The impact of the combination of kidney and physical function on cognitive decline over 2 years in older adults with pre-dialysis chronic kidney disease

Original Article

The impact of the combination of kidney and physical function on cognitive decline over 2 years in older adults with pre-dialysis chronic kidney disease

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Concise Title: Kidney and physical function for cognitive decline

Abstract

Background: No longitudinal study has investigated the impact of combination of kidney function (KF) and physical function (PF) on cognitive decline in these patients.

Methods: We conducted a 2-year prospective cohort study enrolling 131 patients ≥65 years with pre-dialysis chronic kidney disease (CKD). We assessed cognitive function with the Japanese version of the Montreal Cognitive Assessment (MoCA-J). We calculated %MoCA-J based on the rate of change between baseline and follow-up MoCA-J scores and defined cognitive decline over 2-years as a %MoCA-J of less than the first quartile value. We defined eGFR ≥ 30 as mild-to-moderate and eGFR < 30 mL/min per 1.73 m^2 as severe. And low PF was defined as low handgrip strength (< 26 for men and < 18 kgf for women) and/or low gait speed (< 0.8 m/s). Patients were classified into 4 groups: group 1, patients with mild-to-moderate impairment in KF and high PF; group 2, with mild-to-moderate impairment in KF and low PF; group 3, with severe impairment in KF and high PF; and group 4, with severe impairment in KF and low PF.

Results: Eighty-four patients completed follow-up assessment. Multivariate logistic regression analysis showed that the combination of severe impairment in KF and low PF was significantly associated with cognitive decline (odds ratio, 5.73). However, no significant cognitive decline was observed in patients with either severe impairment in KF or low PF alone.

Conclusions: We may need to focus on maintaining PF in older patients with advanced CKD may help prevent cognitive decline.

Key Words chronic kidney disease (CKD), cognitive decline, kidney function, physical function

Introduction

The number of chronic kidney disease (CKD) patients has increased. Approximately 13.3 million Japanese have CKD [1]. The prevalence of CKD increases with age [2], and it is present in more than 20% of the older Japanese population [1]. Thus, we believe it is necessary to pay attention to older adults with CKD.

Although end-stage kidney disease patients receiving dialysis are well known to have significant risk factors for various comorbidities, pre-dialysis CKD is also a risk factor for comorbidities such as cardiovascular disease and heart failure, which can lead to greater mortality [3] and a decline in physical function [4, 5]. More recently, pre-dialysis CKD has been identified as a risk factor for declining cognitive function and dementia, even in moderate stages of CKD [6, 7]. Since poor cognitive function may have been linked to poor health literacy and poor adherence to medical treatment [8] and CKD-related cognitive impairment may affect the choice of the dialysis modalities [9]. Therefore, this problem warrants significant attention.

There are several factors associated with cognitive impairment in patients with CKD. First, kidney function itself is reported to be associated with cognitive function. Kidney impairment was independently associated with new cognitive impairment [10] and onset of dementia [6]. Furthermore, in meta-analysis, kidney impairment is independent factor for cognitive decline [7]. Second, decreased physical function has also been identified as a risk factor for cognitive impairment. For example, slow gait speed, one of the markers of physical function, is a risk factor for cognitive decline in community-dwelling older adults [11]. We also reported that physical function was associated with cognitive impairment in older adults with pre-dialysis CKD in a cross-sectional study [12]. Because physical function and kidney function were reported to be interrelated in patients with pre-dialysis CKD [13], both these two factors should be investigated together to determine their effect on declining cognitive function. However, the utility of combining these factors has not been investigated in a longitudinal manner.

The purpose of our study was to examine the impact of both kidney and physical function on longitudinal cognitive decline in older adults with pre-dialysis CKD.

Materials and Methods

Study Design and Patient Population

In this 2-year prospective cohort study, we enrolled 131 consecutive patients aged ≥ 65 years with pre-dialysis CKD treated on an outpatient basis in our Nephrology and Hypertension Clinic in the Department of Medicine, St. Marianna University School of Medicine Hospital, from July 2014 to October 2015. Patients with pre-dialysis CKD were defined as those with stage 3-5 CKD who were not yet receiving dialysis. CKD stages 3, 4 and 5 included patients with an estimated glomerular

filtration rate (eGFR) between 30 and 59, 15 and 29, and <15 mL/min/1.73m^2, respectively [14]. The eGFR was calculated from the equation devised for Japanese subjects [15]. The exclusion criteria were as follows: patients diagnosed with dementia, neurological or orthopedic disease, significant peripheral arterial disease of Fontaine stage II or more, those requiring gait assistance, and those refusing to provide consent.

