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ORIGINAL ARTICLE

# Cognitive function and advanced kidney disease: longitudinal trends and impact on decision-making

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## Abstract

**Background:** Cognitive impairment commonly affects renal patients. But little is known about the influence of dialysis modality on cognitive trends or the influence of cognitive impairment on decision-making in renal patients. This study evaluated cognitive trends amongst chronic kidney disease (CKD), haemodialysis (HD) and peritoneal dialysis (PD) patients. The relationship between cognitive impairment and decision-making capacity (DMC) was also assessed.

**Methods:** Patients were recruited from three outpatient clinics. Cognitive function was assessed 4-monthly for up to 2 years, using the Montreal Cognitive Assessment (MoCA) tool. Cognitive trends were assessed using mixed model analysis. DMC was assessed using the Macarthur Competency Assessment tool (MacCAT-T). MacCAT-T scores were compared between patients with cognitive impairment (MoCA <26) and those without.

**Results:** In total, 102 (41 HD, 25 PD and 36 CKD) patients were recruited into the prospective study. After multivariate analysis, the total MoCA scores declined faster in dialysis compared with CKD patients [coefficient = −0.03, 95% confidence interval (95% CI) = −0.056 to − 0.004; P = 0.025]. The MoCA executive scores declined faster in the HD compared with PD patients (coefficient = −0.12, 95% CI = −0.233 to − 0.007; P = 0.037). DMC was assessed in 10 patients. Those with cognitive impairment had lower MacCAT-T compared with those without [median (interquartile range) 19 (17.9–19.6) versus 17.4 (16.3–18.4); P = 0.049].

**Conclusions:** Cognition declines faster in dialysis patients compared with CKD patients and in HD patients compared with PD patients. Cognitive impairment affects DMC in patients with advanced kidney disease.

**Key words:** chronic kidney disease, cognitive impairment, decision-making capacity, dialysis, executive function

This observational study assessed cognitive trends in patients with advanced kidney disease. It showed that cognitive function declines faster in dialysis patients as compared with chronic kidney disease (CKD) patients, with executive function declining faster in haemodialysis (HD) compared with peritoneal dialysis (PD) patients. Cognitive impairment affects decision-making capacity (DMC) in patients with advanced kidney disease.

## Introduction

Older people are the fastest growing cohort on dialysis. Although cognitive impairment is more common in patients with CKD than in the general population, it remains poorly recognized clinically. The REasons for Geographic and Racial Differences in Stroke (REGARDS) Study, reported an 11% increase in the risk of cognitive impairment for every 10 mL decrease in estimated glomerular

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filtration rate (eGFR) below 60 mL/min/1.73 $m^2$ with a 20% prevalence in those with eGFR <20 mL/min/1.73 $m^2$ [1]. In the HD population, the prevalence of cognitive impairment approached 70% in one cross-sectional study, but only 2.9% of the studied population had a prior clinical diagnosis [2]. Similar prevalence rates have been reported in patients on PD [3]. Executive function has been shown to be the predominant cognitive domain affected. It is often impaired before global cognitive dysfunction becomes apparent [4].

Although cerebrovascular disease is thought to underpin cognitive impairment in patients with advanced kidney disease, a complex interaction between vascular-, nephrogenic- and dialysis-related factors has been proposed as a pathogenetic basis [5]. The potential role for dialysis in cognitive impairment is supported by transient changes in cognition that occur during dialysis [6] and improvements in cognitive deficits after transplantation [7, 8]. Yet, direct comparisons between predialysis and dialysis patients are lacking. The influence of dialysis modality on cognitive function is also unclear. A large retrospective study of 121 623 patients found that those on PD had a lower 5-year cumulative risk of dementia compared with those on HD [9]. Small cross-sectional studies have, however, reported similar cognitive performances in HD and PD patients [10]. Prospective studies that evaluate variation in longitudinal cognitive trends between dialysis modalities are lacking.

