs, n (%)									
Atorvastatin	67(21.61)	6(19.35)	0.770	178(52.82)	14(40.00)	0.149	83(45.11)	20(64.52)	0.045
Metformin	-	-	-	181(53.71)	14(40.00)	0.122	74(40.22)	9(29.03)	0.237
Insulin	-	-	-	171(50.74)	8(22.86)	0.002	69(37.50)	14(45.16)	0.418
Acarbose	-	-	-	94(27.89)	17(48.57)	0.011	78(42.39)	18(58.06)	0.104
L-Dopa	252(81.29)	28(90.32)	0.211	-	-	-	143(77.72)	26(83.87)	0.440
MDS-UPDRS (I)	1.0(0.0,2.0)	3.0(2.0,5.0)	<0.001	-	-	-	2.0(1.0,4.0)	5.0(3.0,6.0)	<0.001
MDS-UPDRS (II)	7.0(5.0,8.0)	8.0(6.0,11.0)	0.017	-	-	-	9.0(7.0,14.0)	14.0(12.0,18.0)	<0.001
MDS-UPDRS (III)	17.0(15.0,19.0)	17.0(15.0,23.0)	0.610	-	-	-	21.0(17.0,27.0)	23.0(21.0,29.0)	0.023
MDS-UPDRS (Total)	25.0(21.0,29.0)	26.0(24.0,38.0)	0.016	-	-	-	34.0(28.0,44.8)	44.0(37.0,54.0)	<0.001
H&Y	3.0(2.0,3.0)	3.0(2.0,4.0)	0.236	-	-	-	3.0(2.5,3.0)	3.0(3.0,4.0)	0.008
NMSS	18.0(13.8,24.0)	26.0(17.0,32.0)	<0.001	-	-	-	24.0(18.0,32.0)	32.0(28.0,34.0)	<0.001
MMSE	26.0(24.0,28.0)	15.0(13.0,17.0)	<0.001	27.0(26.0,29.0)	15.0(9.0,19.0)	<0.001	26.0(24.0,27.0)	13.0(11.0,17.0)	<0.001
MoCA	23.0(20.0,25.0)	12.0(9.0,14.0)	<0.001	26.0(24.0,27.0)	12.0(7.0,15.0)	<0.001	22.0(20.0,24.0)	9.0(8.0,13.0)	<0.001
Anxiety or depression, n(%)	131(42.26)	17(54.84)	0.178	52(15.43)	13(37.14)	0.001	76(41.30)	19(61.29)	0.038

All continuous variables are presented as median (interquartile range) and categorical variables are presented as count (proportion). PD- patients with Parkinson disease without type 2 diabetes mellitus; DM- type 2 diabetes mellitus without Parkinson disease; PD-DM- patients with Parkinson disease and type 2 diabetes mellitus; D(-)- without dementia; D(+)- with dementia; L-Dopa- Levodopa and Benserazide; MDS-UPDRS- Movement Disorder Society–Unified Parkinson's Disease Rating Scale; H&Y- the modified Hoehn and Yahr staging scale; NMSS- Non-Motor Symptoms Scale for Parkinson's Disease; MMSE- mini mental state examination; MoCA- Montreal Cognitive Assessment; *The statistically significant differences between patients with dementia and patients without dementia in PD, DM, PD-DM groups were assessed by χ2-test or Mann-Whitney U tests; P-values<0.05 were considered statistically significant.

drinking history, or hyperlipidemia between patients (PD, DM and PD-DM patients) with dementia and those without dementia. There was no significant difference in the level of D-dimer or the proportion of WMLs among PDD, DMD and PD-DMD patients.

Metabolic risk factors for dementia in PD, DM and PD-DM patients

The metabolic risk factors for dementia in PD, DM and PD-DM patients are summarized in Table 2B. First, we found a higher plasma level of Cys C (>0.95mg/L, p<0.05) in PDD and DMD patients than in PD and DM patients without dementia, whereas no significant differences were observed between PD-DMD and PD-DM patients without dementia. Second, higher levels of MCV (>90fL) and HCY (>15μmol/L), more frequent hyperhomocysteinemia, and lower levels of FBG (<5mmol/L) were observed in PDD patients than in PD patients without dementia. Third, higher plasma levels of AST (>40IU/L) and albumin (<35g/L) but lower levels of calcium (<2.1mmol/L) and potassium were

observed in DMD patients than in DM patients without dementia (Table 2B). Higher levels of MCV (>90fL) but lower levels of FBG (<5mmol/L) were noticed in PDD patients than in patients with PD-DMD or DMD (Supplementary Table 2). However, no significant differences in ALT or HbA1c levels were noted between patients (PD, DM and PD-DM patients) with dementia and without dementia. There was no significant difference in AST, albumin, Cys C, HCY, calcium or potassium levels among PDD, DMD and PD-DMD patients.

Multivariable logistic regression analysis of risk factors of dementia in PD and PD-DM patients and the interaction of risk factors with age groups over and less than or equal to 70 years

Our study showed that lower FBG (<5mmol/L, OR=4.380; 95%CI: 1.748-10.975; p=0.002), higher HCY (>15μmol/L, OR=3.131; 95%CI: 1.243-7.888; p=0.015) and hyperlipidemia (OR=3.075; 95%CI: 1.142-8.277; p=0.026) and increased age (OR=1.043;

95%CI: 1.003-1.084; p=0.034) were the most significant risk factors associated with PDD. Elevated level of Cys C (>0.95mg/L, OR=4.413; 95%CI: 1.606-12.124; p=0.004) and hyperlipidemia (OR=4.030; 95%CI: 1.289-12.605; p=0.017) were significantly associated with dementia in PD patients less than 70 years old, whereas lower FBG (<5mmol/L, OR=7.375;

95%CI: 1.689-32.198; p=0.008) was significantly associated with dementia in PD patients over 70 years old (Table 3A and Supplementary Table 3).

In addition, a lower LDL-C (<2mmol/L, OR=4.499; 95%CI: 1.568-12.909; p=0.005) and higher fibrinogen (>4g/L, OR=4.066; 95%CI: 1.467-11.274; p=0.007)
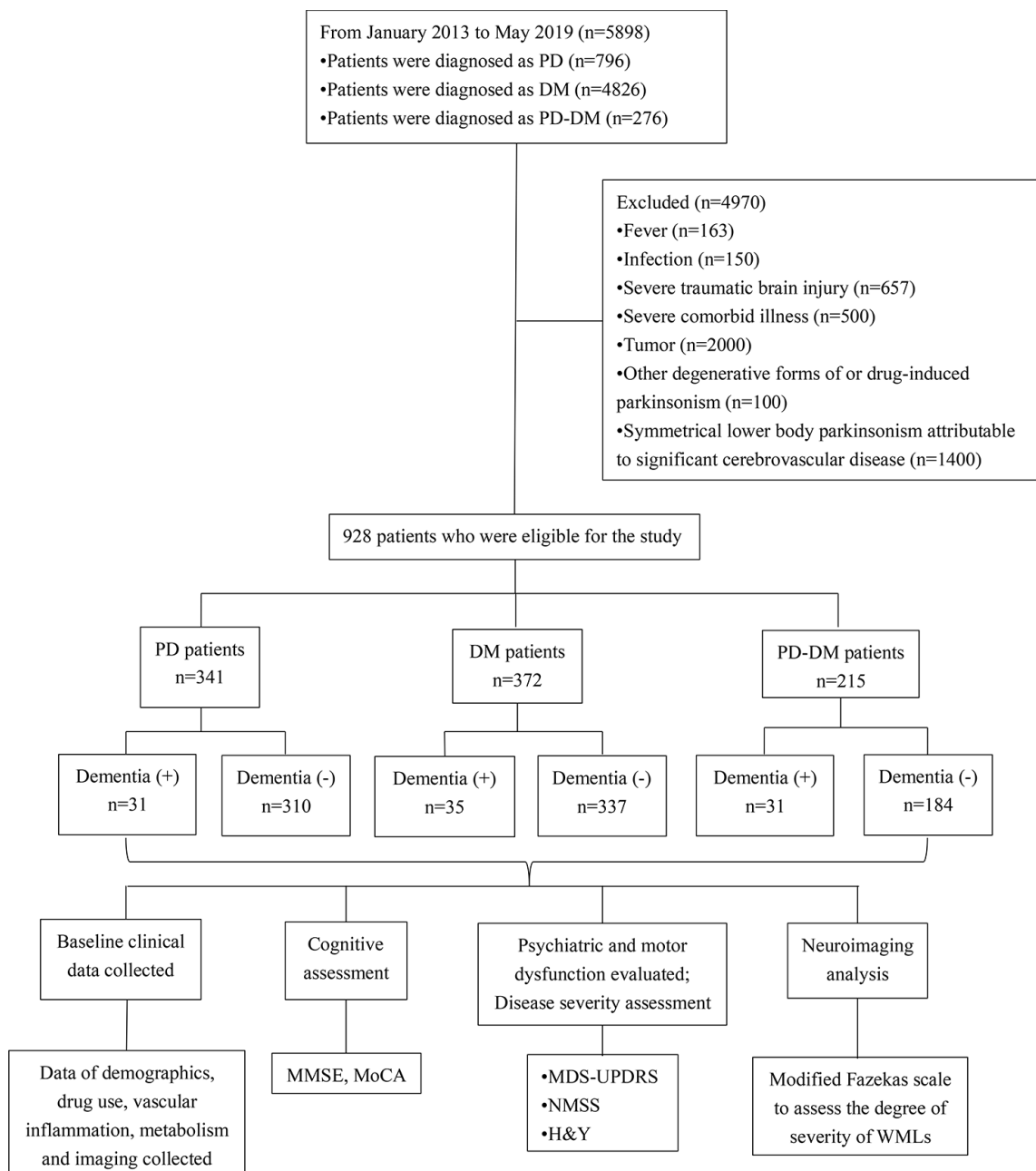

Figure 1. Flow diagram of patients with dementia diagnosed with PD, DM, or PD-DM and the clinical investigations conducted. PD - patients with Parkinson's disease without type 2 diabetes mellitus; DM - type 2 diabetes mellitus without Parkinson's disease; PD-DM - patients with Parkinson's disease and type 2 diabetes mellitus; MDS-UPDRS - Movement Disorder Society–Unified Parkinson's Disease Rating Scale; H&Y - the modified Hoehn and Yahr staging scale; NMSS - nonmotor symptoms scale for Parkinson's Disease; MMSE - Mini Mental State Examination; MoCA - Montreal Cognitive Assessment; WMLs - White matter lesions.

were the most significant risk factors associated with PD-DMD. Decreased LDL-C (<2mmol/L, OR=9.197; 95%CI: 2.342-36.119; p=0.001) and SAE (OR=5.389; 95%CI: 1.270-22.875; p=0.022) were significantly associated with dementia in PD-DM patients over 70 years old (Table 3B). Those variables that were not significantly associated with PDD and PD-DMD are listed in Table 3A and Table 3B. These risk factors were also found to be associated with MMSE score using the multiple linear regression analysis (Supplementary Table 1 and Supplementary File). However, all of these risk factors did not show significant interactions (p>0.05) with these two age groups except Cys C (>0.95mg/L).

