Risk Factors and Clinical Outcomes of Cognitive Impairment in Diabetic Patients Undergoing Peritoneal Dialysis

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Keywords

Cognitive dysfunction · Diabetes mellitus · Peritoneal dialysis

Abstract

Introduction: Cognitive impairment (CI) is common in patients with CKD or diabetes mellitus (DM). However, the relevance between DM and CI in diabetic patients undergoing peritoneal dialysis (PD) has not been clearly established. This study aimed to explore the role of DM in CI, the association of glycemic control with CI, and clinical outcomes of CI in diabetic PD patients. **Methods:** Continuous ambulatory PD (CAPD) patients followed up in our PD center between 2014 and 2016 were enrolled. The participants were followed until an endpoint was reached or December 2017. Demographic data and clinical characteristics were collected, and laboratory parameters were measured. The Montreal Cognitive Assessment (MoCA) was used to evaluate global cognitive function, and a score of <26 was considered to indicate CI. A propensity score matching according to age, gender, and mean arterial pressure was conducted between the DM and

non-DM groups. **Results:** A total of 913 CAPD patients were enrolled, of whom 186 (20.4%) had diabetes. After appropriate matching, 175 patients in the DM group and 270 patients in the non-DM group were included. Patients with diabetes had a higher prevalence of CI and lower scores for visuospatial/executive function, naming, language, delayed recall, and orientation. Higher HbA1c (odds ratio [OR], 1.547; 95% confidence interval [95% CI], 1.013–2.362) and cardiovascular disease (CVD; OR, 2.926; 95% CI, 1.139–7.516) significantly correlated with a risk of CI in diabetic patients. During a median of 26.0 (interquartile range 13.5–35.6) months of follow-up, diabetic patients with CI demonstrated a significantly lower survival rate than those without CI, and CI was an independent risk factor for mortality after adjustment (hazard ratio, 7.224; 95% CI, 1.694–30.806). However, they did not show worse technique survival or higher peritonitis rate than patients without CI. **Conclusions:** HbA1c and CVD are independent risk factors for CI in diabetic patients undergoing CAPD, and CI is independently associated with a higher risk of mortality.

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Introduction

Cognitive impairment (CI) is a common finding in patients with CKD and has been shown to correlate with the severity of renal insufficiency [1]. It has been reported that 17–62% of CKD patients exhibit impairments in cognitive performance [1–3], and this number is even higher among patients with ESRD [4–6]. Cognitive performance includes multiple domains, including memory, attention, information processing, executive functioning, visuospatial skills, and language abilities. Due to the fact that peritoneal dialysis (PD) involves complex medical regimens, impairment in cognitive function may interfere with patients' abilities of decision-making and self-care, implementation of fluid and dietary restriction, and adherence to medication instructions. In addition, CI is associated with dialysis withdrawal [7], a higher hospitalization rate, higher mortality, and a poorer quality of life [8, 9]. Moreover, CI may considerably increase the overall disease burden and healthcare expenditure.

As the leading cause of ESRD in the USA, diabetes mellitus (DM) accounts for 38% of patients with ESRD according to the US Renal Data System (USRDS) [10], and in our PD center, the prevalence of diabetes is ~20–25% [11, 12]. Substantial epidemiologic evidence has established an association between DM and cognitive dysfunction [13, 14], which is particularly strong in older populations. Furthermore, the prognosis of CI is worse in patients with diabetes than in those without [15, 16]. However, the relevance between DM and CI in patients undergoing PD has not been clearly established. Therefore, in the present study, we aimed to explore whether the impact of DM on CI changes in patients undergoing PD, the association of glycemic control with CI, and clinical outcomes of CI in diabetic PD patients.

Materials and Methods

Study Population and Data Collection

The continuous ambulatory PD (CAPD) patients from the First Affiliated Hospital of Sun Yat-sen University were consecutively recruited between January 1, 2014, and December 31, 2016. The eligible patients were ≥ 18 years old and had been undergoing CAPD treatment for ≥ 30 days. Patients who were unable to complete cognitive testing due to pre-existing dementia, mental disorder, severe eyesight loss, illiteracy, or a formal education of < 6 years were excluded from the study. The participants were followed until death, transfer to hemodialysis (HD), kidney transplantation, transfer to another center, or December 31, 2017. The study was conducted in compliance with the ethical principles of the Helsinki Declaration and approved by the Human Ethics Com-

mittee of Sun Yat-sen University. Written informed consent was obtained from all the participants.