Cognitive impairment is associated with adverse outcomes, not least of which includes an impaired capacity to make decisions. Terawaki *et al.*, in a pilot study of 26 patients with CKD 5, evaluated capacity to consent to treatment and cognitive function using the Macarthur Competency Assessment Tool (MacCAT-T) and the MiniMental State Examination (MMSE), respectively. They reported poor performances in the domains of understanding, reasoning and appreciation. In addition to expression of choice, these are recognized as the four domains of DMC. These poor performances were attributed to attentional deficits found after the MMSE [11]. The specific influence of executive dysfunction, commonly affected in renal patients, on DMC has not been evaluated.

This observational study aimed to compare cognitive trends between dialysis and CKD patients and subsequently between HD and PD patients. The relationship between cognitive impairment and DMC was also evaluated.

## Materials and methods

Patients were recruited from three outpatient clinics (one HD, one PD and one CKD) at Imperial College Healthcare NHS trust, between November 2013 and October 2015. Ethical approvals were obtained from the West of Scotland and London – Fulham Research Ethics Committees: reference 13/WS/0241 and 14/LO/2223. All participants gave written informed consent.

### Patient selection and recruitment

The study cohort was obtained based on convenience sampling. It consisted of patients who were enrolled into a prospective cohort study assessing cognitive trends and a small group of patients who participated in a pilot study assessing DMC. For the prospective cohort study, eligible patients were over 55 years of age and free from hospital admission for at least 30 days. Eligible dialysis patients had a vintage of at least 3 months, while CKD patients had an eGFR ≤30 mL/min/1.73 $m^2$. Patients with a life expectancy of <6 months, significant cognitive impairment as well as those unable to understand English, were excluded from the study. The selection criteria were the same for those participating in the decision-making pilot, except for a lower age threshold of over 40 years.

### Study assessment

Study assessments were performed at routine clinic visits in the outpatient department, usually after patients' clinical assessment. For the HD patient, these clinic visits coincided with their midweek dialysis sessions, prior to the start of dialysis. For those enrolled in the prospective cohort study, follow-up assessments were carried out at subsequent clinic visits, every 4 months for up to 2 years.

Demographic and clinical characteristics were collected at baseline, from medical records and during the assessment. Comorbidity burden was evaluated using the Stoke–Davies comorbidity score [12]. This is a validated score that assigns a value of 1 for the presence of each of the following: diabetes mellitus, ischaemic heart disease, peripheral vascular disease, left ventricular dysfunction, malignancy, systemic collagenous vascular disorders and other diagnoses that impact on survival.

'Cognitive function' was assessed using the Montreal Cognitive Assessment (MoCA). It assesses cognitive function in seven domains with scores ranging from 0 to 30. It has advantages over the widely used MMSE. This is because it assesses executive function, a domain that is commonly affected in patients with CKD. It has been shown to be sensitive to changes in cognition in patients on dialysis. A score <26 is suggestive of cognitive impairment, although a cut-off of 24 has been suggested for HD patients [13].

The Patient Health Questionnaire-9 (PHQ-9) was used to evaluate depressive symptoms. It is a 9-item questionnaire that evaluates symptoms of depression over the preceding 2 weeks. Scores range from 0 to 27, with higher scores indicative of more severe depression [14]. A score above 5, 10 and 15 are indicative of mild, moderate and severe depression, respectively.

MacCAT-T was used to evaluate capacity to consent to treatment as a surrogate for decision-making abilities. This semi-structured interview, which is considered to be the gold standard for assessing capacity to consent, was administered by a trained researcher. The interview was based on proposed treatment options discussed at the preceding clinic visit. The four recognized domains of mental capacity (understanding, appreciation, reasoning and expression of choice) were evaluated. The MacCAT-T is not designed to provide a no cut-off score that designates a lack of capacity. Rather, it assists with what is ultimately a clinical judgement.