ROC curves of risk factors in PD-DM patients with dementia

ROC curves were constructed to explore which factor could provide useful discrimination between PD-DM patients with dementia and without dementia. ROC curves for disease duration, age and MDS-UPDRS (total) revealed that the AUC was 0.564 (95%CI: 0.458-0.669, p=0.262), 0.664 (95%CI: 0.568-0.760, p=0.004) and 0.710 (95%CI: 0.622-0.798, p<0.001). ROC curves for fibrinogen and LDL-C analysis revealed AUC values of 0.650 (95%CI: 0.537-0.763, p=0.015) and 0.651 (95%CI: 0.534-0.769, p=0.009), respectively. However, the combination of fibrinogen and LDL-C
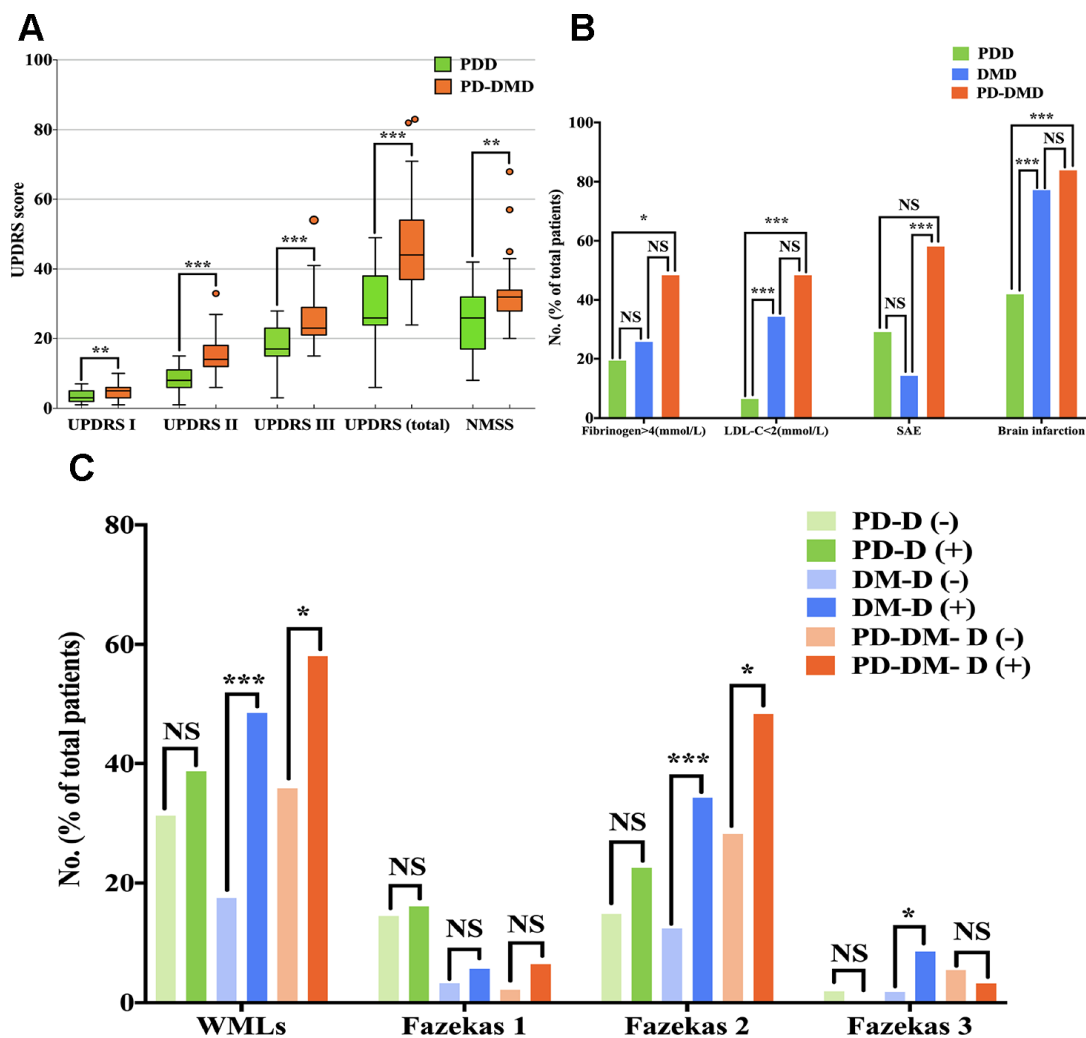

Figure 2. Comparison of UPDRS score (**A**) and the percentage of patients with fibrinogen>4 (mmol/L), LDL<2 (mmol/L), SAE, brain infarctions (**B**) and WMLs with Fazekas scale scores (**C**) among PDD, DMD and PD-DMD patients. PD - patients with Parkinson's disease without type 2 diabetes mellitus; DM - type 2 diabetes mellitus without Parkinson's disease; PD-DM - patients with Parkinson's disease and type 2 diabetes mellitus; PDD - patients with Parkinson's disease with dementia; DMD - type 2 diabetes mellitus with dementia; PD-DMD - patients with Parkinson's disease and type 2 diabetes mellitus and dementia; D(-) - without dementia; D(+) - with dementia; UPDRS - Unified Parkinson's Disease Rating Scale; NMSS - nonmotor symptoms scale for Parkinson's Disease; LDL-C - low-density lipoprotein cholesterol; SAE - subcortical arteriosclerotic encephalopathy; WMLs - white matter lesions; NS - not significant. *p<0.05, **p<0.01, ***p<0.001.

Table 2A. Vascular and inflammatory risk factors for dementia in PD, DM and PD-DM patients.

Vascular and inflammatory risk factors	PD(n=341)			DM(n=372)			PD-DM(n=215)		
	D (-) (n=310)	D (+) (n=31)	p*	D (-) (n=337)	D (+) (n=35)	p*	D (-) (n=184)	D (+) (n=31)	p*
SBP (mmHg)	125.0(120.0,135.0)	120.0(118.0,135.0)	0.104	136.0(124.0,151.0)	146.0(128.0,153.0)	0.104	137.0(125.0,151.0)	132.0(120.0,152.0)	0.333
DBP (mmHg)	80.0(75.0,82.0)	80.0(78.0,81.0)	0.974	81.0(76.5,90.0)	85.0(80.0,95.0)	0.196	77.0(70.0,84.0)	78.0(69.0,87.0)	0.821
Smoking history, n (%)	14(4.52)	2(6.45)	0.647	48(14.24)	7(20.00)	0.361	11(5.98)	3(9.68)	0.432
Drinking history, n (%)	10(3.23)	0	0.608	30(8.90)	5(14.29)	0.355	6(3.26)	1(3.23)	1.000
BMI	22.5(21.0,25.0)	23.0(22.0,25.0)	0.064	24.0(22.0,26.0)	24.0(22.0,26.0)	0.823	23(21,26)	24(21,25)	0.710
LDL-C (mmol/L)	2.9(2.3,3.5)	2.5(2.3,3.2)	0.270	**3.1(2.4,3.6)**	**2.7(1.9,3.1)**	**0.010**	**2.8(2.1,3.5)**	**1.9(1.6,3.0)**	**0.009**
LDL-C<2.00 (mmol/L), n (%)	31(10.00)	2(6.45)	0.753	**67(19.88)**	**12(34.29)**	**0.047**	**36(19.57)**	**15(48.39)**	**<0.001**
D-Dimer (mg/L)	0.4(0.3,0.6)	0.6(0.3,1.1)	0.083	0.4(0.3,0.5)	0.4(0.3,0.9)	0.311	0.6(0.4,1.4)	0.6(0.4,1.4)	0.622
D-Dimer>0.50 (mg/L), n (%)	57(18.39)	10(32.26)	0.064	**25(7.42)**	**8(22.86)**	**0.007**	50(27.17)	10(32.26)	0.559
Fibrinogen (g/L)	3.1(2.7,3.5)	3.5(2.8,4.0)	0.052	3.5(3.0,4.1)	3.3(3.0,4.6)	0.863	**3.5(3.0,4.4)**	**4.1(3.5,5.1)**	**0.015**
Fibrinogen>4.00 (g/L), n (%)	27(8.71)	6(19.35)	0.101	**42(12.46)**	**9(25.71)**	**0.039**	**45(24.46)**	**15(48.39)**	**0.006**
WBC (g/L)	6.3(5.3,7.4)	6.1(5.0,7.2)	0.533	6.9(6.0,8.3)	7.3(6.0,9.5)	0.152	7.2(6.1,8.8)	7.4(6.1,9.9)	0.387
Lymphocyte (%)	30.4(25.8,35.9)	30.7(24.2,34.8)	0.740	**30.9(25.2,37.5)**	**25.3(18.6,32.1)**	**0.002**	**27.3(19.0,32.6)**	**20.5(12.2,28.0)**	**0.008**
Neutrophil (%)	58.3(52.3,64.3)	58.6(52.5,67.5)	0.860	**58.7(52.5,65.5)**	**64.0(58.3,70.2)**	**0.001**	**63.2(57.2,71.8)**	**71.5(61.6,82.8)**	**0.007**
hs-CRP (mg/L)	1.1(0.6,4.1)	0.6(0.6,2.0)	0.094	**1.8(0.6,5.2)**	**3.6(1.5,7.1)**	**0.019**	3.6(0.7,10.6)	4.5(0.7,47.1)	0.861
hs-CRP>3.00 (mg/L), n (%)	34(10.97)	2(6.45)	0.757	**52(15.43)**	**11(31.43)**	**0.016**	43(23.37)	8(25.81)	0.768
Hyperlipidemia, n(%)	33(10.65)	7(22.58)	0.072	61(18.10)	3(8.57)	0.155	24(13.04)	2(6.45)	0.385
Brain infarction, n(%)	90(29.03)	13(41.94)	0.140	**128(37.98)**	**27(77.14)**	**<0.001**	**86(46.73)**	**26(83.87)**	**<0.001**
SAE, n(%)	70(22.58)	9(29.03)	0.417	**13(3.86)**	**5(14.29)**	**0.019**	**48(26.09)**	**18(58.06)**	**<0.001**
WMLs, n (%)	97(31.29)	12(38.71)	0.398	**59(17.51)**	**17(48.57)**	**<0.001**	**66(35.87)**	**18(58.06)**	**0.019**
Fazekas 1	45(14.52)	5(16.13)	0.791	11(3.26)	2(5.71)	0.350	4(2.17)	2(6.45)	0.208
Fazekas 2	46(14.84)	7(22.58)	0.295	**42(12.46)**	**12(34.29)**	**<0.001**	**52(28.26)**	**15(48.39)**	**0.025**
Fazekas 3	6(1.94)	0	1.000	**6(1.78)**	**3(8.57)**	**0.043**	10(5.43)	1(3.23)	1.000