Demographic and Clinical Characteristics

We investigated demographic and clinical characteristics at baseline by review of medical records. These included age, sex, body mass index (BMI), smoking and alcohol consumption (categorized as never, past use, or current use), living status (alone or otherwise), primary kidney disease, and history of diabetes mellitus, hypertension and cardiovascular disease, and habitual use of sleeping drugs. Primary kidney disease was diagnosed by nephrologists as nephrosclerosis, diabetic nephropathy, chronic glomerulonephritis, others, or unknown. Comorbidities was diagnosed by a nephrologist or other medical doctor. Hemoglobin, serum albumin, eGFR, and proteinuria (categorized as < 0.15 g/gCr, 0.15–0.49 g/gCr, or ≥ 0.50 g/gCr) [16] were also investigated. We defined eGFR ≥ 30 mL/min/1.73 m^2 as mild to moderate impairment in kidney function and eGFR < 30 mL/min/1.73 m^2 as severe impairment in kidney function in this study. Education level was categorized as ≤ 12 years and > 12 years.

Physical Function and ADL

Physical function was assessed at baseline by measurement of handgrip strength and gait speed. Handgrip strength was measured using the Jamar Digital Hand Dynamometer (Sammons Preston, Inc., Bolingbrook, IL, USA), set at the second grip position for all patients [17]. Two measurements were obtained for each hand, with the highest value (kgf) used in the analysis. To determine gait speed, patients performed two 4-m gait trials at their usual pace on a flat surface [18]. Gait speed was calculated as the time taken (s) to complete the 4-m distance (m/s), with highest speed from the two trials used in the analysis. Low physical function was defined as low handgrip strength (< 26 kgf for men and < 18 kgf for women) and/or low gait speed (< 0.8 m/s), and values above these were defined as high physical function [19].

Activities of daily living (ADL) were assessed at baseline using the Barthel Index. The Barthel index is a widely used measure of function disability in ADL, i.e., feeding, chair transfer, grooming, toileting, bathing, mobility, stair climbing, dressing, and bowel and bladder control [20].

Classification of patients

Patients were classified into four groups according to various combinations of kidney function and physical function values using the definitions previously mentioned: group 1, patients with mild to moderate impairment in kidney function and high physical function; group 2, with mild to moderate impairment in kidney function and low physical function; group

3, with severe impairment in kidney function and high physical function; and group 4, with severe impairment in kidney function and low physical function.

Cognitive Function

Cognitive function was assessed at baseline and at follow-up (2 years later) using the Japanese version of the Montreal Cognitive Assessment (MoCA-J) [21]. The MoCA-J is a brief screening tool for mild cognitive impairment that considers multiple cognitive domains: attention, concentration, executive function, memory, language, visuospatial, conceptual thinking, calculations, and orientation [21,22]. To correct for education effects, we added 1 point for patients with an education level of ≤ 12 years [21]. The rate of change between the baseline and follow-up MoCA-J scores (%MoCA-J) was calculated as follows: (MoCA-J score at follow-up / MoCA-J score at baseline) × 100.

Incidentally, the minimal detectable change in MoCA-J has not been reported because the MoCA-J is a relatively new assessment. A previous study defined cognitive decline as a change in the score in the lowest quartile [23]. Therefore, we defined a %MoCA-J value in the lowest quartile (a %MoCA-J of < 92% in this study) as cognitive decline over the 2-year follow-up period.

Statistical Analysis

One-way analysis of variance, Kruskal-Wallis test, and chi-squared test were used to examine the differences among the four groups as appropriate. We used multivariate logistic regression analysis to examine the effect of a combination of kidney function and physical function on cognitive decline during the 2-year follow-up period. In the logistic regression analysis, the four patient groups were used as the independent variables (reference, group 1), and the presence/absence of cognitive decline was used as the dependent variable. To adjust for confounding factors in the logistic regression model, we included variables as covariates with a P value < 0.05 in univariate analysis. A P-value < 0.05 was considered to be statistically significant. All statistical analyses were performed using IBM SPSS 20.0 J statistical software (IBM SPSS Japan. Inc., Tokyo, Japan).