Demographic and clinical data were collected that included age, gender, level of education, BMI, the histories of smoking, diabetes, hypertension, cardiovascular disease (CVD), the duration of dialysis, and the use of erythropoietin. Hypertension was defined when a systolic blood pressure (SBP) ≥ 140 mm Hg and/or a diastolic blood pressure ≥ 90 mm Hg. CVD was defined as a history of coronary heart disease, heart failure, cerebrovascular disease, peripheral artery disease, or other types of vascular diseases [11]. Cerebrovascular disease was recorded separately. Laboratory data including Kt/V, measured glomerular filtration rate (mGFR), normalized protein catabolic rate, SBP, diastolic blood pressure, mean arterial pressure (MAP), hemoglobin concentration, hematocrit, high-sensitivity C-reactive protein (hsCRP), serum albumin, serum calcium, serum phosphorus, intact parathyroid hormone, serum sodium, serum potassium, BUN, serum Cr, serum uric acid, serum lipid, serum glucose, and HbA1c were also measured. mGFR was measured as the mean of urea and Cr clearance calculated from 24-h urine collections and adjusted for the body surface area. The normalized protein catabolic rate is a nutritional indicator used to estimate protein intake. It was calculated from 24-h urine and dialysate effluent collections and normalized to ideal body weight. The weekly total Kt/V (urea clearance index) was calculated from 24-h urine and dialysate effluent collections. The volume of distribution of urea was estimated from the Watson formula [17].

Measurement of Cognitive Function

Participants were assessed using the Chinese mandarin version of Montreal Cognitive Assessment (MoCA) for global cognition. Cognitive dysfunction refers to a deficit of key brain functions in one or more cognitive domains. It ranges from mild cognitive impairment to severe dementia [18]. The MoCA is a rapid screening instrument for mild cognitive dysfunction, which is considered as a prodromal stage of dementia. It can assess different domains of cognitive function, including attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. Compared to other cognitive screening tools, such as the Mini-Mental State Examination, the clock-drawing test, Memory Impairment Screen, Mental Status Questionnaire, Mini-Cog verbal fluency, 8-Item Informant Interview, Functional Activities Questionnaire, 7-Minute Screen, and Abbreviated Mental Test, the MoCA is easy to administer and has been validated to be more or equally sensitive [19–21]. The highest possible score is 30 points, and a score below 26 is considered cognitively impaired. Those who received ≤ 12 years of formal education are given 1 additional point (www.mocatest.org). It took approximately 10 min to administer the MoCA. The assessment was performed by PD nurses receiving standardized training during the patients' regular monthly visits, since it would be more convenient for the PD nurses to perform assessment if including MoCA in the routine screening. But a full diagnosis of CI still needs further confirmation by a specialist after screening.

Statistical Analysis

Categorical variables are expressed as frequencies and percentages, and continuous variables are expressed as means $\pm$ standard deviations (SDs) for normally distributed data and medians (interquartile ranges [IQRs]) for nonnormally distributed data. For

Fig. 1. Flowchart of patient selection. PD, peritoneal dialysis.

comparisons between groups, independent sample *t*-tests were performed for normally distributed variables, Mann-Whitney U tests were used to compare nonnormally distributed variables, and the χ^2 -tests were applied for categorical variables. To compensate for the differences between the DM and non-DM groups, a propensity score was calculated using a logistic regression with age, gender, and MAP. Patients in the DM group were matched at a ratio of 1:2 with those in the non-DM group by individual propensity scores. Patients who were successfully matched were selected for the following analyses. The associations between DM and CI were examined by multivariable logistic regression models. Variables with $p < 0.1$ in the univariate analysis were selected for the multivariate adjusted model. The final full model included age, gender, level of education, history of diabetes, history of CVD, dialysis vintage, SBP, serum Cr, and high-density lipoprotein cholesterol (HDL-C). To identify the risk factors related to CI in diabetic patients, a multivariable logistic regression model including age, gender, education, BMI, history of smoking, CVD, MAP, total cholesterol, serum Cr, glucose, or HbA1c was used. The results are presented as odds ratios (ORs) and 95% confidence intervals (95% CIs). The relationships of CI with patient survival and technique survival were determined using Kaplan-Meier estimates, and the relationship between CI and the incidence of peritonitis was assessed using a Poisson regression analysis. After univariate analyses, multivariate Cox proportional hazards regression was calculated to determine the risk of mortality. The results are presented as hazard ratios (HRs) and 95% CIs. A *p*-value of less than 0.05 was considered statistically significant. All statistical analyses were carried out using SPSS version 24.0 (SPSS Inc., Armonk, NY, USA).