All continuous variables are presented as median (interquartile range) and categorical variables are presented as count (proportion). PD- patients with Parkinson disease without type 2 diabetes mellitus; DM- type 2 diabetes mellitus without Parkinson disease; PD-DM- patients with Parkinson disease and type 2 diabetes mellitus; D(-)- without dementia; D(+)- with dementia; SBP- systolic blood pressure; DBP- diastolic blood pressure; BMI- body mass index; LDL-C- low density lipoprotein cholesterol; WBC- White blood cell count; hs- CRP- hypersensitive C-reactive protein; SAE- subcortical arteriosclerotic encephalopathy; WMLs- White matter lesions. *The statistically significant differences between patients with dementia and patients without dementia in PD, DM, PD-DM groups were assessed by χ2-test or Mann-Whitney U tests; P-values<0.05 were considered statistically significant.

Table 2B. Metabolic risk factors for dementia in PD, DM and PD-DM patients.

Metabolic risk factors	PD(n=341)			DM(n=372)			PD-DM(n=215)		
	D (-) (n=310)	D (+) (n=31)	p*	D (-) (n=337)	D (+) (n=35)	p*	D (-) (n=184)	D (+) (n=31)	p*
AST>40(IU/L), n (%)	7(2.26)	0	1.000	**9(2.67)**	**5(14.29)**	**0.006**	14(7.61)	3(9.68)	0.718
ALT(IU/L)	14.0(10.0,21.0)	15.0(9.0,22.0)	0.782	18.0(13.0,27.0)	22.0(15.0,28.0)	0.138	15.0(10.0,22.0)	14.0(11.0,30.0)	0.350
Albumin (g/L)	40.5(38.0,43.0)	40.3(38.0,41.8)	0.575	**41.4(39.0,43.9)**	**39.3(36.2,42.9)**	**0.020**	39.8(37.0,42.0)	36.9(36.0,42.1)	0.166
Albumin<35.00 (g/L), n (%)	14(4.52)	2(6.45)	0.647	**8(2.37)**	**4(11.43)**	**0.019**	27(14.67)	7(22.58)	0.288
Calcium (mmol/L)	2.3(2.2,2.3)	2.3(2.2,2.4)	0.529	**2.3(2.2,2.4)**	**2.2(2.2,2.3)**	**0.004**	2.3(2.2,2.4)	2.2(2.1,2.3)	0.134
Calcium<2.10 (mmol/L), n (%)	28(9.03)	5(16.13)	0.203	**12(3.56)**	**6(17.14)**	**0.004**	24(13.04)	8(25.81)	0.097

Potassium (mmol/L)	3.9(3.7,4.1)	3.8(3.6,4.1)	0.159	**4.0(3.7,4.2)**	**3.9(3.6,4.0)**	**0.041**	3.9(3.6,4.3)	3.8(3.4,4.3)	0.289
MCV (fL)	**91.0(88.2,93.9)**	**92.7(91.1,97.4)**	**0.003**	88.1(85.1,90.6)	87.2(83.5,93.3)	0.866	89.9(86.9,93.2)	89.9(88.2,93.2)	0.700
MCV>90.00 (fL), n (%)	**187(60.32)**	**25(80.65)**	**0.026**	103(30.56)	13(37.14)	0.424	88(47.83)	14(45.16)	0.783
HCY (µmol/L)	13.4(10.7,17.0)	15.8(12.0,17.8)	0.177	11.2(9.2,14.5)	11.3(8.5,15.3)	0.973	12.6(9.5,15.8)	12.3(8.7,18.0)	0.714
HCY>15.00 (µmol/L), n (%)	**41(13.23)**	**9(29.03)**	**0.029**	36(10.68)	5(14.29)	0.568	24(13.04)	5(16.13)	0.580
Hyperhomocysteinemia, n (%)	**11(3.55)**	**4(12.90)**	**0.038**	5(1.48)	0	1.000	2(1.09)	1(3.23)	0.375
Cys C (mg/L)	**1.0(0.9,1.1)**	**1.1(1.0,1.2)**	**0.031**	0.9(0.8,1.0)	1.0(0.9,1.1)	0.066	1.1(0.9,1.3)	1.0(0.9,1.5)	0.834
Cys C>0.95 (mg/L), n (%)	**95(30.65)**	**15(48.39)**	**0.044**	**24(7.12)**	**8(22.86)**	**0.006**	48(26.09)	7(22.58)	0.679
FBG (mmol/L)	**4.9(4.6,5.4)**	**4.7(4.3,5.1)**	**0.004**	8.2(6.2,12.0)	7.6(5.8,11.6)	0.275	7.4(5.9,9.1)	7.1(6.1,10.0)	0.756
FBG<5.00 (mmol/L), n (%)	**151(48.71)**	**23(74.19)**	**0.007**	34(10.09)	5(14.29)	0.393	21(11.41)	1(3.23)	0.213
Hypoglycaemic episodes (FBG≤3.9mmol/L), n (%)	6(1.94)	1(3.23)	0.490	**6(1.78)**	**3(8.57)**	**0.043**	3(1.63)	0	1.000
HbA1c (%)	5.8(5.5,6.1)	5.7(5.2,5.9)	0.197	7.8(6.6,9.7)	7.3(6.3,8.9)	0.369	8.0(7.1,9.0)	6.4(6.0,7.4)	0.101

All continuous variables are presented as median (interquartile range) and categorical variables are presented as count (proportion). PD- patients with Parkinson disease without type 2 diabetes mellitus; DM- type 2 diabetes mellitus without Parkinson disease; PD-DM- patients with Parkinson disease and type 2 diabetes mellitus; D(-)- without dementia; D(+)- with dementia; AST- Aspartate transaminase; ALT- Alanine transaminase; MCV- mean corpuscular volume; HCY- homocysteine; Cystatin C- Cys C; FBG- Fasting blood glucose; HbA1c- glycated hemoglobin; *The statistically significant differences between patients with dementia and patients without dementia in PD, DM, PD-DM groups were assessed by χ2-test or Mann-Whitney U tests; P-values<0.05 were considered statistically significant.

Table 3A. Multivariable logistic regression analysis for risk factors of dementia in PD patients and the interaction of risk factors with age groups.

Variables	Univariate		Multivariate Model*		Interaction
	OR (95%CI)	p	Adjusted OR (95% CI)	p	p
Age	**1.035(1.000,1.071)**	**0.050**	**1.043(1.003,1.084)**	**0.034**	-
FBG<5.00 (mmol/L)	**2.704(1.171,6.241)**	**0.020**	**4.380(1.748,10.975)**	**0.002**	
Age≤70 (years)	**2.609 (1.602,4.247)**	**<0.001**	2.216(0.720,6.825)	0.166	0.204
Age>70 (years)	**0.383(0.235,0.624)**	**<0.001**	**7.375(1.689,32.198)**	**0.008**	
HCY>15.00 (µmol/L)	**2.684(1.156,6.231)**	**0.022**	**3.131(1.243,7.888)**	**0.015**	
Age≤70 (years)	**0.468(0.254,0.864)**	**0.015**	2.776(0.751,10.258)	0.126	0.709
Age>70 (years)	**2.135(1.158,3.935)**	**0.015**	4.005(0.977,16.420)	0.054	
Hyperlipidemia	2.448(0.980,6.119)	0.055	**3.075(1.142,8.277)**	**0.026**	
Age≤70 (years)	1.216(0.583,2.536)	0.603	**4.030(1.289,12.605)**	**0.017**	0.271
Age>70 (years)	0.823(0.394,1.716)	0.603	0.957(0.097,9.469)	0.970	
Cys C>0.95 (mg/L)	**2.122(1.008,4.468)**	**0.048**	2.157(0.979,4.752)	0.056	
Age≤70 (years)	0.840(0.517,1.366)	0.483	**4.413(1.606,12.124)**	**0.004**	**0.048**
Age>70 (years)	1.190(0.732,1.934)	0.483	0.710(0.158,3.193)	0.655	

* We performed the logistic regression models considering (a) all patients, (b) less than or equal to 70 years and (c) patients over 70 years. PD- patients with Parkinson disease without type 2 diabetes mellitus; OR- odds ratio; CI- confidence interval; FBG- fasting blood glucose; HCY- homocysteine; Cys C- Cystatin C.

