**Prevalence and trajectories of subjective cognitive complaints and implications for patient outcomes: a prospective study of haemodialysis patients**

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**Abstract**

**Objectives:** Cognitive impairment is common in haemodialysis patients and is associated with increased hospitalisation and mortality. However, subjective cognitive complaints (SCCs), the self-experienced difficulties in everyday cognitive activities, remain poorly understood. This study examined the prevalence and course of SCCs in haemodialysis patients and the longitudinal associations between SCCs and sociodemographic, clinical, and patient-reported variables.

**Design:** Observational prospective study with baseline and 12-month follow-up assessment

**Methods:** Based on a validated cut-off point on the Kidney Disease Quality of Life Cognitive Function subscale, haemodialysis patients (N = 159; 40.3% female, mean age 53.62) were classified into clinical impairment trajectories: (1) resilient (60.4%; no/low SCCs throughout); (2) persistent (8.8%; stable high SCCs indicative of clinical impairments); (3) deterioration (17.6%; from no to probable impairments); and (4) recovery (13.2%; from probable to no impairment). Sociodemographic/clinical variables, self-efficacy, self-management skills, adherence, mood, and biochemical assays were measured at both assessments and compared among trajectories using mixed ANOVAs.

**Results:** Interaction effects indicated significant improvements in the recovery group in clinical outcomes (i.e., decreased phosphorus and calcium-phosphorus product), self-efficacy, and mood over time. Group effects indicated significantly poorer self-efficacy, self-management skills, and adherence in the persistent group than other trajectories across both assessments. None of the sociodemographic/clinical characteristics was associated with SCC trajectories.

**Conclusions:** Clinically significant SCCs vary over time across haemodialysis patients. Routine screening of SCCs in dialysis settings may help identifying patients at risk of poor self-management and worse prognosis. Strategies that compensate for cognitive lapses may mitigate the perceived cognitive burden of this population.

*Keywords:* subjective cognitive complaint; cognitive impairment; haemodialysis; self-management; adherence; self-efficacy

**Introduction**

End-stage renal disease (ESRD) is the most advanced stage of chronic kidney disease where kidney function is irreversibly lost, necessitating kidney dialysis or transplantation (Himmelfarb et al., 2020; Levey & Coresh, 2012). Although the use of dialysis and transplantation has transformed ESRD from an acute life-limiting disease to a chronic disease, ESRD is accompanied by substantial treatment and symptom burden that interferes with patients’ daily functioning and quality of life (Curtin et al., 2002; Goh & Griva, 2018; Hedayati & Finkelstein, 2009; Weisbord et al., 2005; Zhang et al., 2020).

The burden of cognitive impairments (CIs) in ESRD has been well documented in the literature. CIs refer to deficits in cognitive domains such as attention, memory, and executive function and its severity can range from mild impairments to dementia. These impairments may start to manifest in early stages of chronic kidney disease (Berger et al., 2016; Brodski et al., 2019) and are not fully reversible by dialysis or transplantation (Joshee et al., 2018; San et al., 2017; Shea et al., 2019; Wolfgram, 2018). CIs have been found to be more prevalent in haemodialysis (HD) patients compared to the general population (O’Lone et al., 2016; San et al., 2017) and are also associated with increased risks of functional disability, hospitalisation, mortality, and dialysis withdrawal (Griva et al., 2010; Kallenberg et al., 2016; Murray, 2008). These associations are usually thought to be due to CIs interfering with self-management capabilities, adherence behaviours, and decision-making processes (Berger et al., 2016; Iyasere et al., 2017; Tian et al., 2019), however evidence is scarce.

Although CIs in ESRD patients have been extensively researched in the past decades, our understanding of the practical implications of CIs in this population is still limited. Most prior work relied on standardised neuropsychological tests (Berger et al., 2016; Shea et al., 2019; Tian et al., 2019; Vanderlinden et al., 2019), which albeit sensitive in detecting CIs, are considered to be less reflective of patients’ self-experienced cognitive difficulties in everyday activities (Law et al., 2012; Song et al., 2015; Thornton & Dumke, 2005). Some patients may perform within the normal range on neuropsychological tests but are starting to experience subtle cognitive changes and increasing cognitive efforts in everyday tasks (Rabin et al., 2017). Subjective cognitive complaints (SCCs), the self-reported difficulties in everyday cognitive tasks based on patients’ accumulative experience, may therefore provide additional meaningful information on the everyday manifestation of CIs. Importantly, the presence of SCCs constitutes the earliest symptomatic manifestation of cognitive decline (Jessen et al., 2014) which may predict progression to dementia (Rabin et al., 2017). Understanding SCCs is therefore crucial for improving patient-centred care and allowing early detection of CIs.

We also have very limited information on the association between cognition and other real-world functioning outcomes such as self-management skills and adherence behaviours in the context of ESRD. Successful self-management of ESRD requires patients to actively process, access and act upon health information in order to monitor and evaluate their health condition (e.g., weight gain), manage symptoms, and effectively communicate with the healthcare team (Cukor et al., 2020). The HD regime comprises complex behaviours related to diet, fluid, and medication intake that are novel and cognitively demanding. For patients with CIs or SCCs, these tasks may be particularly taxing and therefore they may be less likely to have optimal self-management as limited cognitive capabilities may interfere with activation and performance of health actions and may undermine self-confidence and motivation for self-management. Song et al. (2015) found that only HD patients’ SCCs, and not objective cognitive function, were associated with daily functioning assessed by the basic and instrumental Activities of Daily Living scale. SCCs therefore, may have additional utility on top of objective tests in predicting real-world outcomes.