Results

Patient Characteristics

Of the 1,148 CAPD patients who attended the unit during the study period, 173 did not give informed con-

sent, 10 were on CAPD for <1 month, 12 were <18 years old, and 40 were unable to complete cognitive testing due to dementia (5 patients), a formal education of <6 years (33 patients), severe eyesight loss (1 patient), or mental disorder (1 patient). Finally, the remaining 913 patients were enrolled in this study (Fig. 1). Their mean ($\pm$ SD) age was 48.7 ± 14.6 years; 60.4% ($n = 551$) were male, and 20.4% ($n = 186$) had diabetes. The median duration of PD was 25.5 (IQR 6.0–52.6) months, and the mean BMI was 21.9 (IQR 19.8–24.2) kg/m². Of these patients, 92.8% had a history of hypertension and 22.3% had a history of CVD. The 186 diabetic patients had a mean ($\pm$ SD) age of 60.8 ± 11.0 years, and 68.8% ($n = 128$) were male. Overall, 97.8% of them had a history of hypertension and 47.3% had a history of CVD. Compared with the nondiabetic patients, diabetic patients in this study were older and more often men. They also had higher BMI, a higher prevalence of hypertension and CVD, a higher proportion of assisted PD, a higher level of hsCRP, triglyceride, serum potassium, blood glucose, and HbA1c but shorter dialysis vintage, a lower level of MAP, serum albumin, calcium, phosphate, Cr, low-density lipoprotein cholesterol, and HDL-C. There were no significant differences between groups in mGFR, Kt/V, hemoglobin, serum sodium, BUN, uric acid, and total cholesterol (Table 1 and see online suppl. Fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000514172).

After propensity score matching according to age, gender, and MAP, 175 of the 186 patients in the DM group and 270 of the 727 patients in the non-DM group were matched. No significant differences were observed

Table 1. Comparison of patient characteristics between the DM and non-DM group before and after propensity score matching