Results

Of the original 131 patients enrolled, 84 patients completed the 2-year follow-up assessment. The other 47 patients were excluded for the reason shown in Fig. 1. There was no significant difference in basic demographic and clinical characteristics between patients completed assessment and excluded.

The characteristics of the patients are shown in Table 1. The overall mean age of the patients was 77.3±6.8 years, of whom 62 (73.8%) were men, and the mean eGFR was 31.1±11.6 mL/min per 1.73 m^2). In this study, 34 patients were

classified in group 1 (mild to moderate impairment in kidney function and high physical function), 11 in group 2 (mild to moderate impairment in kidney function and low physical function), 24 in group 3 (severe impairment in kidney function and high physical function), and 15 patients in group 4 (severe impairment in kidney function and low physical function). Significant differences other than eGFR and physical function observed between the four groups were patient age ($p < 0.01$), hemoglobin level ($p < 0.01$), proteinuria ($p < 0.01$), and MoCA-J score at baseline ($p = 0.04$) and at follow-up ($p = 0.02$).

The results of the logistic regression analysis for cognitive decline in the four patient groups over the 2-year follow-up period are shown in Table 2. In the crude model, group 4 was significantly associated with cognitive decline ($p = 0.009$), with an odds ratio of 5.79 and 95% confidence interval of 1.54–21.79. After adjustment for covariates (patient's age, hemoglobin level, proteinuria, and MoCA-J score at baseline) in the adjusted model, as in the crude model, group 4 was still significantly associated with cognitive decline ($p = 0.049$), with an odds ratio of 5.73 and 95% confidence interval of 1.01–32.52.

Discussion

To our knowledge, this is the first study to show the effect of the combination of kidney function and physical function on subsequent cognitive decline during a 2-year follow-up period among older adults with pre-dialysis CKD. The results showed that there was no significant cognitive decline in those patients with either severe impairment in kidney or low physical function alone. However, there was significant cognitive decline in those patients with both severe impairment in kidney function and low physical function.

In this study, cognitive function declined in 29.8% of the patients over the 2-year follow-up period. We defined decline of cognition if their %MoCA-J value was in the lowest quartile, which was less than 92% in the present study (indicating a decline of 8% or more from baseline).

To our knowledge, the significance of a minimal detectable change in %MoCA-J is not clear. Even a slight decline in cognitive function might be defined as cognitive deterioration, but such definition may not be appropriate because it would mean that a decline by even only 1 point would be defined as cognitive deterioration, although this might be a change by chance. However, the definition of cognitive decline in this study was reasonable because it is possible to exclude changes by chance.

Kidney function has been reported to be one of the risk factors of cognitive decline in CKD patients. More advanced stages of CKD were associated with an increased risk for longitudinal cognitive decline [10, 24]. It is thought that various factors caused by impairment in kidney function such as anemia, cerebrovascular injury, uremic toxin, and oxidative stress may be involved in the pathogenesis [25,26]. However, in the present study, it is very intriguing that even patients with severe impaired of kidney function did not suffer from significant cognitive decline if their physical function was high. In

other words, the results suggested that even in patients with severe CKD, maintaining high physical function may prevent cognitive decline.

By contrast, cognitive function declined in the patients with both severe kidney dysfunction and low physical function. This association remained significant even after adjusting for covariates such as age, hemoglobin, proteinuria, and cognitive function at baseline, which are known to affect cognitive decline [27, 28]. Thus, although either of impairment in kidney function kidney function or low physical function is an individual risk factor for cognitive decline, when both factors are combined, the risk of cognitive decline increases much more significantly.