### Statistical analysis

All analyses were carried out using the SPSS programme (version 22). Continuous variables were expressed as mean and standard errors (SE) for parametric data, and as median and interquartile ranges (IQR) for non-parametric data. Categorical variables were expressed as percentages.

In the prospective cohort study, the baseline cognitive scores were compared between the HD, PD and CKD cohorts, using the Kruskal–Wallis and Fisher's exact tests where appropriate. Generalized linear mixed model (GLMM) analysis was used to evaluate changes in cognitive scores over time. The outcome variables of interest were the MoCA score and the MoCA executive score, respectively. As the cognitive scores followed a skewed distribution, a gamma error structure was used. Multivariable models were used to compare cognitive trends

first between the dialysis and CKD cohorts and subsequently between the HD and PD cohorts.

To evaluate influence of cognitive function on decision-making in patients with advanced kidney disease, the median MacCAT-T scores were compared between patients with cognitive impairment and those without, using the Mann–Whitney test. Patients were deemed to have cognitive impairment if the MoCA score was <26. Spearman's correlation was used to evaluate the relationship between the cognitive domains assessed by MoCA and the four MacCAT-T domains.

## Results

In total, 198 patients were eligible for the prospective cohort study at baseline. A total of 39 patients refused consent (19.6%), 16 moved out of area (8.1%), 9 patients were transplanted (4.5%), 11 patients died prior to enrolment (5.6%) and 1 patient was discharged from clinic (0.5%). In total, 20 patients could not be approached due to lack of regular clinic attendance; 102 patients were eventually recruited; 10 other patients participated in the pilot interviews, assessing cognitive function and the capacity to consent to treatment.

Of the 102 participants, 41 were on HD, 25 on PD and 36 were CKD patients. The median follow-up period was 12 months (interquartile range (IQR) 6–18 months).

### Patient characteristics

Table 1 shows the baseline characteristics for the study cohort. The case mix was similar between study participants and non-participants, in terms of age, gender and ethnicity. The HD cohort had longer dialysis vintage compared with the PD ($P < 0.001$). There was also a trend towards a lower mean age in the HD cohort ($P = 0.068$). The study cohort was predominantly male (70%) and 72.5% of the study cohort had been educated for at least 12 years. There were no significant differences in gender, ethnicity or level of education between HD, CKD and PD participants. For the CKD group, the mean baseline eGFR was $17 \pm 0.9$ mL/min/1.73 m$^2$. The eGFR did not change significantly during follow-up [estimated change in eGFR/year = −1.2 (−6.9 to 4.7); $P = 0.45$].

The prevalence of diabetes and ischaemic heart disease in the cohort was 53% and 46%, respectively. Diabetic nephropathy was the most common cause of renal failure (57%). The comorbidity burden did not differ significantly between HD, PD and CKD participants.

### Baseline study measures

Overall, 60.5% of the study cohort met the criterion for cognitive impairment (MoCA score <26), while 19.6% met the criteria for depression (PHQ-9 >9). Totally, 24% of those with cognitive impairment also met the criteria for depression. There were no significant differences in cognitive or depression scores at baseline, between the HD, PD and CKD cohorts (Table 2).

### Effect of dialysis on cognitive trends

GLMM analysis was used to compare changes in the total MoCA score over time between dialysis and CKD patients. In univariate analysis, age, ethnicity and years of education were significantly associated with the MoCA scores, while comorbidities, dialysis vintage and laboratory parameters were not. After adjusting for these variables, the total MoCA scores declined faster in the dialysis cohort compared with CKD