Variable	Before matching, <i>n</i> (%)			After matching, <i>n</i> (%)		
	total (<i>n</i> = 913)	DM (<i>n</i> = 186)	non-DM (<i>n</i> = 727)	total (<i>n</i> = 455)	DM (<i>n</i> = 175)	non-DM (<i>n</i> = 280)
Age, years	48.7±14.6	60.8±11.0	45.5±13.8	58.8±10.8	60.0±10.6	58.0±10.8
Gender, male	551 (60.4)	128 (68.8)	423 (58.2)	303 (66.6)	120 (68.6)	183 (65.4)
Level of education						
Primary school	139 (15.2)	40 (21.5)	99 (13.6)	87 (19.1)	37 (21.1)	50 (17.9)
Middle school	263 (28.8)	49 (26.3)	214 (29.4)	138 (30.3)	47 (26.9)	91 (32.5)
High school	254 (27.8)	61 (32.8)	193 (26.5)	131 (28.8)	57 (32.6)	74 (26.4)
College or above	257 (28.1)	36 (19.4)	221 (30.4)	99 (21.8)	34 (19.4)	65 (23.2)
BMI, kg/m ²	21.9 (19.8–24.2)	23.4 (21.9–25.7)	21.5 (19.5–23.8)	22.8 (20.8–25.0)	23.5 (22.0–25.8)	22.2 (20.2–24.2)
Smoking	214 (23.4)	69 (37.1)	145 (19.9)	136 (29.9)	67 (38.3)	69 (24.6)
Hypertension	847 (92.8)	182 (97.8)	665 (91.6)	418 (91.9)	171 (97.7)	247 (88.2)
CVD	204 (22.3)	88 (47.3)	116 (16.0)	161 (35.4)	82 (46.9)	79 (28.2)
Cerebrovascular disease	103 (11.3)	40 (21.5)	63 (8.7)	88 (19.3)	38 (21.7)	50 (17.9)
Dialysis vintage, months	25.5 (6.0–52.6)	21.2 (5.1–45.5)	27.8 (6.3–54.3)	29.1 (6.5–54.2)	21.2 (5.0–45.2)	38.2 (8.7–59.4)
Assisted PD	146 (16.0)	75 (40.3)	71 (9.8)	121 (26.6)	69 (39.4)	52 (18.6)
Use of EPO	830 (91.2)	165 (89.2)	665 (91.7)	411 (90.5)	155 (89.1)	256 (91.4)
mGFR, ml/min/1.73 m ²	1.25 (0.05–3.37)	1.63 (0.13–3.83)	1.20 (0.04–3.23)	1.24 (0.05–3.38)	1.51 (0.12–3.71)	1.20 (0.03–3.22)
nPCR, g/kg·d ⁻¹	0.88 (0.77–1.03)	0.85 (0.73–1.03)	0.89 (0.78–1.04)	0.87 (0.75–1.01)	0.84 (0.72–1.02)	0.89 (0.76–1.01)
Kt/V	2.18 (1.84–2.60)	2.16 (1.85–2.55)	2.18 (1.84–2.61)	2.16 (1.85–2.54)	2.14 (1.83–2.53)	2.17 (1.86–2.57)
SBP, mm Hg	136 (121–148)	141 (127–154)	135 (120–146)	137 (122–150)	141 (127–154)	135 (120–146)
DBP, mm Hg	83 (74–92)	76 (67–84)	85 (76–94)	79 (70–87)	76 (67–84)	80 (72–90)
MAP, mm Hg	100 (91–110)	98 (88–107)	101 (91–111)	98 (90–107)	98 (88–106)	99 (90–108)
Hemoglobin, g/L	112±20	110±23	112±19	112±20	110±23	113±18
Hematocrit	0.34 (0.30–0.38)	0.34 (0.29–0.38)	0.34 (0.30–0.38)	0.34 (0.30–0.38)	0.34 (0.29–0.38)	0.35 (0.31–0.38)
hsCRP, mg/L	1.57 (0.61–4.66)	2.22 (1.09–6.19)	1.36 (0.54–4.44)	2.38 (0.95–6.99)	2.20 (1.10–6.23)	2.58 (0.92–7.71)
Serum albumin, g/L	36.6 (33.3–39.3)	34.8 (31.4–37.6)	37.1 (33.8–39.6)	35.5 (32.3–38.6)	34.7 (31.5–37.7)	35.9 (32.6–39.0)
Serum calcium, mmol/L	2.30 (2.18–2.43)	2.23 (2.12–2.37)	2.32 (2.20–2.44)	2.27 (2.16–2.41)	2.23 (2.12–2.37)	2.31 (2.19–2.46)
Serum phosphorus, mmol/L	1.56 (1.25–1.93)	1.49 (1.19–1.90)	1.58 (1.27–1.93)	1.53 (1.21–1.89)	1.49 (1.19–1.89)	1.55 (1.22–1.88)
iPTH, pg/mL	299 (151–592)	236 (124–495)	315 (168–646)	304 (135–573)	235 (127–500)	333 (148–667)
Serum sodium, mmol/L	139 (137–141)	139 (137–141)	139 (137–141)	139 (137–141)	139 (137–141)	139 (136–141)
Potassium, mmol/L	4.02 (3.61–4.53)	4.27 (3.52–4.85)	3.99 (3.62–4.48)	4.02 (3.54–4.56)	4.27 (3.57–4.89)	3.96 (3.53–4.40)
BUN, mmol/L	17.4 (14.0–21.4)	17.8 (14.2–22.1)	17.4 (14.0–21.1)	18.0 (14.3–21.7)	17.9 (14.1–22.0)	18.1 (14.5–21.5)
Serum Cr, μmol/L	959 (729–1,184)	829 (630–1,055)	995 (760–1,238)	901 (699–1,124)	840 (635–1,057)	946 (733–1,184)
Uric acid, μmol/L	405 (362–451)	399 (358–445)	406 (363–452)	405 (364–456)	399 (359–444)	409 (366–462)
Total cholesterol, mmol/L	4.90 (4.20–5.80)	4.80 (4.00–5.70)	5.00 (4.30–5.80)	4.90 (4.20–5.80)	4.80 (4.00–5.73)	5.00 (4.30–5.80)
Triglyceride, mmol/L	1.50 (1.07–2.06)	1.75 (1.17–2.64)	1.47 (1.06–2.01)	1.63 (1.12–2.26)	1.76 (1.16–2.63)	1.56 (1.10–2.12)
HDL-C, mmol/L	1.13 (0.95–1.39)	1.04 (0.86–1.25)	1.15 (0.97–1.42)	1.08 (0.90–1.31)	1.04 (0.87–1.26)	1.10 (0.93–1.67)
LDL-C, mmol/L	3.13 (2.54–3.72)	2.92 (2.34–3.68)	3.16 (2.61–3.74)	3.13 (2.48–3.74)	2.88 (2.34–3.68)	3.25 (2.58–3.78)
Glucose, mmol/L	4.90 (4.50–5.60)	7.30 (5.50–9.90)	4.80 (4.40–5.20)	5.30 (4.70–6.80)	7.30 (5.60–9.90)	4.90 (4.40–5.50)
HbA1c, %	5.30 (4.90–5.80)	6.25 (5.80–7.10)	5.10 (4.80–5.50)	5.60 (5.20–6.20)	6.40 (5.80–7.10)	5.30 (5.00–5.60)

Data are presented as mean ± SD, median (IQR), or *n* (%). DM, diabetes mellitus; CVD, cardiovascular disease; EPO, erythropoietin; mGFR, measured glomerular filtration rate; nPCR, normalized protein catabolic rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; hsCRP, high sensitivity C-reactive protein; iPTH, intact parathyroid hormone; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HbA1c, glycated hemoglobin; PD, peritoneal dialysis; IQR, interquartile range; SD, standard deviation.