Table 3B. Multivariable logistic regression analysis for risk factors of dementia in PD-DM patients and the interaction of risk factors with age groups.

Variables	Univariate		Multivariate Model*		Interaction
	OR (95%CI)	p	Adjusted OR (95% CI)	p	p
Age	**1.069(1.022,1.119)**	**0.004**	1.037(0.965,1.114)	0.325	-
Fibrinogen>4.00 (g/L)	**2.896(1.327,6.320)**	**0.008**	**4.066(1.467,11.274)**	**0.007**	
Age≤70 (years)	0.609(0.319,1.164)	0.134	4.805(0.397,58.185)	0.217	0.757

Age>70 (years)	1.641(0.859,3.136)	0.134	**3.109(0.955,10.128)**	**0.060**	
LDL-C<2.00 (mmol/L)	**3.869(1.710,8.754)**	**0.001**	**4.499(1.568,12.909)**	**0.005**	
Age≤70 (years)	**0.323(0.150,0.694)**	**0.004**	0.702(0.019,26.634)	0.849	0.194
Age>70 (years)	**3.100(1.441,6.668)**	**0.004**	**9.197(2.342,36.119)**	**0.001**	
SAE	**3.923(1.788,8.606)**	**0.001**	2.570(0.798,8.277)	0.114	
Age≤70 (years)	**0.449(0.234,0.860)**	**0.016**	3.631(0.136,97.022)	0.442	0.829
Age>70 (years)	**2.227(1.162,4.268)**	**0.016**	**5.389(1.270,22.875)**	**0.022**	
WMLs	**2.476(1.141,5.370)**	**0.022**	2.900(0.804,10.456)	0.104	
Age≤70 (years)	0.882(0.498,1.564)	0.668	3.808(0.114,127.097)	0.455	0.773
Age>70 (years)	1.133(0.639,2.009)	0.668	2.179(0.511,9.296)	0.293	
Brain infarction	**5.926(2.180,16.107)**	**<0.001**	2.101(0.598,7.382)	0.247	
Age≤70 (years)	0.584(0.334,1.024)	0.061	1.647(0.096,28.102)	0.730	0.862
Age>70 (years)	1.711(0.976,2.998)	0.061	2.183(0.510,9.339)	0.293	
Anxiety or depression	**2.250(1.031,4.908)**	**0.042**	1.898(0.682,5.279)	0.220	
Age≤70 (years)	**1.849(1.054,3.245)**	**0.032**	1.144(0.063,20.765)	0.927	0.723
Age>70 (years)	**0.541(0.308,0.949)**	**0.032**	2.011(0.636,6.359)	0.234	
Neutrophil	**1.057(1.019,1.097)**	**0.003**	1.102(0.920,1.320)	0.293	
Age≤70 (years)	**0.942(0.914,0.971)**	**<0.001**	1.456(0.830,2.552)	0.190	0.408
Age>70 (years)	**1.061(1.029,1.094)**	**<0.001**	1.129(0.911,1.400)	0.268	
Lymphocyte	**0.945(0.906,0.986)**	**0.009**	1.097(0.894,1.346)	0.374	
Age≤70 (years)	**1.077(1.040,1.116)**	**<0.001**	1.335(0.741,2.402)	0.336	0.664
Age>70 (years)	**0.928(0.896,0.962)**	**<0.001**	1.159(0.903,1.487)	0.248	

* We performed the logistic regression models considering (a) all patients, (b) less than or equal to 70 years and (c) patients over 70 years. PD-DM- patients with Parkinson disease and type 2 diabetes mellitus; OR- odds ratio; CI- confidence interval; LDL-C- low density lipoprotein cholesterol; SAE- subcortical arteriosclerotic encephalopathy; WMLs- White matter lesions.

increased the AUC to 0.717 (95%CI: 0.606-0.828, p=0.001), with a sensitivity of 80.0% and a specificity of 62.8% at a cutoff value of 0.155 on the predicted risk algorithm (Table 4 and Figure 3).

DISCUSSION

We conducted the first comparative study between PD-DMD and PDD patients. We highlighted that PD-DMD patients exhibited more severe motor and nonmotor symptoms and vascular inflammation derangements than PDD patients. Vascular inflammatory risk factors such as LDL-C and fibrinogen were more prevalently associated with PD-DMD than PDD and might have prognostic and treatment implications (Supplementary Table 5). We identified LDL-C<2.00 (mmol/L) and fibrinogen>4.00 (g/L) as the most significant risk factors for PD-DMD and FBG<5.00 (mmol/L), HCY>15.00 (μmol/L) and hyperlipidemia for PDD patients. Preventing a lower LDL-C<2.00 (mmol/L) and a higher fibrinogen>4.00 (g/L) might be effective to reduce dementia in PD-DM patients.

There are possible explanations for the relative difference in the association of the vascular and inflammatory risk factors between PD-DMD and PD-DM without dementia. PD-DM patients have been shown to be more prone to develop cognitive impairment in the course of their disease than patients with PD but without DM [14]. It is possible that upregulation of vascular inflammatory factors in comorbid PD and DM, exacerbates brain toxicity, leading to the development of dementia [22]. This observation is consistent with emerging evidence that interactions between several vascular inflammatory risk factors are linked to target organ damage [23]. Vascular inflammation may exacerbate the progression of PD-DM patients, including greater fragmentation of capillaries and chronic inflammatory damage to the capillary network in multiple brain regions, particularly in the frontal cortex, hippocampus, temporal lobe and prefrontal lobe. These cognition-related cerebral damages caused by vascular inflammation will lead to more accelerated decline of cognition in PD-DM patients [24–26]. Thus, treatments that regulate vascular inflammation can potentially improve vascular remodeling in the brain and provide a novel target to ameliorate the disease burden in PD-DM patients [11, 27].

A previous study that showed a high level of Cys C and HCY in PD, and their levels were higher in PD patients with dementia than in those without dementia [28]. This is consistent with our findings that high levels of homocysteine (HCY>15 μmol/L) and elevated Cys C (Cys C>0.95 mg/L) are the important risk factors for

Table 4. ROC curves for the traditional diagnostic and novel risk factors in the diagnosis of PD-DM patients with dementia.

Variable	Traditional diagnostic factors			Novel risk factors		
	Disease duration	Age	MDS-UPDRS (Total)	Fibrinogen (g/L)	LDL-C (mmol/L)	Combination (LDL-C & Fibrinogen)
AUC	**0.564**	**0.664**	**0.710**	**0.650**	**0.651**	**0.717**
Cut-off value	0.170	0.257	0.375	0.308	0.335	0.428
P value	0.262	**0.004**	**<0.001**	**0.015**	**0.009**	**0.001**
95%CI	0.458-0.669	0.568-0.760	0.622-0.798	0.537-0.763	0.534-0.769	0.606-0.828
Sensitivity	**0.903**	**0.806**	**0.742**	**0.808**	0.552	**0.800**
Specificity	0.267	0.451	**0.633**	0.500	**0.783**	**0.628**

PD-DM- patients with Parkinson's disease and type 2 diabetes mellitus; LDL-C- low density lipoprotein cholesterol; AUC- area under the curve; MDS-UPDRS- Movement Disorder Society–Unified Parkinson's Disease Rating Scale; CI- confidence interval; ROC- receiver operating characteristic.

PDD patients (Table 3A). The dysregulation of iron metabolism associated with cellular damage (MCV of erythrocyte increased) and oxidative stress are common in PDD [29]. Furthermore, hyperlipidemia, especially hypercholesterolemia, is a recognized risk factor in cardiovascular disease, and the total lifelong cholesterol burden contributes to the risk, which might also lead to dementia in PD [22].
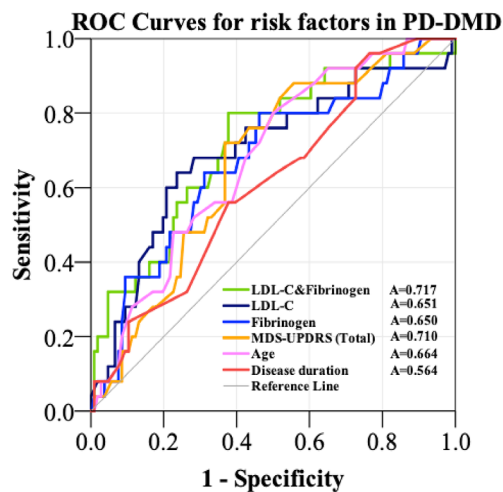

Figure 3. ROC curves to evaluate the utility of novel risk factors (LDL-C and Fibrinogen, LDL-C, Fibrinogen) and traditional diagnostic factors (MDS-UPDRS, age, disease duration) for the discrimination of PD-DM patients with dementia from PD-DM patients without dementia. The AUC was 0.650 for fibrinogen (blue curve), 0.651 for LDL-C (black curve) and 0.717 for the combination of LDL-C and fibrinogen (green curve). The AUC was 0.564 for disease duration (red curve), 0.664 for age (purple curve) and 0.710 for MDS-UPDRS (orange curve). PD-DMD- patients with Parkinson's Disease and type 2 diabetes mellitus and dementia; LDL-C- low density lipoprotein cholesterol; A- area under the curve; MDS-UPDRS- Movement Disorder Society–Unified Parkinson's Disease Rating Scale; ROC- Receiver Operating Characteristic.