The longitudinal course of cognition over the HD treatment course is currently not well understood. While several longitudinal studies investigated changes in objective neuropsychological test performance over time in HD patients, evidence is mixed. One study noted a significant loss of executive function in incident dialysis patients following dialysis initiation (Kurella Tamura et al., 2017) and studies on prevalent dialysis patients reported decline in global cognition over one (Bossola et al., 2011) and two years (Iyasere et al., 2017). Murali et al. (2021) noted that the course may not be uniform as memory function was shown to improve in those newly-initiated onto dialysis in the past year but remain stable for those with a dialysis vintage longer than a year. SCCs on the other hand have also been shown to improve over time in HD patients (Song et al., 2018). The observed inconsistencies highlight potential inter-individual variability in the patterns of change and the need to further study cognitive trajectories, factors associated with these trajectories, and their implications in terms of clinical, behavioural, and psychosocial outcomes.

To address these critical gaps, this prospective study aimed (1) to examine the prevalence and course of SCCs over 12 months in HD patients, (2) to explore the proportion of patients exhibiting different cognitive complaint trajectories over time, and (3) to examine the associations of these trajectories with sociodemographic and clinical profile, key clinical outcomes (e.g., potassium, phosphorus, etc.), and patient-reported outcomes (i.e., self-efficacy, self-management skills, treatment adherence, and mood symptoms).

**Methods**

**Design**

The current study is based on data from two studies undertaken at the same period in the National Kidney Foundation (NKF) of Singapore: an observational study of HD patients (Ng et al., 2015) and a randomised controlled trial evaluating the effectiveness of a self-management intervention for HD patients (Griva, Nandakumar, et al., 2018). Data collected at baseline and at 12-month follow-up were used. For the randomised controlled trial, only data from the control group (no intervention) were used. NKF is a non-profit organisation in Singapore that provides community-based HD treatment. The study protocols were approved by the institutional review board of National University of Singapore and are in compliance with the Helsinki declaration (Griva et al., 2011). Details of the recruitment procedure can be found in previous publications (Griva et al., 2011; Griva, Lam, et al., 2018; Griva, Nandakumar, et al., 2018; Ng et al., 2015).

**Participants**

Participants were recruited from 14 NKF dialysis centres across Singapore. The inclusion criteria were being 21 years of age or older, established on HD treatment in one of the NKF dialysis centres, and fluent in either English, Mandarin, or Malay. Individuals were excluded if they were only able to converse in dialects or Tamil, or had documented major sensory, motor, or cognitive impairments that would prohibit informed consent, or limited life expectancy due to comorbidity such as advanced stage/terminal malignancy. Individuals enlisted to participate in other interventions not part of usual care during the study duration were also excluded.

**Procedure**

A list of eligible patients was provided by the nurse manager in each participating dialysis centre who were aware of the eligibility criteria. A research team member fluent in the patients’ preferred language approached each patient for invitation to the study. Patients were administered the questionnaires (sociodemographic information and patient-reported outcomes) if they consented to participate. Upon completion, participants were given a small cash reimbursement. Questionnaires were administered at baseline and at a 12-month follow-up. Procedures for both assessments were similar.

**Measures**

**Sociodemographic and clinical information.** Self-reported demographic information was collected from each participant including gender, age, ethnicity, educational level, marital and employment status, and household income. Clinical variables extracted from the medical record included age at ESRD diagnosis; primary kidney disease diagnosis; duration on HD; presence of cerebrovascular disease, hypertension, and diabetes; the Charlson Comorbidity Index (CCI) (Charlson et al., 1987; Hemmelgarn et al., 2003); dialysis adequacy (Kt/V); biochemical lab assays including serum phosphorus, serum potassium, and calcium-phosphorus product (Ca × PO4); and relative interdialytic weight gain (IDWGr), which is the ratio of absolute IDWG to a patient’s dry weight at each midweek dialysis session during the assessment period. The lab test results and IDWGr were collect at both baseline and 12-month follow-up.

**Subjective cognitive complaints.** SCCs were measured at both time points by the Kidney Disease Quality of Life Cognitive Function subscale (KDQOL-CF). The KDQOL is a measure of quality of life in patients with kidney disease (Hays et al., 1994; Rao et al., 2000) and has been validated in HD patients in Singapore (Chen et al., 2016; Yang et al., 2013). The KDQOL-CF subscale assesses SCCs using three items: “During the past 4 weeks, how much of the time did you (1) react slowly to things that were said or done, (2) have difficulty concentrating or thinking, and (3) become confused” (Kurella et al., 2004). Participants were asked to respond on a six-point Likert scale ranging from “none of the time” to “all of the time” (Kurella et al., 2004). The total score of KDQOL-CF ranges from 0 to 100, with higher scores indicating better self-perceived cognitive functioning (Hays et al., 1994; Rao et al., 2000). A cut-off point of 60 on the KDQOL-CF was recommended by Kurella et al. (2004) to differentiate ESRD patients with and without probable CIs.

**Self-efficacy.** Self-efficacy was measured by two scales: the 6-item Self-Efficacy to Manage Chronic Disease (SEMCD) scale to measure self-efficacy for general demands of chronic disease (e.g., “How confident are you that you can keep the physical discomfort or pain of your disease from interfering with the things you want to do”) (Ritter & Lorig, 2014) and a dialysis-specific scale, the Self-Efficacy to Adhere to Treatment Recommendations (SEATR) scale. The latter was developed following formative qualitative work with HD patients (Griva et al., 2013), review by expert panel of renal health professionals, and a pilot with four HD patients (Griva et al., 2011). The SEATR contains eight items that assess participants’ self-confidence to adhere to their treatment recommendations related to fluid intake, diet, and medication (e.g., “How confident are you that you can limit your fluid intake”). For both questionnaires, participants were asked to rate on a 10-point Likert scale, ranging from “not at all confident” to “totally confident” (Ritter & Lorig, 2014). Higher total scores indicate higher disease or treatment self-efficacy.