Table 2. Prevalence of cognitive impairment and MoCA score between patients with and without DM

	Score	Total	DM	Non-DM	<i>p</i> value
Cognitive impairment, %	–	331 (72.7)	141 (80.6)	190 (67.9)	0.003
Total score	30	22.0±4.7	20.7±4.9	22.9±4.4	<0.001
Visuospatial/executive	5	3.47±1.32	3.10±1.34	3.71±1.25	<0.001
Naming	3	2.39±0.86	2.24±0.95	2.48±0.78	0.003
Attention	6	5.17±1.03	5.05±1.10	5.24±0.99	0.055
Language	3	1.90±0.84	1.77±0.86	1.99±0.81	<0.006
Abstraction	2	0.00 (0.00–1.00)	0.00 (0.00–1.00)	0.00 (0.00–1.00)	0.130
Delayed recall	5	2.37±1.75	2.03±1.74	2.59±1.73	0.001
Orientation	6	5.73±0.70	5.57±0.89	5.83±0.52	<0.001

Data are presented as mean ± SD, median (IQR), or *n* (%). DM, diabetes mellitus; IQR, interquartile range; SD, standard deviation.

Table 3. Associated factors for cognitive impairment in diabetic patients

Variable	Unadjusted		Model 1		Model 2	
	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value
Age, years	1.025 (0.989–1.062)	0.172	1.019 (0.976–1.064)	0.397	1.019 (0.975–1.066)	0.404
Gender, male	0.502 (0.204–1.237)	0.134	0.568 (0.189–1.708)	0.314	0.478 (0.157–1.457)	0.194
12-year education	0.610 (0.284–1.313)	0.207	0.715 (0.313–1.630)	0.425	0.671 (0.293–1.540)	0.347
BMI, kg/m ²	0.934 (0.825–1.058)	0.282	0.899 (0.767–1.053)	0.187	0.874 (0.743–1.028)	0.105
Smoking	0.860 (0.401–1.846)	0.699	1.027 (0.412–2.557)	0.955	0.958 (0.382–2.400)	0.927
CVD	2.121 (0.962–4.676)	0.062	2.810 (1.111–7.107)	0.029	2.926 (1.139–7.516)	0.026
MAP, mm Hg	1.007 (0.980–1.035)	0.594	1.021 (0.990–1.053)	0.194	1.025 (0.993–1.059)	0.128
Serum Cr, μmol/L	0.999 (0.998–1.000)	0.182	1.000 (0.999–1.002)	0.800	1.000 (0.999–1.002)	0.787
Total cholesterol, mmol/L	1.314 (0.951–1.816)	0.098	1.274 (0.890–1.823)	0.185	1.354 (0.945–1.939)	0.098
Glucose, mmol/L	1.144 (1.006–1.301)	0.040	1.122 (0.974–1.293)	0.111	–	–
HbA1c, %	1.397 (0.981–1.991)	0.064	–	–	1.547 (1.013–2.362)	0.043

OR, odds ratio; 95% CI, 95% confidence interval; CVD, cardiovascular disease; MAP, mean arterial pressure; HbA1c, glycated hemoglobin.

between the 2 groups in age, gender, and MAP. They had comparable education level, mGFR, hsCRP, Kt/V, hemoglobin, serum phosphate, serum sodium, BUN, uric acid, total cholesterol, and triglyceride levels. 455 patients after matching had a mean (±SD) age of 58.8 ± 10.8 years and 66.6% (*n* = 303) were male. The median duration of PD was 29.1 (IQR 6.5–54.2) months. Among them, 91.9% had a history of hypertension and 35.4% had a history of CVD. The mean (±SD) age of the diabetic patients was 60.0 ± 10.6 years and 68.6% (*n* = 120) were male (Table 1).

DM and Cognitive Impairment

The prevalence of CI was 72.7% (*n* = 331) in the matched population, and the mean (±SD) MoCA score was 22.0 ± 4.7 points. The patients with DM had a sig-

nificantly higher prevalence of CI (80.6%) than those without (67.9%). Furthermore, they had significantly lower scores for visuospatial/executive function (3.10 ± 1.34 vs. 3.71 ± 1.25 points), naming (2.24 ± 0.95 vs. 2.48 ± 0.78 points), language (1.77 ± 0.86 vs. 1.99 ± 0.81 points), delayed recall (2.03 ± 1.74 vs. 2.59 ± 1.73 points), and orientation (5.57 ± 0.89 vs. 5.83 ± 0.52 points) (Table 2). The association between DM and CI was significant by univariate logistic analysis (OR, 1.964; 95% CI, 1.252–3.083). After adjusting for confounders, DM was associated with a 1.677-fold higher risk of CI (online suppl. Table 1). No clear correlation was found between the hemoglobin level and the MoCA score (online suppl. Fig. 2).