**Table 1.** Demographic details for study cohort

| Demographic characteristics | HD ($n = 41$) | PD ($n = 25$) | CKD ($n = 36$) | P-value[a] |
|---|---|---|---|---|
| Mean age in years (± SE)[b] | 68.9 ± 1.3 | 72.8 ± 1.6 | 72.5 ± 1.5 | 0.068 |
| Age range (years)[c] (%) | | | | |
| 55–64 | 34.1 | 16.0 | 16.7 | |
| 65–74 | 36.6 | 44.0 | 44.4 | 0.212 |
| 75–84 | 29.3 | 28.0 | 27.8 | |
| >85 | 0.0 | 12.0 | 11.1 | |
| Male gender[c] (%) | 70.7 | 76.0 | 63.9 | 0.587 |
| Ethnicity[c] (%) | | | | |
| White European | 39 | 64 | 33.3 | |
| Afro-Caribbean | 14.6 | 8 | 13.9 | |
| Asian | 43.9 | 24 | 52.8 | 0.216 |
| Other | 2.4 | 4 | 0.0 | |
| Years of education[c] (%) | | | | |
| 0–6 | 5.6 | 0.0 | 5.0 | |
| 6–12 | 33.3 | 0.0 | 30.0 | 0.219 |
| >12 | 61.1 | 100.0 | 65.5 | |
| Months on dialysis [median (IQR)][d] | 35 (15.5–60) | 8 (5–32) | 0 | **<0.001** |
| Cause of renal failure (%)[c] | | | | |
| Diabetic nephropathy | 24.4 | 40.0 | 63.9 | 0.197 |
| Glomerulonephritis | 26.8 | 20.0 | 5.6 | |
| ADPKD | 7.3 | 4.0 | 2.8 | |
| RVD | 2.4 | 12.0 | 5.6 | |
| Tubulointerstitial disease | 7.3 | 8.0 | 2.8 | |
| Unknown | 22.0 | 16.0 | 13.9 | |
| Other | 6.8 | 0.0 | 5.4 | |
| Comorbidities[c] (%) | | | | |
| Diabetes | 46.3 | 44 | 66.7 | 0.120 |
| IHD | 46.3 | 40 | 50 | 0.742 |
| PVD | 17.1 | 32.0 | 22.2 | 0.371 |
| LV dysfunction | 9.8 | 16.0 | 13.9 | 0.737 |
| Malignancy | 7.3 | 8.0 | 2.8 | 0.612 |
| Collagen vascular disorder | 19.5 | 4.0 | 8.3 | 0.121 |
| Stoke comorbidity score [median (IQR)][d] | 2 (1–3) | 1 (1–2) | 2 (1–2) | 0.402 |

ADPKD - Autosomal Dominant Polycystic Kidney Disease; RVD - Renovascular disease; IHD - Ischaemic Heart Disease; PVD - Peripheral Vascular Disease; LV - Left Ventricular

[a]Compares HD, PD and CKD cohorts.

[b]ANOVA.

[c]Fisher's exact test.

[d]Kruskal–Wallis test.

**Table 2.** Baseline outcome measures

| Outcome measures | HD | PD | CKD | P-value |
|---|---|---|---|---|
| MoCA score | 23 (20–27) | 24 (23–27) | 25 (23–27) | 0.774 |
| MoCA <26 (%) | 63.6 | 64.3 | 53.8 | 0.831 |
| MoCA subscales, median (IQR) | | | | |
| Executive function | 4 (3–4) | 3 (3–4) | 4 (2–4) | 0.902 |
| Naming | 3 (2–3) | 3 (2–3) | 3 (2–3) | 0.838 |
| Memory | 3 (1–3) | 2 (1–3) | 3 (2–3) | 0.906 |
| Orientation | 6 | 6 | 6 | 0.653 |
| Attention | 5 (4–6) | 6 (5–6) | 6 (5–6) | 0.397 |
| Language | 3 (2–3) | 3 (2–3) | 3 (3–3) | 0.102 |
| Median PHQ-9 (IQR) | 5.5 (3–9) | 7 (3–10) | 8 (2–10) | 0.275 |
| PHQ-9 ≥10 (%) | 21.1 | 30.4 | 11.1 | 0.182 |