**Self-management skills**. Self-management skills were measured by the skills and technique acquisition, self-monitoring and insight, and health services navigation subscales of the Health Education Impact Questionnaire (heiQ) (Osborne et al., 2007). The skills and technique acquisition subscale assesses knowledge-based skills and techniques that help patients manage symptoms or health problems (e.g., “When I have symptoms, I have the skills that help me cope”) (Osborne et al., 2007). The self-monitoring and insight subscale assesses patients’ ability to monitor their health condition (e.g., “I carefully watch my health and do what is necessary to keep as healthy as possible”) (Osborne et al., 2007). The health services navigation subscale measures patients’ ability to communicate and negotiate with healthcare providers to get their needs met (e.g., “I communicate very confidently with my doctor about my healthcare needs”) (Osborne et al., 2007). Higher scores indicate better self-management skills in these domains.

**Treatment adherence.** Medication adherence was assessed with the Medication Adherence Report Scale (MARS-5 ©Professor Rob Horne) (Chan et al., 2020; Horne & Weinman, 2002; Wei et al., 2017) that includes 5 items (e.g., “I alter the dose”) rated on a five-point Likert scale ranging from “never” to “always”. Higher total scores signify higher medication adherence. To measure adherence with regards to the other treatment aspects, we used the 25-item Renal Adherence Behaviour Questionnaire (RABQ) (Rushe & Mcgee, 1998) that comprises 5 subscales: fluid restrictions, potassium and phosphate intake, sodium intake, adherence in times of particular difficulty, and self-care, all rated on a five-point scale ranging from “never” to “always”. Higher subscale and total scores indicate higher adherence.

**Mood symptoms.** Given the consistently documented associations between SCCs and mood (Jessen et al., 2014, 2020; Molinuevo et al., 2017; Rabin et al., 2017), the Hospital Anxiety and Depression Scale (HADS) was administered (Leung et al., 1993; Zigmond & Snaith, 1983). HADS is a 14-item self-report measure that assesses depression (7 items; e.g., “I feel miserable and sad”) and anxiety (7 items; e.g., “I get sudden feelings of panic”). Individuals respond to each item on a four-point Likert-type scale that varies depending on the item, but generally reflects frequency (i.e., 0 = not at all to 3 = all the time) during the past week. Higher scores indicate more severe depressive or anxious symptoms.

**Statistical analyses**

Descriptive statistics were computed for demographic, clinical, and patient-reported variables. Two variables were derived from the KDQOL-CF scores: (1) total sum score of the KDQOL-CF as a continuous variable to indicate frequency of SCCs in line with prior work (Griva et al., 2012), and (2) binary classification of KDQOL-CF scores into “probable CIs” (i.e., < 60) vs. “no CI” groups (i.e., ≥ 60) based on a validated cut-off point (Kurella et al., 2004). A paired-samples t-test was run to examine overall change in the continuous KDQOL-CF scores from baseline to follow-up in the entire sample. A Chi-squared test was also run to examine change in the proportion of patients classified into the “probable CIs” group from baseline to follow-up.

Based on the binary classification of KDQOL-CF at two time points, individual trajectories of SCCs over the 12-month period were then determined by categorising patients into four groups: (1) resilient (i.e., no CI at both time points); (2) persistent (i.e., probable CIs at both time points); (3) deterioration/new-onset CIs (i.e., no CI at baseline with new-onset complaints signifying probable CIs at follow-up); and (4) recovery (i.e., probable CIs at baseline but no CI at follow-up). Prevalence of each trajectory was calculated. ANOVAs and Chi-squared tests were conducted to compare baseline sociodemographic and clinical characteristics between the four trajectory groups. We also performed a series of 4 (trajectory groups) × 2 (time points) mixed ANOVAs examining longitudinal changes in clinical outcomes (i.e., serum phosphorus, serum potassium, Ca × PO4, and IDWGr) and patient-reported outcomes (i.e., self-efficacy, self-management skills, treatment adherence, and mood symptoms) across the four trajectory groups. Significant main effects or interactions were followed up by post-hoc comparisons (i.e., paired samples t-tests, independent samples t-tests, or one-way ANOVAs).

Since depressive and anxious symptoms were found to be strongly associated with SCCs (Jessen et al., 2014, 2020; Molinuevo et al., 2017; Rabin et al., 2017) and were also considered as important predictors of self-efficacy (Paterson et al., 2018) and adherence (Clark et al., 2014; Ghimire et al., 2015), it is possible that any association between SCCs and patient outcomes that emerged from our analyses is mainly driven by mood symptoms. Therefore, as sensitivity analyses, we performed another series of 4 (trajectory groups) × 2 (time points) mixed ANOVAs on clinical outcomes (i.e., serum phosphorus, serum potassium, Ca × PO4, and IDWGr) and health behaviour outcomes (i.e., self-efficacy, self-management skills, treatment adherence) while controlling for mood.

**Results**

**Sample characteristics**

Of the 1076 patients screened, 652 were eligible and 305 (46.8%) provided consent to participate. Patients in the intervention arm of the randomised controlled trial were excluded from the present paper. Within the remaining 201 patients, 42 (20.9%) dropped out after baseline. Therefore, only 159 patients who completed both assessments were included in the analyses. The main reasons for dropout were lack of time or interest.

The majority of patients were male (59.7%), of Chinese (50.6%) or Malay (40.3%) ancestry, received secondary education or lower (82.9%), were in a relationship (70.4%), unemployed (53.3%), and reported a household income lower than S$2000 a month (55.6%). The mean duration of HD was 50.60 months. Sociodemographic and clinical characteristics of the 159 participants are presented in Table 1.

**Overall change in cognitive complaints over 12 months**

The average KDQOL-CF score in the whole sample was 70.38 (SD = 22.26) at baseline and 68.72 (SD = 21.46) at follow-up, which indicated that patients experienced SCCs from “a little of the time” to “some of the time” on average at both time points. A paired-samples t-test revealed no significant difference in KDQOL-CF scores between the two time points, *t*(158) = 0.86, *p* = .394, *d* = 0.07.