Interestingly, we identified more brain infarctions in PD-DMD patients than in PDD patients; SAE was more significantly associated with dementia in PD-DM patients over 70 years old (Figure 2 and Table 3B). This finding is similar to that of previous observations relating such brain imaging changes to cognitive impairment in PD [6, 12, 30, 31]. This finding further indicates that cerebrovascular lesions or degeneration may be more prevalent in PD-DMD patients than in PDD patients and may contribute more to dementia with comorbid DM and PD patients. Thus, treatments that prevent vascular degeneration or ameliorate brain infarctions may improve vascular remodeling in the brain and provide a novel target to ameliorate the cognitive burden in patients with PD-DMD.

Fibrinogen is highly expressed in PD-DMD patients and is the most significant risk factor for dementia in PD-DM patients (Table 3B). Fibrinogen is a vascular inflammatory mediator that has recently been shown to drive the neurodegenerative process in dementia, cerebrovascular stroke and PD. It is postulated that this maybe via the activation of CNS vascular inflammation, the dysregulation of microcirculatory function and the disruption of the BBB and neurovascular units (NVUs) [32, 33]. Investigators have shown that following BBB disruption, fibrin and fibrinogen interact with receptors on nervous system cells to activate downstream signaling, regulate basic cellular functions and influence inflammatory and neurodegenerative processes in disease [32]. Fibrin deposition precedes neuronal degenerative changes and behavioral deficits in pericyte-mutant mice, suggesting that fibrin entry into the CNS is a critical factor that initiates or potentiates neurodegenerative processes after vascular disruption [32].

Cholesterol is a major component of the brain, and a lower cholesterol level in elderly individuals is associated with cerebral atrophy, a typical anatomic syndrome of dementia [34, 35]. We showed that a low

level of LDL-C (<2 mmol/L, Table 3B) may increase dementia risk, especially in PD-DM patients over 70 years. This could be due to aggravation of cerebral atrophy, malnutrition and the reduction in neuron impairment or facilitation of the compensatory repair of injured neurons.

After selecting the potential risk factors including fibrinogen and LDL for dementia in PD-DM patients using logistic regression, we further explored their utility using ROC analysis to compare the discriminatory ability of predictors of dementia in PD-DM patients. Conventionally, it is accepted that the AUC in ROC analysis should be >0.7 to be of clinical value for screening. During the discovery phase, the AUC for the combination of fibrinogen and LDL-C proved to be better than using either alone (with the AUC increasing from 0.650 and 0.651 for either alone to 0.717, with a sensitivity of 80.0% and a specificity of 62.8%) or traditional diagnostic factors (disease duration, age, MDS-UPDRS) in the prediction of dementia.

Our study has some inherent limitations. The hospital-based setting of our study may have resulted in a selection bias for structural brain imaging based on clinical decisions, which is likely to overestimate the general prevalence of cerebrovascular disease in patients with PD and DM. The diagnosis of PD and PD-DM in our cohort was based on clinical diagnostic criteria, with no post mortem confirmation [31]. Our study has certain strengths. We have investigated a large number of patients with comorbid DM and PD. This is the first comparative study on vascular, inflammatory and metabolic risk factors on PDD and PD-DMD, and the inclusion of PD patients without DM and DM patients without PD as control groups is a major strength.

CONCLUSION

PD-DMD patients impose considerable public health burdens and are commonly encountered in clinical practice. The interactions between PD, cognitive dysfunction and diabetes mellitus are likely to be complex. Our study identified controllable clinical factors, including LDL-C and fibrinogen, as the most significant risk factors for PD-DMD patients; they were more prevalently associated with PD-DMD than PDD patients. As these vascular, inflammatory and metabolic risk factors are modifiable, monitoring and corrections of these factors could potentially improve clinical care and provide a new treatment paradigm for PD and PD-DM patients. Furthermore, our findings can also lead to identification of novel therapeutic targets for preventing cognitive impairment in PD and PD-DM patients.

MATERIALS AND METHODS

Population

We recruited a total of 928 patients from outpatient clinics. A total of 215 PD-DM patients (including 31 PD-DM with dementia, PD-DMD), 341 PD patients without DM (including 31 PDD) and 372 DM patients without PD (including 35 DM with dementia, DMD) were included for this comparative study. PD patients without DM and DM patients without PD were set as controls. All PD and PD-DM patients underwent a standardized neurological examination by two movement disorder specialists in a blinded manner. The PD patients recruited in this present study (Figure 1) satisfied the 2015 Movement Disorder Society criteria for the diagnosis of idiopathic PD [36]. The diagnosis of DM was made by 2 physicians according to the following diagnostic criteria: a tested fasting glucose level higher than 7.0 mmol/L, a 2-h postprandial glucose level higher than 11.1 mmol/L, or pre-diagnosed type 2 diabetes [37]. Those who failed to meet the 2015 Movement Disorder Society criteria for PD or the diagnostic criteria for DM or were younger than 18 years (Figure 1) were excluded. Patients with fever (n=163), infection (n=150), severe traumatic brain injury (n=657), sever comorbid illness (n=500), tumor (n=2000) which might significantly impact movement and cognition, other degenerative forms of or drug-induced parkinsonism (n=100) and symmetrical lower body parkinsonism attributable to significant cerebrovascular disease (n=1400) were also excluded. Other information can be found in the Supplementary Files.

Study design and ethics statement

The data were retrospectively collected from patients with PD, DM and PD-DM with or without dementia at Zhujiang Hospital of Southern Medical University, Guangzhou, Guangdong, China over a 6-year period (January 2013 to May 2019). This study was approved by the Human Research Committee at Zhujiang Hospital of Southern Medical University (No: 2019-KY-030-02). Written informed consent was obtained from all participants or their legal guardians.

Experienced neurologists were recruited to perform the evaluations and completed the neurological examinations for all subjects. All subjects completed the following battery of standard assessment measures: a standard demography form, the Movement Disorder Society–Unified Parkinson's Disease Rating Scale (MDS-UPDRS) [38], and the modified Hoehn and Yahr (H&Y) staging scale. The UPDRS (I) 'mentation' and UPDRS (II) 'daily life' subscales were used to evaluate

psychiatric dysfunction and disease severity. The UPDRS (III) 'motor' and H&Y subscales were used to evaluate motor dysfunction and disease severity. The degree of nonmotor symptoms (NMSs) in every patient was measured by the NMS scale (NMSS) [39]. Cognitive abilities were evaluated with the Mini Mental State Examination (MMSE) [40] and the Montreal Cognitive Assessment (MoCA). MoCA scores were adjusted for years of education. Predetermined diagnostic cut-offs were used to categorize cases into dementia (21 or less with functional impairment) to reflect the core criteria for PD dementia (PDD) with or without DM as defined by the Movement Disorder Society Task Force [41, 42]. All scales were available and validated. Patients were considered to present with anxiety or depression, brain infarction, WMLs, SAE or hyperlipidemia if there was a self-reported or doctor-diagnosed history of these conditions or if they were using disease-related medications. When WMLs result from hypoxic-ischemic brain lesions and lead to cognitive impairment, this complex disorder is characterized as SAE [17]. Individuals were considered to have hyperlipidemia at screening if they had a total cholesterol level of more than 6.2 mmol/L (240 mg/dL), serum triglycerides concentrations more than 2.3 mmol/L (200 mg/dL), serum LDL-C concentrations more than 4.1 mmol/L (160 mg/dL) or serum HDL-C concentrations less than 1.0 mmol/L (40 mg/dL) [43–47]. Hypoglycemia was defined in subjects with a plasma glucose of ≤3.9mmol/L and/or self-reported probable hypoglycemic symptoms [48].

In addition, routine examinations and imaging scans during hospitalization were completed. Venous blood samples from all participants were collected into Ethylene Diamine Tetraacetic Acid (EDTA) tubes by trained nurses in the morning. Blood samples were sent to the clinical pathology department immediately. The serum levels of all biochemical factors were measured by clinical pathologists. The serum hsCRP, Cys C and albumin were measured by immunoturbidimetric assay (Orion Diagnostica, Espoo, Finland); serum LDL-C and D-dimer were measured with direct enzymatic methods; serum AST and ALT were measured using the International Federation of Clinical Chemistry (IFCC) method. Serum HCY levels were measured using HCY reagent (Maccura Biotechnology Co., Ltd., Chengdu, China) through enzymatic cycling assay by Hitachi Automatic Analyzer 7600–210 (Hitachi, Tokyo, Japan). Serum fibrinogen levels were examined with com-mercial kits following the manufacturer's instructions by a coagulometer (SC40 semi-automatic coagulation analyzer, Taizhou Steellex Biotechnology Co., LTD., China). All participants underwent T1-weighted, T2-weighted, and fluid-attenuated inversion recovery (FLAIR) imaging using a 3.0-T MRI scanner (Philips

Healthcare, Andover, MA). Two neuroradiologists blinded to the clinical information of patients independently rated periventricular white matter hyper-intensities and deep white matter hyperintensities using a modified Fazekas scale to assess the degree of severity of WMLs on T2 MR images [24, 49]. The enrolled patients were divided into 3 groups according to age (Table 1): less than 55, 55 to 70 and more than 70 years old [50–53]. The relative variables [LDL-C, D-Dimer, fibrinogen, hypersensitive C-reactive protein (hs-CRP), aspartate transaminase (AST), albumin, calcium, mean corpuscular volume (MCV), HCY, Cys C, FBG] were categorized according to the normal reference range, and we considered the levels of biochemical indicators as the commonly used thresholds in this study (Supplementary Files).