Table 3. GLMM- Dialysis vs CKD

| Outcome variable—total MoCA score dialysis versus CKD ($n = 102$) | | | |
|---|---|---|---|
| Predictors | Coefficient | 95% CI (lower–upper) | P-value |
| Age | −0.005 | −0.008 to − 0.001 | 0.013 |
| Ethnicity | | | |
| White European | 0.168 | −0.061 to 0.397 | 0.145 |
| Afro-Caribbean | 0.014 | −0.266 to 0.255 | 0.905 |
| Asian | 0.168 | −0.132 to 0.328 | 0.396 |
| <12 years of education | −0.027 | −0.102 to 0.048 | 0.496 |
| Time | −0.020 | −0.001 to 0.042 | 0.060 |
| Dialysis versus CKD | −0.009 | −0.080 to 0.063 | 0.808 |
| Dialysis* time | −0.030 | −0.056 to −0.004 | 0.025 |
| CKD* time (reference) | | | – |

CI, confidence interval.

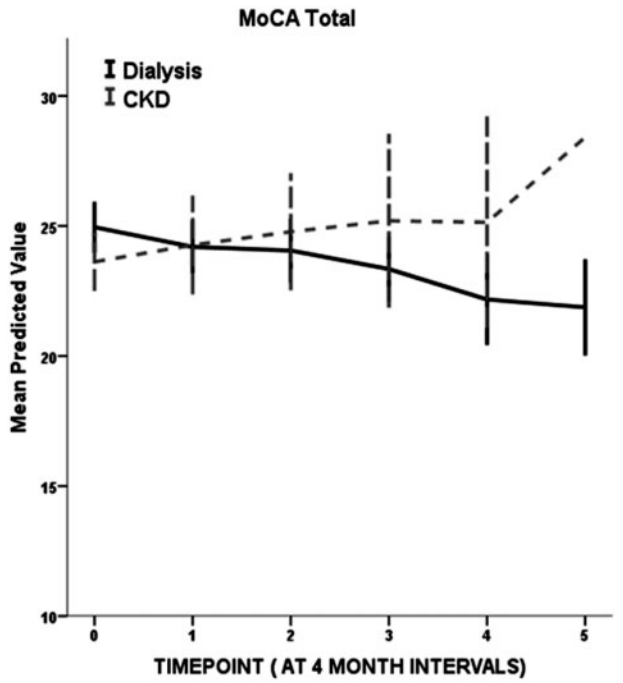


Fig. 1. Longitudinal change in total MoCA scores [dialysis (solid line) versus CKD (dashed line)].

(coefficient = −0.03; P = 0.025; Table 3). Figure 1 shows the profile plot of estimated MoCA scores over time using the model in Table 3. There was no significant difference in the rate of change of the MoCA executive score between the dialysis and CKD cohorts (coefficient = −0.07; P = 0.10).

## Effect of dialysis modality on cognitive trends

To compare cognitive trends between HD and PD, the mixed model analysis was repeated in the dialysis cohort ($n = 66$; HD = 41, PD = 25), adjusting for age, ethnicity, years of education and dialysis vintage. There was no significant difference in the rate of change in the total MoCA scores between PD and HD patients. The MoCA executive score did, however, decline more rapidly in the HD patients compared with PD patients (Table 4, Figure 2), after adjusting for the same variables.