Using the cut-off point of 60 on KDQOL-CF (Kurella et al., 2004), participants were classified into two groups at both time points. Thirty-five patients (22.0%) were considered to have probable CIs (i.e., scored below 60 on KDQOL-CF) at baseline. Forty-two patients (26.4%) had probable CIs at follow-up. A Chi-squared test between baseline grouping and follow-up grouping showed a significant result, χ2(1) = 4.26, p = .039, *V* = 0.16, indicating a significant increase in the proportion of patients reporting probable CIs from baseline (22.0%) to follow-up (26.4%).

**Individual trajectories of change in cognitive complaints**

Using the cut-off point of 60 on KDQOL-CF (Kurella et al., 2004), patients were classified into four trajectories: (1) resilient (i.e., stable levels of no/low complaints across time; N = 96, 60.4%); (2) persistent (i.e., stable levels of frequent complaints indicating probable CIs at both time points; N = 14, 8.8%); (3) deterioration (i.e., no CI at baseline with increased complaints at follow-up indicating probable CIs; N = 28, 17.6%); and (4) recovery (i.e., probable CIs at baseline with diminished complaints at follow-up; N = 21, 13.2%). Means and standard deviations of KDQOL-CF scores in the four trajectory groups at both time points are reported in Table 2.

**Differences between trajectories in sociodemographic and clinical characteristics**

ANOVAs and Chi-squared tests were performed to evaluate differences between trajectory groups in baseline sociodemographic and clinical characteristics (see Table 1). None of the sociodemographic and clinical characteristics was associated with patterns of change in SCCs over time in HD patients.

Table 1. *Sociodemographic and clinical characteristics of study participants and comparisons between trajectory groups.*

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|   | Total(N = 159; 100.0%) | Resilient(N = 96; 60.4%) | Persistent(N = 14; 8.8%) | Deterioration(N = 28; 17.6%) | Recovery(N = 21; 13.2%) | *p* value | Effect size |
| Mean (SD) / N (%) |
| Sociodemographic variables |  |  |  |  |  |  |  |
|  | Gender |  |  |  |  |  | .367 | 0.14 |
|  |  | Female | 64 (40.3%) | 41 (42.7%) | 7 (50.0%) | 11 (39.3%) | 5 (23.8%) |  |  |
|  |  | Male | 95 (59.7%) | 55 (57.3%) | 7 (50.0%) | 17 (60.7%) | 16 (76.2%) |  |  |
|  | Age (years) | 53.62 (10.75) | 53.17 (10.80) | 52.00 (9.36) | 53.07 (13.45) | 57.52 (6.28) | .346 | 0.02 |
|  | Ethnicity |  |  |  |  |  | .746 | 0.11 |
|  |  | Chinese | 78 (50.6%) | 44 (47.3%) | 9 (64.3%) | 12 (46.2%) | 13 (61.9%) |  |  |
|  |  | Malay | 62 (40.3%) | 41 (44.1%) | 5 (35.7%) | 10 (38.5%) | 6 (28.6%) |  |  |
|  |  | Indian | 13 (8.4%) | 7 (7.5%) | 0 (0.0%) | 4 (15.4%) | 2 (9.5%) |  |  |
|  |  | Others | 1 (0.6%) | 1 (1.1%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |  |  |
|  | Highest education |  |  |  |  |  | .696 | 0.10 |
|  |  | Secondary or lower | 131 (82.9%) | 78 (81.3%) | 13 (92.9%) | 24 (85.7%) | 16 (80.0%) |  |  |
|  |  | Post-secondary or higher | 27 (17.1%) | 18 (18.8%) | 1 (7.1%) | 4 (14.3%) | 4 (20.0%) |  |  |
|  | Relationship status |  |  |  |  |  | .315 | 0.15 |
|  |  | In a relationship | 112 (70.4%) | 64 (66.7%) | 9 (64.3%) | 21 (75.0%) | 18 (85.7%) |  |  |
|  |  | Not in a relationship | 47 (29.6%) | 32 (33.3%) | 5 (35.7%) | 7 (25.0%) | 3 (14.3%) |  |  |
|  | Working status |  |  |  |  |  | .196 | 0.19 |
|  |  | Working | 64 (46.7%) | 41 (46.6%) | 3 (25.0%) | 10 (45.5%) | 10 (66.7%) |  |  |
|  |  | Not working | 73 (53.3%) | 47 (53.4%) | 9 (75.0%) | 12 (54.5%) | 5 (33.3%) |  |  |
|  | Household income |  |  |  |  |  | .068 | 0.24 |
|  |  | S$2000 or below | 69 (55.6%) | 37 (49.3%) | 8 (66.7%) | 16 (80.0%) | 8 (47.1%) |  |  |
|  |  | Above S$2000 | 55 (44.4%) | 38 (50.7%) | 4 (33.3%) | 4 (20.0%) | 9 (52.9%) |  |  |
| Clinical characteristics |  |  |  |  |  |  |  |
|  | Age at ESRD diagnosis | 45.69 (14.04) | 44.21 (14.43) | 44.50 (13.15) | 46.25 (15.03) | 52.85 (9.07) | .092 | 0.04 |
|  | Primary kidney disease diagnosis |  |  |  |  | .460 | 0.18 |
|  |  | Diabetic nephropathy | 58 (38.7%) | 32 (34.8%) | 3 (21.4%) | 12 (48.0%) | 11 (57.9%) |  |  |
|  |  | Primary glomerulonephritis | 44 (29.3%) | 30 (32.6%) | 3 (21.4%) | 7 (28.0%) | 4 (21.1%) |  |  |
|  |  | Hypertension | 13 (8.7%) | 8 (8.7%) | 1 (7.1%) | 2 (8.0%) | 1 (5.3%) |  |  |
|  |  | IgA nephropathy | 7 (4.7%) | 3 (3.3%) | 2 (14.3%) | 2 (8.0%) | 1 (5.3%) |  |  |
|  |  | Polycystic kidney disease | 3 (2.0%) | 1 (1.1%) | 1 (7.1%) | 0 (0.0%) | 1 (5.3%) |  |  |
|  |  | Others/uncertain aetiology | 25 (16.7%) | 18 (19.6%) | 4 (28.6%) | 2 (8.0%) | 1 (5.3%) |  |  |
|  | Duration on HD (months) | 50.60 (53.79) | 57.93 (56.35) | 47.50 (45.15) | 40.46 (56.45) | 33.05 (37.83) | .169 | 0.03 |
|  | Presence of cerebrovascular disease |  |  |  |  | .394 | 0.14 |
|  |  | No | 136 (85.5%) | 82 (85.4%) | 10 (71.4%) | 25 (89.3%) | 19 (90.5%) |  |  |
|  |  | Yes | 23 (14.5%) | 14 (14.6%) | 4 (28.6%) | 3 (10.7%) | 2 (9.5%) |  |  |
|  | Presence of hypertension |  |  |  |  |  | .291 | 0.15 |
|  |  | No | 13 (8.2%) | 11 (11.5%) | 0 (0.0%) | 1 (3.6%) | 1 (4.8%) |  |  |
|  |  | Yes | 146 (91.8%) | 85 (88.5%) | 14 (100.0%) | 26 (96.4%) | 20 (95.2%) |  |  |
|  | Presence of diabetes |  |  |  |  |  | .502 | 0.12 |
|  |  | No | 88 (55.7%) | 56 (58.9%) | 9 (64.3%) | 13 (46.4%) | 10 (47.6%) |  |  |
|  |  | Yes | 70 (44.3%) | 39 (41.1%) | 5 (35.7%) | 15 (53.6%) | 11 (52.4%) |  |  |
|  | Charlson comorbidity index accounted for age | 4.82 (2.16) | 4.80 (2.32) | 4.57 (2.28) | 4.71 (2.03) | 5.19 (1.47) | .834 | 0.01 |
|   | Dialysis adequacy (Kt/V) | 1.48 (0.57) | 1.53 (0.63) | 1.49 (0.32) | 1.43 (0.60) | 1.31 (0.29) | .443 | 0.02 |
| \* *p* < .050. |  |  |  |  |  |  |  |