Fig. 2. Kaplan-Meier estimates of survival for patients with CI and without CI in the DM (**A**) and non-DM (**B**) groups. CI, cognitive impairment; DM, diabetes mellitus.

Factors Associated with Cognitive Impairment in Diabetic Patients Undergoing PD

Compared with diabetic PD patients without CI, those with CI had a lower level of education, and more of them need assisted PD (online suppl. Table 2). To analyze the risk factors related to CI in diabetic patients, variables that were considered clinically relevant to CI or with a p value <0.1 in univariate tests were included in the multivariate model. In the multivariable regression analysis, the factors age, gender, education, BMI, history of smoking, CVD, MAP, total cholesterol, serum Cr, and glucose were included, and a history of CVD (OR, 2.810; 95% CI, 1.111–7.107) was associated with CI. In model 2, all the factors in model 1 plus HbA1c were included, and a history of CVD (OR, 2.926; 95% CI, 1.139–7.516) and high HbA1c (OR, 1.547; 95% CI, 1.013–2.362) were independently associated with a risk of CI (Table 3).

Patient Outcomes

By the end of the study, 73 (51.8%) diabetic patients with CI remained on PD, 45 (31.9%) died, 20 (14.2%) were transferred to HD, 2 (1.4%) received kidney transplantation, and 1 (0.7%) withdrew from PD for other reasons. While in diabetic patients without CI, 19 (55.9%) remained on PD, 2 (5.9%) died, 8 (23.5%) were transferred to HD, and 5 (14.7%) received kidney transplanta-

tion (online suppl. Table 3). During a median of 26.0 months (IQR 13.5–35.6 months) of follow-up period, 47 (26.9%) diabetic patients died. Of these deaths, 28 (59.6%) were caused by CVD, 8 (17.0%) by infection, 3 (6.4%) by malignancy, 3 (6.4%) by cachexia, 2 (4.3%) by other factors, and 3 (6.4%) by an unknown reason. Except for 1 death caused by CVD and 1 by infection, the other 45 patients had CI. The Kaplan-Meier estimates of survival curves for patients with and without CI are shown in Figure 2. The log-rank test revealed that diabetic patients with CI had a lower rate of survival than those without CI ($\chi^2 = 6.45$, $p = 0.011$) (Fig. 2A). In the univariate Cox regression analyses, CI, advanced age, history of CVD, a longer duration of dialysis, lower mGFR, hemoglobin, HDL-C, and low-density lipoprotein cholesterol were significantly associated with all-cause mortality. And CI was an independent risk factor for mortality in diabetic patients after adjustment for age, CVD, dialysis vintage, and mGFR (HR, 7.224; 95% CI, 1.694–30.806) (Table 4). Whereas in nondiabetic patients, CVD (HR, 1.915; 95% CI, 1.093–3.356), instead of CI, was a significant risk factor for mortality after adjustment.

During the follow-up period, 61 episodes of peritonitis were observed in 40 diabetic PD patients (0.17 episodes per patient-year). The Poisson analysis showed that these DM patients with CI had a significantly lower incidence

Table 4. Associations between cognitive impairment and mortality in diabetic patients by Cox regression analysis

Variable	Univariate model		Multivariate model	
	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value
Age, years	1.075 (1.040–1.111)	<0.001	1.079 (1.042–1.117)	<0.001
Smoking	0.869 (0.482–1.567)	0.641	–	–
CVD	1.944 (1.084–3.487)	0.026	1.160 (0.623–2.159)	0.640
Cerebrovascular disease	1.341 (0.695–2.586)	0.382	–	–
Dialysis vintage, month	1.017 (1.008–1.026)	<0.001	1.018 (1.004–1.031)	0.010
Assisted PD	1.609 (0.908–2.854)	0.104	–	–
mGFR, ml/min/1.73 m ²	0.816 (0.691–0.964)	0.017	0.872 (0.706–1.075)	0.200
Hemoglobin, g/L	0.986 (0.974–0.999)	0.033	–	–
iPTH, pg/mL	1.001 (1.000–1.001)	0.051	–	–
HDL-C, mmol/L	0.221 (0.075–0.651)	0.006	–	–
LDL-C, mmol/L	0.628 (0.434–0.909)	0.014	–	–
Cognitive impairment	5.185 (1.256–21.399)	0.023	7.224 (1.694–30.806)	0.008

HR, hazard ratio; 95% CI, 95% confidence interval; CVD, cardiovascular disease; PD, peritoneal dialysis; mGFR, measured glomerular filtration rate; iPTH, intact parathyroid hormone; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MoCA, Montreal Cognitive Assessment.

of peritonitis (0.14 vs. 0.29 episodes per patient-year) than patients without CI. Compared to the diabetic PD patients without CI, those with CI had a much higher proportion of assisted PD (44.7 vs. 17.6%, $p < 0.05$), although they were at a similar age. But this effect was not observed in non-DM patients. The patients with CI had a higher risk of peritonitis than those without CI (0.20 vs. 0.09 episodes per patient-year). During the follow-up period, 28 (16.0%) diabetic patients were transferred to HD. There was no significant difference between the 2 groups with regard to technique survival.