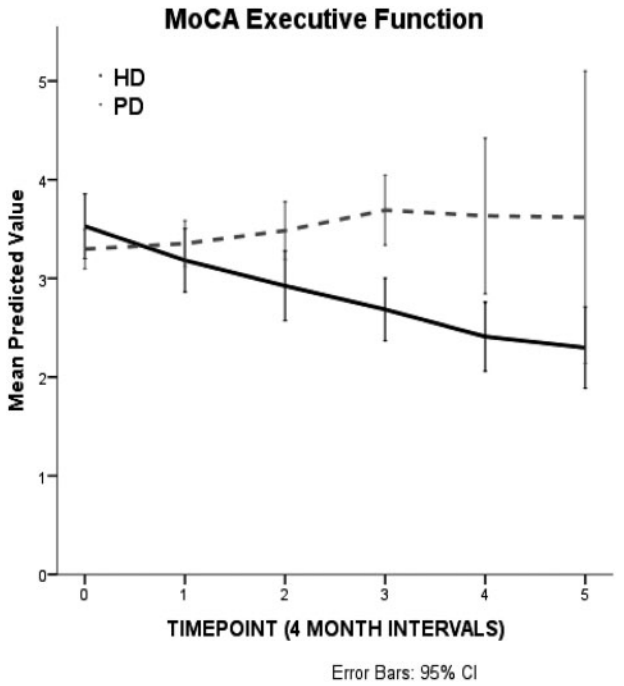


Fig. 2. Longitudinal trends in executive function [HD (solid line) versus PD (dashed line)].

Table 4. Generalized linear model—HD versus PD

| Outcome variable—MoCA executive function HD versus PD ($n = 76$) | | | |
|---|---|---|---|
| Predictors | Coefficient | 95% CI (lower–upper) | P-value |
| Age | −0.014 | −0.025 to − 0.004 | 0.010 |
| Ethnicity | | | |
| White European | −0.448 | −0.153 to 1.048 | 0.138 |
| Afro-Caribbean | −0.401 | −0.262 to 1.064 | 0.227 |
| Asian | −0.400 | −0.194 to 0.994 | 0.179 |
| <12 years of education | −0.056 | −0.326 to 0.214 | 0.678 |
| Months on dialysis | −0.002 | −0.004 to −0.001 | 0.009 |
| HD versus PD | 0.112 | −0.104 to 0.329 | 0.302 |
| Time | 0.013 | −0.008 to 0.114 | 0.796 |
| HD* time | −0.120 | −0.233 to −0.007 | 0.037 |
| PD* time (reference) | – | | – |

CI, confidence interval.

## Cognitive function and DMC in renal disease

In total, 10 patients participated in a pilot study evaluating the relationship between cognitive function and DMC. This cohort consisted of five PD, three CKD and two HD patients. All patients were of male gender with a mean age of 54.3 years; seven patients had a degree of cognitive impairment (MoCA <26).

The patients with cognitive impairment had significantly lower total MacCAT-T scores compared with those with normal cognitive function [median (IQR) 19 (17.9–19.6) versus 17.4 (16.3–18.4); P = 0.049]. There was also a trend towards lower scores in the reasoning domain of the MacCAT-T test in those with cognitive impairment [6.0 (5.0–6.5) versus 7.5 (6.3–8.0); P = 0.071]. There were no differences in scores related to understanding [5.8 (5.5–6.0) versus 5.9 (5.6–6.0); P = 0.51], appreciation [4.0 (3.8–4.0) versus 4.0 (4.0–4.0)] or expression of choice [2.0 (1.5–2.0) versus 2.0 (1.3–2.0)] between patients with cognitive impairment

and those with normal cognitive function. There was also no significant correlation between the four domains of the MacCAT-T [understanding ($r = -0.13$; $P = 0.71$), reasoning ($r = 0.32$; $P = 0.37$), appreciation ($r = 0.36$; $P = 0.34$), expression of choice ($r = -0.19$; $P = 0.60$)] and executive function.

## Discussion

In this study, we hypothesized that dialysis would be associated with a decline in cognitive function compared with CKD patients. The results suggest that global cognitive function declines over time for patients on dialysis compared with CKD patients. We had also anticipated that cognitive function would be better preserved in patients on PD compared with those on HD. Global cognitive trends did not differ between the HD and PD cohorts. However, executive function was better preserved over time in the PD group compared with those on the HD.