Notes. Effect sizes are either partial eta-square (ANOVA) or Cramer’s V (Chi-squared). N = Sample size; SD = Standard deviation; ESRD = End-stage renal disease; HD = Haemodialysis.

**Differences between trajectories in clinical and patient-reported outcomes**

A series of 4 (trajectory groups) × 2 (time) mixed ANOVAs were performed to examine longitudinal changes in clinical (i.e., serum phosphorus, serum potassium, Ca × PO4, and IDWGr) and patient-reported outcomes (i.e., self-efficacy, self-management skills, treatment adherence, and mood) across the four trajectory groups (see Table 2 and Figures 1-4). The main effect of time was found to be non-significant in all mixed ANOVAs, indicating that overall, there was no change in clinical or patient-reported outcomes from baseline to follow-up.

**Clinical outcomes.** The ANOVAs on serum potassium and IDWGr showed no significant main effect or interaction. However, a significant interaction was found for serum phosphorus (see Figure 1). Post-hoc comparisons showed that serum phosphorus decreased significantly from baseline to follow-up in the recovery group, *t*(19) = 3.18, *p* = .005, *d* = 0.71, but remained unchanged in the other three groups. Although there was no difference between groups in serum phosphorus at baseline, the recovery group had significantly lower serum phosphorus than the deterioration group at follow-up, *t*(43.92) = 3.61, *p* < .001, *d* = 1.00.

Similarly, there was a significant interaction for Ca × PO4 (see Figure 1). Post-hoc comparisons showed that Ca × PO4 decreased significantly from baseline to follow-up in the recovery group, *t*(19) = 3.45, *p* = .003, *d* = 0.77, whereas the other three groups showed no difference between time points. Although there was no difference between groups in Ca × PO4 at baseline, the recovery group had significantly lower Ca × PO4 than the deterioration group at follow-up, *t*(44.63) = 2.96, *p* = .005, *d* = 0.82.



*Figure 1.* Mixed ANOVAs comparing serum phosphorus and calcium-phosphorus product among four trajectory groups across two time points.

**Self-efficacy.** The ANOVA on patients’ disease self-efficacy (SEMCD) revealed a significant group effect and a significant interaction (see Figure 2). Post-hoc comparisons showed that disease self-efficacy increased significantly over time in the recovery group, *t*(20) = -2.62, *p* = .016, *d* = 0.57, but remained unchanged in the other three groups. Also, at baseline, the resilient group had significantly higher disease self-efficacy than the persistent group, *t*(108) = 4.61, *p* < .001, *d* = 1.32. At follow-up, both the resilient and recovery groups had higher disease self-efficacy than the persistent and deterioration groups, *F*(3, 154) = 9.30, *p* < .001, *η2* = 0.15.

In terms of treatment self-efficacy (SEATR), only the main effect of group was significant (see Figure 2). Pairwise comparisons showed that the persistent group had significantly lower treatment self-efficacy compared to the other three groups regardless of time.



*Figure 2.* Mixed ANOVAs comparing disease and treatment self-efficacy among four trajectory groups across two time points.

**Self-management skills.** The ANOVAs on the skills and technique acquisition, self-monitoring and insight, and health services navigation subscales of the heiQ also revealed significant main effects of group (see Figure 3). For the skills and technique acquisition subscale, pairwise comparisons showed that the persistent group had poorer skills and techniques to manage symptoms or health problems than the resilient group regardless of time. For the self-monitoring and insight subscale, pairwise comparisons showed that the persistent group had poorer ability to monitor their own health than the resilient group and the recovery group regardless of time. For the health services navigation subscale, pairwise comparisons showed that the persistent group had poorer ability to communicate with healthcare providers than the other three groups regardless of time.