Statistical analyses

All continuous variables, including age, PD duration, MDS-UPDRS, H&Y, NMSS, MMSE, and MoCA scores; vascular and inflammatory risk factors, including systolic blood pressure (SBP), diastolic blood pressure (DBP), body mass index (BMI), and LDL-C, D-dimer, fibrinogen, WBC, and hs-CRP levels; and metabolic-related risk mediators, including AST, alanine transaminase (ALT), albumin, calcium, potassium, MCV, HCY, Cys C, FBG and glycated hemoglobin (HbA1c) levels, are presented as the median (interquartile range, IQR) as they were not normally distributed. All categorical variables including male gender; smoking history; drinking history; drug use, including atorvastatin, metformin, insulin, acarbose, levodopa and benserazide (L-Dopa); anxiety or depression; vascular and inflammatory risk factors including hyperlipidemia, brain infarction, SAE, WMLs, lymphocytes, and neutrophils; and metabolic risk factors, including hyperhomocysteinemia, are presented as the count (proportion). We selected these most common used lipid-lowering drug (atorvastatin), hypoglycemic drugs (metformin and acarbose) and drug for Parkinson's disease (L-Dopa) in clinics as covariates to exclude their effects on dementia. The statistically significant differences between patients with dementia and patients without dementia in the PD, DM, and PD-DM groups were assessed by the χ^2-test or Mann-Whitney U tests. P-values<0.05 were considered statistically significant, but when multiple testing was performed, the Bonferroni method was used to adjust the significance level. If statistically significant, continuous variables were assessed by Kruskal–Wallis test (nonparametric one-way analysis of variance, ANOVA) followed by post-hoc analysis with Bonferroni adjustment to compare differences among PDD, DMD and PD-DMD groups and were prior adjusted for age using multivariate linear regression

analyses. Categorical parameters were analyzed using the χ2-test with Bonferroni adjustment for multiple testing. Mann-Whitney U test were used to compare differences between PDD and PD-DMD groups. Binary logistic regression was applied to explore the potential risk factors and in PDD and PD-DMD patients. The presence or absence of dementia was used as a dependent variable. All vascular inflammatory and metabolic risk factors demonstrating significant differences between patients with and without dementia (selection criterion p<0.05) were included in the binary logistic regression analysis with enter selection (Table 3). The results are presented as odds ratios (ORs) and 95% confidence intervals (CIs). Since several lines of evidence showed that age around 70 years would be critical age for dementia in PD and PD-DM patients[50, 52–54], we performed the logistic regression models considering (a) all patients, (b) less than or equal to 70 years and (c) patients over 70 years. In addition, multiple linear regression (enter method) was also used to investigate whether the MMSE score was associated with the risk factors of dementia. Receiver operating characteristic (ROC) curves of logistic regression prediction models for PD-DMD were used with the risk factors (LDL-C and fibrinogen) in PD-DM patients. We also compared the accuracy, sensitivity and specificity of novel (LDL-C and fibrinogen) and traditional (disease duration, age, MDS-UPDRS) risk factors and used bootstrap validation with 1000 repeats (Supplementary Figure 1). All statistical procedures were conducted using Statistical Package for the Social Sciences (SPSS) version 20.0 and GraphPad Prism 7.0. P-values<0.05 were considered statistically significant.

Abbreviations

AST: Aspartate transaminase; ALT: Alanine transaminase; AUC: area under the curve; BMI: body mass index; BBB: blood brain barrier; Cystatin C: Cys C; CNS: Central Nervous System; CI: confidence interval; DM: type 2 diabetes mellitus without Parkinson disease; DMD: type 2 diabetes mellitus with dementia; DBP: diastolic blood pressure; EDTA: Ethylene Diamine Tetraacetic Acid; FBG: Fasting blood glucose; hs- CRP: hypersensitive C-reactive protein; HCY: homocysteine; HbA1c: glycated hemoglobin; H&Y: the modified Hoehn and Yahr staging scale; IQR: interquartile range; L-Dopa: Levodopa and Benserazide; LDL-C: low density lipoprotein cholesterol; MDS-UPDRS: Movement Disorder Society–Unified Parkinson's Disease Rating Scale; MCV: mean corpuscular volume; MoCA: Montreal Cognitive Assessment; MMSE: mini mental state examination; MRI: magnetic resonance imaging; NMSS: Non-Motor Symptoms Scale for Parkinson's Disease; NVU: neurovascular units; OR: odds ratio; PD: patients with Parkinson disease without type 2 diabetes mellitus; PD-DM: patients with Parkinson disease and type 2 diabetes mellitus; PD-DMD: patients with Parkinson disease and type 2 diabetes mellitus and dementia; PSP: progressive superanuclear palsy; ROC: receiver operating characteristic analysis; SBP: systolic blood pressure; SAE: subcortical arteriosclerotic encephalopathy; SPSS: Statistical Package for the Social Sciences; WBC: White blood cell count; WMLs: White matter lesions.

AUTHOR CONTRIBUTIONS

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CONFLICTS OF INTEREST

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SUPPLEMENTARY MATERIALS

Supplementary Methods

Personal history of smoking behavior was calculated by "pack/years" quantifying the packs smoked per day multiplied by years as a smoker, with the threshold was set to 15. Drinking was defined as an average of alcoholic drink ($\geq$ 50 ml) at least once per week lasting more than half a year. Body-mass index (BMI) was calculated as body weight (kg) divided by heights squared (m^2).

The following variables were categorized according to the normal reference range [1–11] and we considered the following levels of biochemical indicators as the commonly used thresholds in this study: the low LDL level as less than 2.00 mmol/L [1], the high level of D-Dimer as more than 0.50mg/L [2], the high level of fibrinogen as more than 4.00g/L [3], the high level of hypersensitive C-reactive protein (hs-CRP) as more than 3.00mg/L [4], the high level of aspartate transaminase (AST) as more than 40IU/L [5], the low level of albumin as less than 35.00g/L [6], the low level of calcium as less than 2.10mmol/L [7], the high level of mean corpuscular volume (MCV), as more than 90.00fL [8], the high level of HCY as more than 15 mmol/L (the cutoff for hyperhomocysteinemia) [9], the high level of Cys C as more than 0.95mg/L [10] and the low level of fasting blood glucose (FBG) as less than 5.00mmol/L [11].

Supplementary Results

Multiple linear regression analysis for the association of risk factors of dementia and MMSE score in PD, DM and PD-DM patients

Using multiple linear regression analysis, we found that a lower FBG (<5.00 mmol/L, B= -1.052, SE=0.433, β=-0.126, p=0.016), higher HCY (>15.00 μmol/L, B= -1.336, SE=0.595, β= -0.115, p=0.026), and Cys C (>0.95 mg/L, B= -0.908, SE=0.452, β= -0.103, p=0.046), and age (B=-0.140, SE=0.019, β= -0.376, p<0.001) were associated with lower MMSE score. No significant association was observed between MMSE score and hyperlipidemia (B= -1.232, SE=0.641, β=-0.098, p=0.056) in PD patients (adjusted R^2=0.173, F=14.469, p<0.001). In addition, higher fibrinogen (>4.00 g/L, B= -1.857, SE=0.663, β= -0.174, p=0.006), lower LDL-C (<2.00 mmol/L, B= -1.876, SE=0.674, β= -0.173, p=0.006), age (B= -0.171, SE=0.032, β= -0.342, p<0.001) and SAE (B= -2.196, SE=0.640, β= -0.216, p<0.001) were associated with lower MMSE score in PD-DM patients (adjusted R^2=0.275, F=19.383,

p<0.001). A higher AST (>40 IU/L, B= -3.278, SE=1.023, β= -0.141, p=0.001) and Cys C (>0.95 mg/L, B= -1.878, SE=0.690, β= -0.119, p=0.007), anxiety or depression (B= -1.579, SE=0.531, β= -0.135, p=0.003), male gender (B= -1.182, SE=0.398, β= -0.131, p=0.003) and age (B= -0.163, SE=0.015, β= -0.481, p<0.001) were associated with lower MMSE score in DM patients (adjusted R^2=0.310, F=34.277, p<0.001) (Supplementary Table 1). These observations are consistent with the results of multivariable logistic regression analysis for risk factors in dementia in PD, DM and PD-DM patients (Table 3A, Table 3B, Supplementary Table 4).

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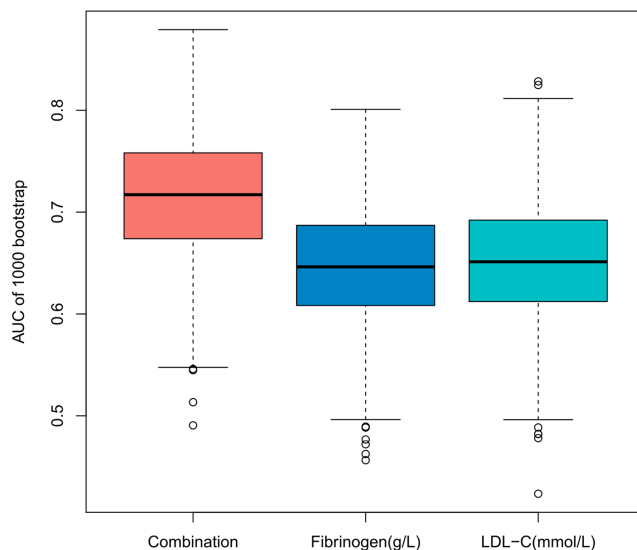
Supplementary Figure 1. The AUC distributions of 1000 bootstrap samples. The bias-corrected and accelerated (BCA) bootstrap 95% confidence interval of AUC for Fibrinogen(g/L), LDL-C(mmol/L), and their combination are 0.648 [BCA 95%CI: 0.537~0.756], 0.655 [BCA 95%CI: 0.516~0.760], and 0.716 [BCA 95%CI: 0.595~0.818]. AUC- area under the curve; LDL-C- low density lipoprotein cholesterol.