Low physical function causes physical inactivity, which may have an effect on cognitive decline. Low grip strength and slower gait speed are indicative of frailty and can lead to decreased physical activity based on the "Cycle of Frailty" [29]. There are several reasons why low physical activity and cognitive function are related. First, physical inactivity causes decreases in brain-derived neurotrophic factor (BDNF). BDNF is a nerve growth factor and is involved in the control of neuronal differentiation, cell survival, and synapse formation [30, 31]. Physical activity is associated with the serum BDNF level [32]. We surmise that low physical activity causes a low serum BDNF level that results in cognitive decline. Second, there is an association between physical activity and vascular endothelial function. Endothelial dysfunction can lead to the development of atherosclerosis [33]. As a result, endothelial function might be involved in the pathogenesis of silent lacunar infarcts and ischemic white matter lesions, which are risk factors for dementia and cognitive impairment [34, 35]. Low physical function has been reported to be related to endothelial dysfunction [36]. In this way, we consider that low physical function leads to physical inactivity, which caused a negative mechanism in the body that may result in cognitive decline. However, as a limitation of the present study, we did not investigate physical activity, BDNF level, and endothelial function and therefore cannot prove these hypotheses.

This study has some other important limitations. First, the follow-up period for cognitive decline of 2 years is relatively short. Second, we only used the MoCA-J to assess cognitive decline, which provides an assessment of global cognition and not several cognitive domains, and we did not evaluate brain images and psychological factors such as depression. Third, we defined cognitive decline as a change in the score in the lowest quartile based on a previous study [23]. However, this is not an established definition. Therefore, we may have overestimated the number of patients in whom cognitive function declined. Finally, 31% of the patients dropped out of this study. Many of the dropouts were due to death or the induction of dialysis. Therefore, it is possible that cognitive decline had also occurred in the patients who dropped out, but this is unknown. The dropout rate was especially high in the patients in group 2 (mild to moderate impaired kidney function and low physical function). In a previous study on community-dwelling older adults, only low physical function was risk factor for cognitive decline [37, 38]. This result is different from that of our study. We surmise that the results in those studies may have been affected by many dropouts, small sample size, and inadequate statistical power.

In conclusion, among older adults with pre-dialysis CKD, those with both impairment in kidney function and low physical function had more significant subsequent decline in cognitive function than those with impairment in kidney or low physical function alone during a 2-year follow-up period. Even in patients with a severe impairment in kidney function, no significant impact on cognitive decline was observed if their physical function remained high, suggesting that maintaining high physical function in older adults with advanced CKD may help prevent cognitive decline.

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Compliance with ethical standards

Conflict of interest

All authors have no conflicts of interest to disclose.

Ethical approval

All procedures performed in studies involving human participants were in accordance with ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study protocol was reviewed and approved by the Institutional Committee on Human Research of St. Marianna University School of Medicine (IRB approval No. 2691).

Informed consent

Informed consent was obtained from all individual participants included in this study.