*Figure 3.* Mixed ANOVAs comparing self-management skills among four trajectory groups across two time points.

**Treatment adherence.** The ANOVAs on MARS-5 and RABQ total scores both revealed a significant main effect of group (see Figure 4). For MARS-5, pairwise comparisons showed that the persistent group had poorer medication adherence compared to the other three groups regardless of time. Regarding RABQ, pairwise comparisons showed that the persistent group had poorer adherence in other treatment aspects (e.g., diet, fluid, etc.) compared to the recovery group regardless of time.



*Figure 4.* Mixed ANOVAs comparing treatment adherence among four trajectory groups across two time points.

**Mood symptoms.** The ANOVA on depressive symptoms showed a significant main effect of group and a significant interaction. Post-hoc comparisons showed that there was a significant decrease in depressive symptoms from baseline to follow-up in the recovery group, *t*(20) = 2.94, *p* = .008, *d* = 0.64, while the other three groups showed no difference across time. At baseline, the recovery group had similar levels of depressive symptoms to the persistent group, and both were higher than the resilient group, *F*(3, 155) = 9.08, *p* < .001, *η2* = 0.15. However, at follow-up, the recovery group had similar levels of depressive symptoms to the resilient group, and both were lower than the persistent complaints group, *F*(3, 155) = 11.24, *p* < .001, *η2* = 0.18. In addition, although at baseline there was no difference between resilient and deterioration groups, *t*(122) = -1.86, *p* = .066, *d* = 0.40, the latter developed significantly higher depressive symptoms than the former at follow-up, *t*(122) = -3.85, *p* < .001, *d* = 0.83.

The ANOVA on anxious symptoms also showed a significant main effect of group and a significant interaction. Post-hoc comparisons showed that anxious symptoms diminished from baseline to follow-up in the recovery group, *t*(20) = 3.77, *p* = .001, *d* = 0.82, but remained unchanged in the other three groups. At baseline, the resilient group had significantly fewer anxious symptoms than the other three groups, *F*(3, 155) = 10.44, *p* < .001, *η2* = 0.17. However, at follow-up, the difference between resilient and recovery groups became non-significant, and both reported fewer anxious symptoms than the persistent group, *F*(3, 154) = 9.60, *p* < .001, *η2* = 0.16.

**Mood symptoms as covariates.** As mentioned, to determine whether the reported associations were driven by mood symptoms, we performed an additional series of mixed ANOVAs on clinical (i.e., serum phosphorus, serum potassium, Ca × PO4, and IDWGr) and health behaviour outcomes (i.e., self-efficacy, self-management skills, and treatment adherence) while controlling for change scores of depressive and anxious symptoms. Importantly, the results remained largely unchanged even after considering the effects of mood symptoms, indicating that the associations of SCCs with clinical and health behaviour outcomes were not fully accounted by mood.