Supplementary Tables

Supplementary Table 1. Association of the risk factors of dementia and MMSE score in PD, DM and PD-DM patients.

Model	Predictor variables	B	SE	β	p	R²	Adjusted R²	F	p
PD	FBG<5.00 (mmol/L)	-1.052	0.433	-0.126	**0.016**				
	HCY>15.00 (μmol/L)	-1.336	0.595	-0.115	**0.026**				
	Age	-0.140	0.019	-0.376	**<0.001**	0.185	0.173	14.469	<0.001
	Cys C>0.95 (mg/L)	-0.908	0.452	-0.103	**0.046**				
	Hyperlipidemia	-1.232	0.641	-0.098	0.056				
PD-DM	Fibrinogen>4.00 (g/L)	-1.857	0.663	-0.174	**0.006**				
	LDL-C<2.00 (mmol/L)	-1.876	0.674	-0.173	**0.006**	0.290	0.275	19.383	<0.001
	Age	-0.171	0.032	-0.342	**<0.001**				
	SAE	-2.196	0.640	-0.216	**0.001**				
DM	AST>40 (IU/L)	-3.278	1.023	-0.141	**0.001**				
	Cys C>0.95 (mg/L)	-1.878	0.690	-0.119	**0.007**				
	Anxiety or depression	-1.579	0.531	-0.135	**0.003**	0.319	0.310	34.277	<0.001
	Male	-1.182	0.398	-0.131	**0.003**				
	Age	-0.163	0.015	-0.481	**<0.001**				

B- Unstandardized coefficient; β- Standardized coefficient; R² represents the model explanatory power with according standardized β weights, showing the contribution of each independent variable to the proposed model; SE- Standard Error; MMSE- mini mental state examination; PD- patients with Parkinson disease without type 2 diabetes mellitus; PD-DM- patients with Parkinson disease and type 2 diabetes mellitus; DM- type 2 diabetes mellitus without Parkinson disease; FBG- Fasting blood glucose; HCY- homocysteine; Cystatin C- Cys C; LDL-C- low density lipoprotein cholesterol; SAE- subcortical arteriosclerotic encephalopathy; AST- Aspartate transaminase.

Supplementary Table 2. Differences of risk factors among PDD, DMD and PD-DMD groups.

Clinical variables	PDD (n=31)	DMD (n=35)	PD-DMD (n=31)	p*	Multiple comparisons **
Age, years	69.0(59.0,79.0)	68.0(57.0,74.0)	79.0(72.0,84.0)	**<0.001**	**PD-DMD>PDD=DMD**
<55, n (%)	3(9.68)	7(20.00)	0	-	-
55–70, n (%)	16(51.61)	14(40.00)	5(16.13)	-	-
>70, n (%)	12 (38.71)	14(40.00)	26(83.87)	**<0.001**	**PD-DMD>PDD=DMD**
Male, n (%)	18(58.06)	27(77.14)	16(51.61)	0.080	-
PD duration, month	60(24,84)	-	36(12,72)	-	
Dementia, n (%)	31 (100.00)	35 (100.00)	31 (100.00)	0.094	-
Use of drugs, n (%)					
Atorvastatin	6(19.35)	14(40.00)	20(64.52)	**0.001**	**PD-DMD>PDD**
Metformin	-	14(40.00)	9(29.03)	-	-
Insulin	-	8(22.86)	14(45.16)	0.055	-
Acarbose	-	17(48.57)	18(58.06)	0.441	-
L-Dopa	28(90.32)	-	26(83.87)	-	-
MDS-UPDRS (I)	3.0(2.0,5.0)	-	5.0(3.0,6.0)	**0.006**	**PD-DMD>PDD**
MDS-UPDRS (II)	8.0(6.0,11.0)	-	14.0(12.0,18.0)	**<0.001**	**PD-DMD>PDD**
MDS-UPDRS (III)	17.0(15.0,23.0)	-	23.0(21.0,29.0)	**<0.001**	**PD-DMD>PDD**
MDS-UPDRS (Total)	26.0(24.0,38.0)	-	44.0(37.0,54.0)	**<0.001**	**PD-DMD>PDD**
H&Y	3.0(2.0,4.0)	-	3.0(3.0,4.0)	0.072	-
NMSS	26.0(17.0,32.0)	-	32.0(28.0,34.0)	**0.003**	**PD-DMD>PDD**
MMSE	15.0(13.0,17.0)	15.0(9.0,19.0)	13.0(11.0,17.0)	0.613	-
MoCA	12.0(9.0,14.0)	12.0(7.0,15.0)	9.0(8.0,13.0)	0.205	-
Anxiety or depression	17(54.84)	13(37.14)	19(61.29)	0.124	-
Vascular and inflammatory risk factors					
SBP mmHg	120.0(118.0,135.0)	146.0(128.0,153.0)	132.0(120.0,152.0)	-	-

	PDD	DMD	PD-DMD	p	Post-hoc
DBP mmHg	80.0(78.0,81.0)	85.0(80.0,95.0)	78.0(69.0,87.0)	-	-
Smoking history, n (%)	2(6.45)	7(20.00)	3(9.68)	-	-
Drinking history, n (%)	0	5(14.29)	1(3.23)	-	-
BMI	23.0(22.0,25.0)	24.0(22.0,26.0)	24(21,25)	-	-
LDL-C (mmol/L)	2.5(2.3,3.2)	2.7(1.9,3.1)	1.9(1.6,3.0)	0.094	-
LDL-C<2.00 (mmol/L), n (%)	2(6.45)	12(34.29)	15(48.39)	**0.001**	**PD-DMD=DMD>PDD**
D-Dimer (mg/L)	0.6(0.3,1.1)	0.4(0.3,0.9)	0.6(0.4,1.4)	-	-
D-Dimer>0.50 (mg/L), n (%)	10(32.26)	8(22.86)	10(32.26)	0.618	-
Fibrinogen (g/L)	3.5(2.8,4.0)	3.3(3.0,4.6)	4.1(3.5,5.1)	**0.012**	**PD-DMD>PDD**
Fibrinogen>4.00 (g/L), n (%)	6(19.35)	9(25.71)	15(48.39)	**0.033**	**PD-DMD>PDD**
WBC (g/L)	6.1(5.0,7.2)	7.3(6.0,9.5)	7.4(6.1,9.9)	-	-
Lymphocyte (%)	30.7(24.2,34.8)	25.3(18.6,32.1)	20.5(12.2,28.0)	**0.001**	**PD-DMD<PDD**
Neutrophil (%)	58.6(52.5,67.5)	64.0(58.3,70.2)	71.5(61.6,82.8)	**<0.001**	**PD-DMD>PDD**
hs-CRP (mg/L)	0.6(0.6,2.0)	3.6(1.5,7.1)	4.5(0.7,47.1)	0.036	-
hs-CRP>3.00 (mg/L), n (%)	2(6.45)	11(31.43)	8(25.81)	**0.039**	**DMD>PDD**
Hyperlipidemia	7(22.58)	3(8.57)	2(6.45)	-	-
Brain infarction	13(41.94)	27(77.14)	26(83.87)	**0.001**	**PD-DMD=DMD>PDD**
SAE	9(29.03)	5(14.29)	18(58.06)	**0.001**	**PD-DMD>DMD**
WMLs, n (%)	12(38.71)	17(48.57)	18(58.06)	0.313	-
Fazekas 1	5(16.13)	2(5.71)	2(6.45)	-	-
Fazekas 2	7(22.58)	12(34.29)	15(48.39)	0.103	-
Fazekas 3	0	3(8.57)	1(3.23)	0.322	-
Metabolic risk factors					
AST>40(IU/L), n (%)	0	5(14.29)	3(9.68)	0.091	-
ALT	15.0(9.0,22.0)	22.0(15.0,28.0)	14.0(11.0,30.0)	-	-
Albumin	40.3(38.0,41.8)	39.3(36.2,42.9)	36.9(36.0,42.1)	0.204	-
Albumin<35.00 (g/L), n (%)	2(6.45)	4(11.43)	7(22.58)	0.187	-
Calcium (mmol/L)	2.3(2.2,2.4)	2.2(2.2,2.3)	2.2(2.1,2.3)	0.329	-
Calcium<2.10 (mmol/L), n (%)	5(16.13)	6(17.14)	8(25.81)	0.569	-
Potassium (mmol/L)	3.8(3.6,4.1)	3.9(3.6,4.0)	3.8(3.4,4.3)	0.911	-
MCV (fL)	92.7(91.1,97.4)	87.2(83.5,93.3)	89.9(88.2,93.2)	**<0.001**	**PDD>PD-DMD=DMD**
MCV>90.00 (fL), n (%)	25(80.65)	13(37.14)	14(45.16)	**0.001**	**PDD>PD-DMD=DMD**
HCY (μmol/L)	15.8(12.0,17.8)	11.3(8.5,15.3)	12.3(8.7,18.0)	-	-
HCY>15.00 (μmol/L), n (%)	9(29.03)	5(14.29)	5(16.13)	0.270	-
Hyperhomocysteinemia	4(12.90)	0	1(3.23)	0.041	-
Cys C (mg/L)	1.1(1.0,1.2)	1.0(0.9,1.1)	1.0(0.9,1.5)	0.551	-
Cys C>0.95 (mg/L), n (%)	15(48.39)	8(22.86)	7(22.58)	0.039	-
FBG (mmol/L)	4.7(4.3,5.1)	7.6(5.8,11.6)	7.1(6.1,10.0)	**<0.001**	**PD-DMD=DMD>PDD**
FBG<5.00 (mmol/L), n (%)	23(74.19)	5(14.29)	1(3.23)	**<0.001**	**PD-DMD=DMD<PDD**
HbA1c (%)	5.7(5.2,5.9)	7.3(6.3,8.9)	6.4(6.0,7.4)	-	-