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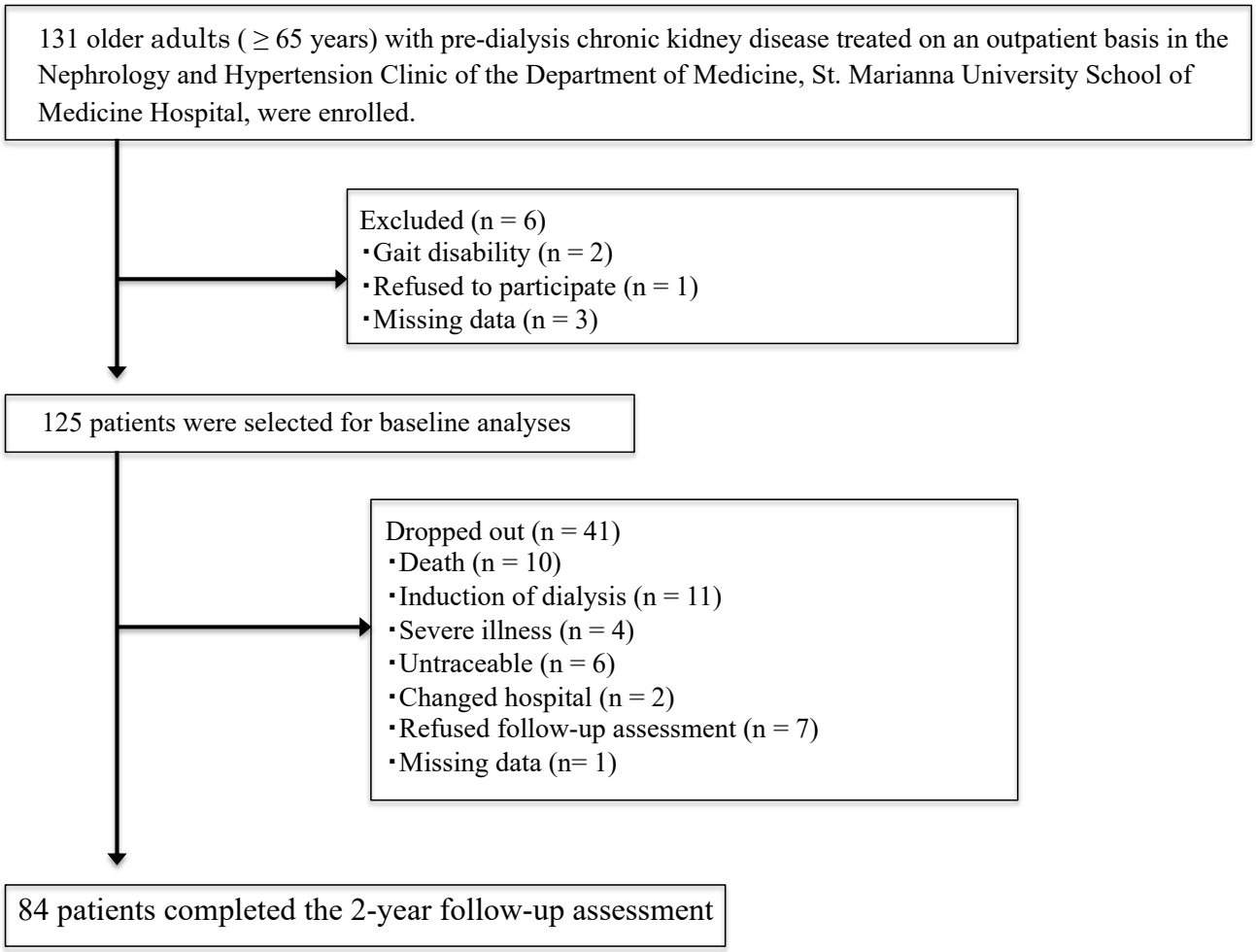

Fig. 1. Diagram of the patient selection process.

Table 1. Patient characteristics

	Overall (n=84)	Group 1 (n=34)	Group 2 (n=11)	Group 3 (n=24)	Group 4 (n=15)	*P* value
Age, mean ± SD	77.3±6.8	75.9±4.8	83.3±7.4	74.7±6.9	80.7±7.1	< 0.01
Gender, male, n (%)	62 (73.8)	27 (79.4)	7 (63.6)	18 (75.0)	10 (66.7)	0.67
BMI, [kg/m^2], median (IQR)	23.6 (21.7–25.3)	23.7 (22.7–25.4)	22.1 (19.1–24.1)	23.7 (21.1–25.5)	23.0 (21.5–25.2)	0.21
Smoking, n (%)	64 (76.2)	27 (79.4)	6 (54.5)	21 (87.5)	10 (66.7)	0.14
Drinking, n (%)	40 (47.6)	17 (50.0)	4 (36.4)	12 (50.0)	7 (46.6)	0.87
Living alone, n (%)	12 (14.3)	5 (14.7)	2 (18.2)	3 (12.5)	2 (13.3)	0.97
Primary kidney disease						0.50
Nephrosclerosis, n (%)	35 (41.6)	16 (47.1)	6 (54.5)	9 (37.5)	4 (26.7)	
Diabetic nephropathy, n (%)	18 (21.4)	5 (14.7)	0 (0)	8 (33.3)	5 (33.3)	
Chronic glomerulonephritis, n (%)	6 (7.2)	2 (5.9)	1 (9.1)	2 (8.3)	1 (6.7)	
Others or unknown, n (%)	25 (29.8)	11 (32.3)	4 (36.4)	5 (20.9)	5 (33.3)	
Hemoglobin [g/dL], mean ± SD	12.2±1.6	13.2±1.7	11.3±1.0	11.7±1.2	11.4±1.4	< 0.01
Albumin [g/dL], mean ± SD	4.1±0.3	4.2±0.3	4.0±0.3	4.0±0.3	4.1±0.2	0.21
eGFR [mL/min/1.73 m^2], mean ± SD	31.1±11.6	39.8±6.5	41.6±8.7	21.6±5.6	19.1±3.7	< 0.01
Proteinuria [g/gCr], n (%)						< 0.01
< 0.15	22 (26.2)	15 (44.1)	4 (36.4)	3 (12.5)	0 (0)	
0.15–0.49	22 (26.2)	10 (29.4)	4 (36.4)	3 (12.5)	5 (33.3)	
≥ 0.50	40 (47.6)	9 (26.5)	3 (27.2)	18 (75.0)	10 (66.7)	
Comorbidity						
Diabetes, n (%)	29 (34.5)	11 (32.4)	3 (27.3)	10 (41.7)	5 (33.3)	0.83
Hypertension, n (%)	76 (90.5)	30 (88.2)	11 (100)	22 (91.7)	13 (86.7)	0.15
CVD, n (%)	23 (23.8)	6 (17.6)	2 (18.2)	10 (41.7)	5 (33.3)	0.19
Sleeping Drug, n (%)	20 (23.8)	8 (23.5)	3 (27.3)	4 (16.7)	5 (33.3)	0.68
Education level						0.47
≤12 years, n (%)	48 (57.1)	18 (52.9)	7 (63.6)	12 (50.0)	11 (73.3)	