Table 2. *Mixed ANOVAs comparing clinical and patient-reported outcomes among four trajectory groups across two time points.*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|   | Resilient(N = 96; 60.4%) | Persistent(N = 14; 8.8%) | Deterioration(N = 28; 17.6%) | Recovery(N = 21; 13.2%) |   | Mixed ANOVA |
| Mean (SD) |   | Trajectory | Time | Interaction |
| Clinical outcomes |  |  |  |  |  |  |  |  |
|  | Serum phosphorus |  |  |  |  |  |  |  |
|  |  | Baseline | 5.12 (1.32) | 5.36 (1.28) | 5.19 (1.30) | 5.16 (1.42) |  | *F*(3, 142) = 1.44,*p* = .234, *η2* = 0.03 | *F*(1, 142) = 0.98,*p* = .325, *η2* = 0.01 | ***F*(3, 142) = 3.98,*p* = .009, *η2* = 0.08** |
|  |  | Follow-up | 5.09 (1.12) | 5.19 (0.71) | 5.65 (1.46) | 4.40 (0.91) |  |
|  | Serum potassium |  |  |  |  |  |  |  |
|  |  | Baseline | 4.77 (0.55) | 4.59 (0.76) | 4.69 (0.71) | 4.59 (0.75) |  | *F*(3, 142) = 0.43,*p* = .733, *η2* = 0.01 | *F*(1, 142) = 1.02,*p* = .315, *η2* = 0.01 | *F*(3, 142) = 0.05,*p* = .985, *η2* = 0.001 |
|  |  | Follow-up | 5.04 (2.26) | 4.67 (0.53) | 4.87 (0.65) | 4.84 (0.63) |  |
|  | Calcium-phosphorus product |  |  |  |  |  |  |  |
|  |  | Baseline | 45.69 (13.75) | 47.57 (11.32) | 46.40 (12.14) | 45.81 (12.10) |  | *F*(3, 142) = 1.01,*p* = .390, *η2* = 0.02 | *F*(1, 142) = 0.62,*p* = .433, *η2* = 0.004 | ***F*(3, 142) = 2.91,*p* = .037, *η2* = 0.06** |
|  |  | Follow-up | 45.62 (10.65) | 46.15 (7.02) | 50.07 (14.11) | 39.90 (9.45) |  |
|  | Relative interdialytic weight gain (IDWGr) |  |  |  |  |  |  |
|  |  | Baseline | 3.77 (1.06) | 3.98 (1.21) | 4.05 (1.11) | 4.13 (1.19) |  | *F*(3, 140) = 1.85,*p* = .141, *η2* = 0.04 | *F*(1, 140) = 0.01,*p* = .937, *η2* = 0.000 | *F*(3, 140) = 1.33,*p* = .269, *η2* = 0.03 |
|  |  | Follow-up | 3.58 (1.21) | 4.32 (1.55) | 4.12 (0.86) | 3.96 (0.96) |  |
| Patient-reported outcomes |  |  |  |  |  |  |  |
|  | KDQOL-CF |  |  |  |  |  |  |  |  |
|  |  | Baseline | 81.91 (13.60) | 36.67 (10.04) | 72.86 (11.32) | 36.83 (13.10) |  | ***F*(3, 155) = 102.76,*p* < .001, *η2* = 0.67** | *F*(1, 155) = 1.26,*p* = .263, *η2* = 0.01 | ***F*(3, 155) = 76.89,*p* < .001, *η2* = 0.60** |
|  |  | Follow-up | 80.21 (13.80) | 44.29 (9.99) | 39.64 (14.75) | 71.27 (11.57) |  |
|  | Disease self-efficacy (SEMCD) |  |  |  |  |  |  |  |
|  |  | Baseline | 6.39 (1.56) | 4.26 (1.86) | 5.70 (1.82) | 5.66 (1.80) |  | ***F*(3, 154) = 9.85,*p* < .001, *η2* = 0.16** | *F*(1, 154) = 2.91,*p* = .090, *η2* = 0.02 | ***F*(3, 154) = 3.93,*p* = .010, *η2* = 0.07** |
|  |  | Follow-up | 6.60 (1.72) | 4.95 (1.39) | 5.07 (1.70) | 6.55 (1.31) |  |
|  | Treatment self-efficacy (SEATR) |  |  |  |  |  |  |  |
|  |  | Baseline | 7.27 (1.36) | 5.37 (1.55) | 6.90 (1.71) | 6.32 (1.82) |  | ***F*(3, 154) = 7.46,*p* < .001, *η2* = 0.13** | *F*(1, 154) = 1.68,*p* = .197, *η2* = 0.02 | *F*(3, 154) = 2.64,*p* = .051, *η2* = 0.05 |
|  |  | Follow-up | 7.12 (1.55) | 5.68 (1.15) | 6.70 (1.68) | 7.23 (1.24) |  |
|  | heiQ-Skills and technique acquisition |  |  |  |  |  |  |  |
|  |  | Baseline | 2.86 (0.39) | 2.55 (0.54) | 2.73 (0.41) | 2.78 (0.52) |  | ***F*(3, 154) = 3.76,*p* = .012, *η2* = 0.07** | *F*(1, 154) = 0.37,*p* = .546, *η2* = 0.002 | *F*(3, 154)=0.32,*p* = .812, *η2* = 0.01 |
|  |  | Follow-up | 2.80 (0.38) | 2.46 (0.45) | 2.73 (0.50) | 2.80 (0.55) |  |
|  | heiQ-Self-monitoring and insight |  |  |  |  |  |  |  |
|  |  | Baseline | 3.08 (0.40) | 2.85 (0.35) | 2.99 (0.24) | 3.06 (0.37) |  | ***F*(3, 154) = 3.21,*p* = .025, *η2* = 0.06** | *F*(1, 154) = 0.99,*p* = .321, *η2* = 0.01 | *F*(3, 154) = 1.30,*p* = .276, *η2* = 0.03 |
|  |  | Follow-up | 2.97 (0.33) | 2.74 (0.32) | 3.01 (0.34) | 3.09 (0.32) |  |
|  | heiQ-Health services navigation |  |  |  |  |  |  |  |
|  |  | Baseline | 3.03 (0.40) | 2.59 (0.35) | 3.04 (0.39) | 3.11 (0.44) |  | ***F*(3, 153) = 5.48,*p* = .001, *η2* = 0.10** | *F*(1, 153) = 2.07,*p* = .152, *η2* = 0.01 | *F*(3, 153)=0.39,*p* = .761, *η2* = 0.01 |
|  |  | Follow-up | 2.94 (0.39) | 2.61 (0.45) | 2.93 (0.44) | 3.04 (0.54) |  |
|  | Medication adherence (MARS-5) |  |  |  |  |  |  |  |
|  |  | Baseline | 3.42 (0.78) | 2.94 (0.68) | 3.51 (0.82) | 3.54 (0.91) |  | ***F*(3, 155) = 3.53,*p* = .016, *η2* = 0.06** | *F*(1, 155) = 0.71,*p* = .401, *η2* = 0.01 | *F*(3, 155) = 0.62,*p* = .601, *η2* = 0.01 |
|  |  | Follow-up | 3.46 (0.78) | 2.72 (0.76) | 3.43 (0.88) | 3.56 (0.68) |  |
|  | RABQ-total |  |  |  |  |  |  |  |  |
|  |  | Baseline | 91.15 (12.62) | 85.43 (9.39) | 93.61 (13.32) | 94.00 (14.61) |  | ***F*(3, 155) = 2.91,*p* = .036, *η2* = 0.05** | *F*(1, 155) = 0.66,*p* = .417, *η2* = 0.004 | *F*(3, 155) = 0.93,*p* = .430, *η2* = 0.02 |
|  |  | Follow-up | 92.21 (11.15) | 81.79 (8.26) | 92.83 (14.11) | 93.89 (13.41) |  |
|  | Depressive symptoms |  |  |  |  |  |  |  |
|  |  | Baseline | 6.97 (3.81) | 11.80 (3.84) | 8.50 (3.94) | 10.19 (4.15) |  | ***F*(3, 155) = 11.51,*p* < .001, *η2* = 0.18** | *F*(1, 155) = 0.13,*p* = .910, *η2* = 0.000 | ***F*(3, 155) = 5.27,*p* = .002, *η2* = 0.09** |
|  |  | Follow-up | 7.05 (3.85) | 12.32 (4.43) | 10.16 (3.46) | 7.76 (3.24) |  |
|  | Anxious symptoms |  |  |  |  |  |  |  |
|  |  | Baseline | 5.62 (3.82) | 10.00 (4.15) | 8.22 (4.33) | 9.71 (4.61) |  | ***F*(3, 154) = 10.98,*p* < .001, *η2* = 0.18** | *F*(1, 154) = 0.19,*p* = .662, *η2* = 0.001 | ***F*(3, 154) = 5.85,*p* = .001, *η2* = 0.10** |
|   |   | Follow-up | 6.08 (4.30) | 11.39 (4.72) | 9.80 (3.99) | 6.97 (4.83) |   |

Notes. Bold text indicates significant effects. N = Sample size; SD = Standard deviation; KDQOL-CF = Kidney disease quality of life cognitive function subscale; SEMCD = Self-efficacy to manage chronic disease scale; SEATR = Self-efficacy to adhere to treatment recommendations scale; MARS = Medication adherence report scale; RABQ = Renal adherence behaviour questionnaire; heiQ = Health education impact questionnaire.