It is well recognized that the risk of cognitive impairment increases as renal function declines [15, 16]. In addition, several studies have shown that cognitive performance is poorer in dialysis patients compared with that in matched healthy controls [2]. Dialysis potentially exerts an independent effect on cognitive function in patients with advanced CKD. This is supported by the improvement in cognitive function in dialysis patients following transplantation [8]. Dialysis is thought to affect cognitive function by a variety of mechanisms. However, supportive evidence for these mechanisms is limited. Observational studies have so far failed to show an association between cognitive function and small solute clearance [17] or dialysis frequency [18]. Data on the influence of intradialytic hypotension (IDH) on cognition are conflicting. Kurella *et al.* found no significant relationship between IDH and cognitive impairment in HD patients enrolled in the Frequent Haemodialysis Network (FHN) trial [4]. More recently, IDH has been directly linked with ischaemic brain injury and potentially, cognitive impairment in HD patients [19].

The faster decline in executive function in HD patients compared with that in PD reported in this study is noteworthy, despite the lack of significant differences in global cognitive trends. It is consistent with studies reporting a lower cumulative incidence of dementia (predominantly vascular in origin) in PD compared with HD patients [9]. Kurella Tamura *et al.* reported a 19% prevalence of isolated executive dysfunction (executive dysfunction despite normal global cognitive function) in a cross-sectional study of 383 HD patients [4]. It is therefore plausible that a decline in executive function predates global cognitive decline. HD has been shown to exert injurious ischaemic effects on the brain. These features are far less common in PD patients and may explain the differences reported in this study.

Patients who met the criteria for cognitive impairment (MoCA score $< 26$) had lower capacity assessment scores. In Terawaki *et al.*'s study of 26 predialysis patients [11], attentional deficits in MMSE correlated significantly with poor understanding and reasoning evaluated by MacCAT-T. While cognitive function was linked with MacCAT-T scores in broad terms, there were no associations between specific cognitive domains and the four domains assessed by MacCAT-T. The mean scores were lower in Terawaki *et al.*'s study compared with those in this pilot study (understanding—$3.72 \pm 1.11$ versus $5.76 \pm 0.08$, appreciation—$2.88 \pm 0.88$ versus $3.88 \pm 0.11$, reasoning—$4.30 \pm 2.11$ versus $6.44 \pm 0.41$). The exclusion of patients with significant cognitive impairment may have contributed to these differences. In addition, the sample was too small to detect significant associations. The results may have been confounded by patient characteristics as the participants were all male and predominantly on PD.

There are other noteworthy limitations. The study was single centre and observational in nature. As such, causality cannot be established and the findings are unlikely to be generalizable. The sample size was not determined by a power calculation. Due to convenience sampling, one cannot exclude the possibility of selection bias. In addition, the effect estimates from the mixed model analysis were small. Longer follow-up would be required to detect clinically important differences in the cognitive trends.

Nevertheless, the findings suggest that dialysis and possibly dialysis modality exert an influence on cognitive function. Future research should aim to identify dialysis techniques that minimize the effect on cognitive function. For example, a recent randomized clinical trial in HD patients has shown that dialysate cooling may reduce the burden of white matter disease [20]. As white matter disease has been recently linked with cognitive impairment [19], dialysate cooling may be beneficial for cognitive function in HD patients. There is also a role for regular screening in dialysis patients, to identify and investigate otherwise unrecognized cognitive impairment. There are implications for treatment compliance and with severe impairment, daily functioning. The potential impact of cognitive impairment on DMC is also relevant to clinical practice. Dialysis education could be adapted to ensure understanding in affected patients and family members. There is also a role for advance care planning in patients with significant cognitive impairment.

In summary, this study suggests that cognitive function declines faster in dialysis patients compared with similar patients with advanced CKD not on dialysis and more so in HD patients compared with those on PD. Cognitive impairment has an impact on DMC in patients with advanced kidney disease. Larger studies are needed to corroborate these findings. Meanwhile, cognitive screening should be incorporated into routine clinical practice in patients with advanced kidney disease.

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## Conflict of interest statement

The results presented in this article have not been published previously in whole or part, except in abstract format. E.B. has received speaker honoraria and research funding from Baxter Healthcare. All other authors have declared no conflict of interest.

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