Discussion

In the present study, we found the prevalence of CI to be 72.7% in the matched PD population, and this rate was up to 80.6% in diabetic patients. A significant association was found between DM and CI. The HbA1c level and CVD were independently associated with a risk of CI, and CI was an independent risk factor for mortality in diabetic patients undergoing PD. CI was also associated with a higher rate of peritonitis in nondiabetic patients but not in the diabetic population.

The prevalence of CI ranged from 17 to 62% in CKD patients reported by previous studies [1–3], and this rate reached as high as 87% in populations undergoing dialysis [4–6]. This discrepancy was probably due to differences in demographic characteristics, recruitment criteria,

or the assessment methods used for CI. However, few studies have assessed CI in diabetic PD populations. In the present study, 72.7% of PD patients were identified as CI, and we found that the prevalence was 80.6% in diabetic patients. Although they had a higher prevalence of CVD than nondiabetic patients, which are risk factors for CI, the 2 groups were balanced in age, gender, MAP, education level, and hsCRP level after propensity score matching. The association between DM and CI remained significant after adjustment. Of the few studies in diabetic patients with CKD, Liao et al. [22] demonstrated that 35% of patients undergoing PD had CI, but the cognitive function was comparable between diabetic patients without retinopathy and nondiabetic patients. Another cohort study showed that 48% of diabetic patients with CKD stage 3 or 4 had neurocognitive disorders [23]. In the general population with DM, a longitudinal cohort study conducted in northern Manhattan reported that 42.5% of diabetic patients had incident CI [15]. Roberts et al. [16] found that 21.4% of patients with type 2 diabetes developed CI, despite the old age. There is a study that has found an interaction between diabetes and renal dysfunction in their effects on cognitive performance. Individuals with both diabetes and renal dysfunction are 4.23 times more likely to have CI than those with neither condition [24]. The potential explanation for this is that several mechanisms involved in CI also play roles in both diabetes and CKD, such as vascular disease, inflammation, and oxidative stress [25, 26]. Thus, the concurrence

of diabetes and impaired renal function considerably increases the risk of CI.

Univariate and multivariate analyses of the present data have demonstrated that high HbA1c and a high prevalence of CVD are associated with a risk of CI in diabetic patients, suggesting that poor glycemic control and vascular dysfunction contribute to these cognitive deficits. The relationship between HbA1c and cognitive function in diabetes has been well established. However, whether these associations exist in patients undergoing PD has rarely been explored. Seidel et al. [27] found that HbA1c was a risk factor for CI in CKD (including dialysis) patients, of whom 38.5% had diabetes. A large volume of the literature manifests that glycemia, especially HbA1c concentration, correlates with cognitive function in diabetes [28]. Both high and low glucose concentrations (including random and fasting blood glucose, and glycated hemoglobin) are associated with a higher risk of dementia, even among people without diabetes [29, 30]. Glucose abnormalities might cause cerebrovascular disease, which is thought to be an important pathogenesis involved in cognitive decline [26]. In the present study, diabetic patients with CI did not show a higher prevalence of cerebrovascular disease than those without CI. Instead, CVD was an independent risk factor for CI in diabetic patients. It is well known that vascular risk factors are important for the development of cognitive impairment in the general population [31, 32]. Unfortunately, explorations regarding these factors and CI in patients with CKD or diabetes are scarce, and evidence is inconsistent. A cross-sectional study of HD patients showed that CVD is associated with poorer executive function [33]. And the role of vascular factors in CI among diabetic patients has been demonstrated by limited research [34, 35]. In view of the high burden of traditional cardiovascular risk factors in CKD and diabetic patients, these factors might also predispose diabetic CKD patients to CI. However, since targeting cardiovascular factors does not show a positive effect, uremic neurotoxins interacting with the nervous system are considered to be more important in CKD-associated CI [9, 32]. Unexpectedly, age was not found to be a risk factor for CI in patients undergoing PD in the present study, unlike in previous studies. Since CI is an age-related comorbidity in the general population, commonly, old age of diabetic subjects may eliminate the difference.