PDD- patients with Parkinson disease with dementia; DMD- type 2 diabetes mellitus with dementia; PD-DMD- patients with Parkinson disease and type 2 diabetes mellitus and dementia; L-Dopa- Levodopa and Benserazide; MDS-UPDRS- Movement Disorder Society–Unified Parkinson's Disease Rating Scale; H&Y- the modified Hoehn and Yahr staging scale; NMSS- Non-Motor Symptoms Scale for Parkinson's Disease; MMSE- mini mental state examination; MoCA- Montreal Cognitive Assessment; SBP- systolic blood pressure; DBP- diastolic blood pressure; BMI- body mass index; LDL-C- low density lipoprotein cholesterol; WBC- White blood cell count; hs- CRP- hypersensitive C-reactive protein; SAE- subcortical arteriosclerotic encephalopathy; WMLs- White matter lesions; AST- Aspartate transaminase; ALT- Alanine transaminase; MCV- mean corpuscular volume; HCY- homocysteine; Cystatin C- Cys C; FBG- Fasting blood glucose; HbA1c- glycated hemoglobin. *The Bonferroni method was used to adjust the significance level to perform multiple testing. **If statistically significant, continuous variables were analyzed by Kruskal-Wallis test followed by post-hoc analysis with Bonferroni adjustment to compare differences among PDD, DMD and PD-DMD groups and were prior adjusted for age using multivariate linear regression. Mann-Whitney U test were used to compare differences between PDD and PD-DMD groups. Categorical parameters were analyzed using χ2-test with Bonferroni adjustment for multiple testing.

Supplementary Table 3. Multivariable logistic regression analysis for risk factors of dementia in PD patients.

(a)

Variables	Univariate		Multivariate model	
	OR (95%CI)	p	Adjusted OR (95% CI)	p
FBG<5.00 (mmol/L)	**2.704(1.171,6.241)**	**0.020**	**4.380(1.748,10.975)**	**0.002**
HCY>15.00 (µmol/L)	**2.684(1.156,6.231)**	**0.022**	**3.131(1.243,7.888)**	**0.015**
Hyperlipidemia	2.448(0.980,6.119)	0.055	**3.075(1.142,8.277)**	**0.026**
Age	1.035(1.000,1.071)	0.050	**1.043(1.003,1.084)**	**0.034**
Cys C>0.95 (mg/L)	**2.122(1.008,4.468)**	**0.048**	2.157(0.979,4.752)	0.056

(b)

Variables	Univariate		Multivariate model	
	OR (95%CI)	p	Adjusted OR (95% CI)	p
HCY>15.00 (µmol/L)	**2.684(1.156,6.231)**	**0.022**	**2.522(1.042,6.104)**	**0.040**
Hyperlipidemia	2.448(0.980,6.119)	0.055	**2.638(1.018,6.840)**	**0.046**
Age	1.035(1.000,1.071)	0.050	1.030(0.992,1.069)	0.124
Cys C>0.95 (mg/L)	**2.122(1.008,4.468)**	**0.048**	2.057(0.947,4.464)	0.068
Hypoglycaemic episodes (FBG≤3.9mmol/L)	1.594(0.186,13.690)	0.671	2.949(0.308,28.262)	0.348

PD- patients with Parkinson disease without type 2 diabetes mellitus; OR- odds ratio; CI- confidence interval; FBG- fasting blood glucose; HCY- homocysteine; Cys C- Cystatin C.

Supplementary Table 4. Multivariable logistic regression analysis for risk factors of dementia in DM patients.

Variables	Univariate		Multivariate model	
	OR (95% CI)	p	Adjusted OR (95% CI)	p
AST>40(IU/L)	**6.074(1.913,19.286)**	**0.002**	**6.472(1.147,36.533)**	**0.034**
Cys C>0.95 (mg/L)	**3.864(1.584,9.424)**	**0.003**	**4.905(1.399,17.206)**	**0.013**
Anxiety or depression	**3.239(1.535,6.833)**	**0.002**	**3.750(1.220,11.526)**	**0.021**
Male	**2.549(1.125,5.775)**	**0.025**	**3.480(1.109,10.918)**	**0.033**
Hypoglycaemic episodes (FBG≤3.9mmol/L)	**5.062(1.208,21.212)**	**0.027**	7.013(0.903,54.463)	0.063
Neutrophil (%)	**1.054(1.017,1.093)**	**0.004**	1.151(0.983,1.348)	0.080
Brain infarction	**5.511(2.429,12.500)**	**<0.001**	2.485(0.788,7.834)	0.120
Calcium<2.10(mmol/L)	**5.414(1.892,15.490)**	**0.002**	3.464(0.694,17.294)	0.130
Lymphocyte (%)	**0.935(0.896,0.974)**	**0.001**	1.144(0.960,1.364)	0.133
Potassium (mmol/L)	**0.381(0.149,0.977)**	**0.045**	0.500(0.145,1.725)	0.273
WMLs	**4.450(2.166,9.142)**	**<0.001**	2.812(0.439,18.002)	0.275
hs-CRP>3.00 (mg/L)	**2.512(1.160,5.439)**	**0.019**	1.850(0.573,5.974)	0.303
LDL-C<2.00(mmol/L)	2.103(0.996,4.440)	0.051	1.712(0.615,4.770)	0.303
SAE	**5.421(2.618,11.224)**	**<0.001**	1.460(0.249,8.548)	0.675
D-Dimer>0.50(mg/L)	**3.698(1.522,8.986)**	**0.004**	1.309(0.318,5.383)	0.709
Albumin<35.00(g/L)	**5.339(1.513,18.846)**	**0.009**	1.207(0.207,7.026)	0.834
Fibrinogen>4.00 (g/L)	**2.431(1.066,5.543)**	**0.035**	1.098(0.306,3.947)	0.886
Age	**1.033(1.005,1.062)**	**0.022**	0.998(0.957,1.042)	0.931

DM- patients with type 2 diabetes mellitus; OR- odds ratio; CI- confidence interval; AST- Aspartate transaminase; Cystatin C- Cys C; FBG- Fasting blood glucose; WMLs- White matter lesions; hs-CRP- hypersensitive C-reactive protein; LDL-C- low density lipoprotein cholesterol; SAE- subcortical arteriosclerotic encephalopathy.

Supplementary Table 5. Multivariable logistic regression analysis for risk factors of dementia in PD (with and without DM) patients and the interaction of risk factors with the existence of DM.

Variables	Univariate		Multivariate Model		Interactioon
	OR (95%CI)	p	Adjusted OR (95% CI)	p	p
Fibrinogen>4.00 (g/L)	**3.002(1.677,5.374)**	**<0.001**	**3.259(1.674-6.345)**	**0.001**	
With DM	**3.613(2.266,5.761)**	**<0.001**	**3.204(1.247,8.233)**	**0.016**	0.979
Without DM	**0.277(0.174,0.441)**	**<0.001**	**3.267(1.059,10.082)**	**0.039**	
LDL-C<2.00 (mmol/L)	**2.129(1.142,3.969)**	**0.017**	1.544(0.783,3.043)	0.210	
With DM	**2.586(1.594,4.197)**	**<0.001**	**3.347(1.305,8.585)**	**0.012**	**0.022**
Without DM	**0.387(0.238,0.627)**	**<0.001**	0.384(0.078,1.890)	0.239	
SAE	**2.458(1.428,4.231)**	**0.001**	1.566(0.848,2.894)	0.152	
With DM	**1.469(1.001,2.156)**	**0.049**	**3.952(1.566,9.971)**	**0.004**	**0.028**
Without DM	**0.681(0.464,0.999)**	**0.049**	0.855(0.312,2.343)	0.761	
FBG<5.00 (mmol/L)	1.100(0.638,1.895)	0.732	**2.364(1.153,4.848)**	**0.019**	
With DM	**0.108(0.067,0.175)**	**<0.001**	0.323(0.036,2.905)	0.313	**0.025**
Without DM	**9.232(5.728,14.880)**	**<0.001**	**5.116(1.879,13.931)**	**0.001**	
HCY>15.00 (μmol/L)	**1.925(1.005,3.687)**	**0.048**	1.724(0.848,3.503)	0.132	
With DM	0.907(0.554,1.1.486)	0.699	0.940(0.283,3.130)	0.920	0.163
Without DM	1.102(0.673,1.804)	0.699	**2.828(1.068,7.492)**	**0.036**	
Hyperlipidemia	1.302(0.610,2.780)	0.495	1.391(0.618,3.133)	0.425	
With DM	1.035(0.612,1.752)	0.898	0.717(0.146,3.506)	0.681	0.141
Without DM	0.966(0.571,1.635)	0.898	**2.996(1.048,8.561)**	**0.041**	
Diabetes	1.685(0.991,2.863)	0.054	1.168(0.573,2.384)	0.669	
Cys C>0.95 (mg/L)	1.350(0.775,2.353)	0.290	1.267(0.681,2.355)	0.455	
With DM	0.722(0.493,1.057)	0.094	0.467(0.155,1.405)	0.175	**0.022**
Without DM	1.385(0.946,2.028)	0.094	**2.360(1.014,5.495)**	**0.046**	
Age	**1.051(1.024,1.078)**	**<0.001**	**1.044(1.010,1.078)**	**0.010**	
With DM	**1.082(1.062,1.103)**	**<0.001**	1.059(0.999,1.123)	0.055	0.854
Without DM	**0.924(0.907,0.942)**	**<0.001**	**1.052(1.007,1.099)**	**0.024**	

PD- patients with Parkinson disease without type 2 diabetes mellitus; DM- type 2 diabetes mellitus without Parkinson disease; OR- odds ratio; CI- confidence interval; LDL-C- low density lipoprotein cholesterol; SAE- subcortical arteriosclerotic encephalopathy; FBG- fasting blood glucose; HCY- homocysteine; Cys C- Cystatin C.