>12 years, n (%)	36 (42.9)	16 (47.1)	4 (36.4)	12 (50.0)	4 (26.7)	
MoCA-J at baseline [points], median (IQR)	25.0 (23.0–26.0)	25.5 (23.0–26.0)	24.0 (21.0–25.0)	25.0 (24.0–27.0)	23.0 (22.0–26.0)	0.04
MoCA-J at follow-up [points], median (IQR)	24.0 (22.0–26.0)	25.0 (23.0–26.0)	24.0 (20.0–24.0)	24.5 (20.5–27.0)	22.0 (20.0–25.0)	0.02
%MoCA-J [%], median (IQR)	96 (92.0–104)	100 (95.3–104)	100 (95.0–100)	96.0 (89.0–100)	92.0 (86.0–100)	0.12
Handgrip strength [kgf], mean ± SD	27.7±8.8	32.3±7.5	19.3±6.3	30.9±5.7	18.3±5.1	< 0.01
Gait speed [m/sec], mean ± SD	1.1±0.3	1.3±0.2	0.9±0.3	1.2±0.2	0.9±0.2	< 0.01
Barthel Index [points], median (IQR)	100 (100–100)	100 (100–100)	100 (100–100)	100 (100–100)	100 (95–100)	0.15

Group 1 = mild to moderate impairment in kidney function and high physical function group; Group 2 = mild to moderate impairment in kidney function and low physical function group; Group 3 = severe impairment in kidney function and high physical function group; Group 4 = severe impairment in kidney function and low physical function group; SD = standard deviation; IQR = interquartile range; BMI = body mass index; eGFR = estimated glomerular filtration rate; CVD = cardiovascular disease; MoCA-J = Japanese version of the Montreal Cognitive Assessment. %MoCA-J was calculated as follows: (MoCA-J score at follow-up / MoCA-J score at baseline) × 100 (%).

Table 2. Logistic regression models of the impact of the combination of kidney and physical function on cognitive decline over 2 years in older adults with pre-dialysis chronic kidney disease

	N	Frequency, n (%)	Crude			Adjusted Model		
			OR	95% CI	*P* value	OR	95% CI	*P* value
Group 1	34	7 (20.6%)	1	Ref.		1	Ref.	
Group 2	11	2 (18.2%)	0.86	0.15–4.90	0.86	0.56	0.07–4.57	0.58
Group 3	24	7 (29.2%)	1.59	0.47–5.33	0.45	1.85	0.49–8.54	0.43
Group 4	15	9 (60.0%)	5.79	1.54–21.79	0.009	5.73	1.01–32.52	0.049

Adjusted Model is adjusted for age, hemoglobin, proteinuria, and MoCA-J at baseline.

Patients with cognitive decline during the 2-year follow-up were defined by %MoCA-J as being in the lowest quartile of all patients.

Group 1 = mild to moderate impairment in kidney function and high physical function group; Group 2 = mild to moderate impairment in kidney function and low physical function group; Group 3 = severe impairment in kidney function and high physical function group; Group 4 = severe impairment in kidney function and low physical function group; OR = odds ratio; 95% CI = 95% confidence interval.