There have been few investigations of clinical outcomes in PD patients relating to CI. Griva et al. [5] found a prevalence of CI in dialysis patients at baseline of 67.6% and a 2.5-fold higher risk of mortality 7 years later. In ad-

dition, Drew et al. [36] demonstrated that poor memory and executive function increase the risk of mortality in HD patients. These associations between CI and increased mortality have also been shown in other clinical populations and community cohorts [37, 38]. Research conducted in patients with ESRD found dementia to be significantly associated with adverse clinical outcomes [39]. The Dialysis Outcomes and Practice Patterns Study (DOPPS) revealed that dementia is associated with a nearly 1.5-fold increased risk of death in HD patients [7]. But the relationship between mild CI and mortality was not evaluated. The present data indicated that diabetic patients with CI had a lower survival rate, which is consistent with the results of previous studies. Moreover, CI represented as an independent risk factor for mortality, rather than CVD, in patients with DM, suggesting that it might be a more powerful factor than CVD to reflect systemic vascular dysfunction. Indeed, diabetic patients with CI were seven times more likely to die than patients without CI. Therefore, CI may represent a strong predictor of mortality in diabetic patients undergoing PD, but further studies will be required to confirm these associations. In nondiabetic patients, however, CVD was still the predominant factor for patient survival, since the prevalence of CI was relatively lower in this population.

Another interesting finding was that diabetic patients without CI had a significantly higher incidence of peritonitis than patients with CI. There are several possible explanations for this finding. First, more of these patients performed their own PD, rather than underwent assisted PD. For older people who have difficulty in peritoneal exchange due to physical disabilities or psychosocial problems, assisted PD is an alternative choice. CI was reported to be associated with PD assistance in patients older than 50 years [40]. Although patients on assisted PD might have shorter patient survival and peritonitis-free survival, they were usually older and had more comorbidities [41, 42]. Many studies also showed that PD assistance did not increase peritonitis risk or were associated with a lower risk of peritonitis in the elderly population [42, 43]. In the current cohort, diabetic patients with different cognitive function were of similar age and had a comparable vascular profile and nutritional status. In addition, the caregivers have received standardized training and have been approved by the PD nurses. Due to advanced age and the burden of comorbidities, self-care PD may increase the risk of peritonitis alongside PD-related comorbidities in elderly patients during peritoneal exchanges. Thus, with adequate standardized training, assisted PD could protect diabetic patients from peritonitis.

Second, patients without CI survived longer, meaning that it was possible for more episodes of peritonitis to occur. Third, because of the small sample size of patients without CI, the possibility of sampling bias cannot be excluded. Accordingly, patients with CI did not show a worse technique survival rate much likely due to the lower rate of peritonitis.

The present study had several limitations. First, as a single-center study, the small sample size and single ethnicity may limit its generalizability. Second, because less healthy patients and patients with severe CI were less likely to participate, the prevalence of CI was likely to have been underestimated. Third, only the MoCA was applied for cognitive assessment in the current study. This is a short screening instrument that cannot evaluate the cognitive function as thoroughly as comprehensive neuropsychological test batteries. Magnetic resonance imaging is also recommended to identify silent brain infarcts, microbleeds, and white matter disease. Another possible limitation is that DM-related confounders, such as medication and dialysate components, were not included due to incomplete data, which might have affected the impact of DM on CI.

In summary, we have found that the prevalence of CI is 72.7% in an age-, gender-, and MAP-matched CAPD population and 80.6% if these patients have DM. The association between DM and CI might at least in part be explained by high HbA1c and a higher risk of CVD, which provides a possible link with CKD-related CI. Diabetic patients with CI had a higher incidence of adverse outcomes. Moreover, CI, rather than CVD, was an independent risk factor for mortality in diabetic patients undergoing PD. For the fact that the underlying mechanisms and potential therapeutic targets for cognitive dysfunction are far from fully understood, the multitude of confounding factors connecting kidney and brain pathologies make the identification of associations difficult. Therefore, a large-scale longitudinal study to explore the causes and outcomes of CI should be performed in patients undergoing PD to determine the prognostic significance of these risk factors.

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Statement of Ethics

All the subjects have given their written informed consent, and the study protocol was approved by the Human Ethics Committee of Sun Yat-sen University on human research (reference number [2016] 215).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All authors have contributed significantly and in keeping with the latest guidelines of the International Committee of Medical Journal Editors. Xiao Yang, Xuan Huang, and Chunyan Yi conceived and designed the study. Chunyan Yi, Yagui Qiu, Xiao Xi, and Jianxiong Lin prepared and performed data collection. Xuan Huang, Meiju Wu, and Haishan Wu analyzed the data. Xuan Huang and Chunyan Yi interpreted the results and drafted the manuscript. Xiao Yang, Hongjian Ye, and Yuan Peng revised the manuscript. Xueqing Yu and Xiao Yang coordinated the study and finally approved the version to be published.

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