**Discussion**

The current study showed no overall change in the continuous KDQOL-CF scores over time, but the rates of patients reporting SCCs indicative of clinical impairments increased from 22.0% to 26.4% over one year on HD treatment. When dividing patients into trajectory groups, descriptive analyses showed that the majority (60.4%) had stable levels of minimal SCCs at both time points (i.e., resilient), whereas 8.8% had persistent SCCs indicative of CIs. Around one third of patients experienced either increased (i.e., deterioration; 17.6%) or diminished (i.e., recovery; 13.2%) levels of SCCs over time. Although baseline sociodemographic and clinical characteristics were unrelated to these trajectories, the four groups showed different patterns of change in critical clinical and patient-reported outcomes. Specifically, the recovery group showed significant improvements from baseline to follow-up in serum phosphorus and calcium-phosphorus product, as well as improvements in self-efficacy and emotional functioning. In contrast, patients who reported persistent SCCs reported significantly lower self-efficacy and poorer self-management skills and treatment adherence compared to other patients across time.

Approximately a quarter of patients at each time point reported high levels of SCCs indicative of clinical CIs, which is similar to a previous study where 24.0% of HD patients reported a KDQOL-CF score below 60 (Sorensen et al., 2012). Although most patients experienced only minimal or episodic SCCs, almost one in 10 HD patients in the present study reported high levels of chronic and persistent complaints. These patients may have higher risks of developing CIs and dementia since previous studies have shown that SCCs may be present as long as 15 years before the onset of objective CIs and are a reliable predictor of future cognitive decline (Lee et al., 2020; Liew, 2020a, 2020b; Rabin et al., 2017).

The observed longitudinal associations of SCCs with serum phosphorus and calcium-phosphorus product are especially noteworthy as these represent important clinical management endpoint for HD. Elevated levels of serum phosphorus in HD patients may lead to calcium deposition in blood vessels, which in the long-term may cause soft-tissue and vascular calcification and hence may increase morbidity and mortality risks (National Kidney Foundation, 2003). According to the National Kidney Foundation clinical practice guidelines, serum phosphorus should be maintained between 3.5 and 5.5mg/dL, and calcium-phosphorus product should be maintained below 55mg2/dL2, in dialysis patients (National Kidney Foundation, 2003). It appears that serum phosphorus levels decreased from a borderline high value at baseline (*M* = 5.16) to a relatively safe value at follow-up (*M* = 4.40) in the recovery group. Also, at follow-up, the deterioration group had significantly higher levels of both serum phosphorus and calcium-phosphorus product compared to the recovery group, and the follow-up value of serum phosphorus in the deterioration group (*M* = 5.65) exceeded the recommended range. These findings suggest that an increase in SCCs may be a risk factor of worse clinical outcomes in HD patients, which may be due to everyday cognitive difficulties interfering with self-care behaviours such as following a low-phosphorus diet and taking phosphate binder medication on time.

SCC trajectories were also associated with patient-reported outcomes. In particular, the recovery group showed a significant improvement in self-efficacy to manage kidney disease over time. By contrast, patients with persistent SCCs indicative of CIs had the lowest levels of self-efficacy, self-management skills, and treatment adherence which significantly differed from the other trajectory groups. ESRD and HD entail complex guidelines on diet, fluid control, and medication intake, which are in most cases compounded by treatment demands of other comorbid conditions. Successful self-management of ESRD requires patients to understand, process, and recall the various medical/health information provided, and to translate this information into appropriate self-care plans and actions (Insel et al., 2006). These processes involve various cognitive domains including language, memory, and executive function (Insel et al., 2006). For patients with probable CIs and especially those whose complaints are persistent, the cognitive demands of ESRD treatment may become particularly burdensome, thus compromising self-confidence, perceived capabilities, and the actual implementation of self-management activities.

Importantly, the associations between SCC trajectories and clinical and patient-reported outcomes remained significant even after controlling for changes in mood symptoms. In line with prior studies (Jessen et al., 2014, 2020; Molinuevo et al., 2017; Rabin et al., 2017), our study findings also showed significant associations and covariation between mood and cognitive complaints. Individuals with depression and anxiety may exhibit information-processing biases which make them hypersensitive to experience of failure in everyday cognitive tasks, resulting in an overestimation of SCCs (Rabin et al., 2017). Our sensitivity analyses confirmed that the SCCs may explain additional variance in HD patients’ clinical and behavioural outcomes on top of depression and anxiety.

To date, the practical implications of CIs in ESRD patients are not well understood. Few studies have investigated the impact of CIs on self-care behaviour in this population. Hain (2008) found that 58.2% of patients with objective CIs had evidence of nonadherence based on their attendance at dialysis sessions, serum phosphorus, and interdialytic weight gain, but no statistical test was performed to examine these associations. Two other studies found that better everyday problem-solving abilities, assessed by a scenario-based task, were associated with better medication adherence in kidney transplantation recipients (Gelb et al., 2010; Paterson et al., 2018). Studies in other populations such as community-dwelling older adults (Insel et al., 2006), heart failure (Alosco et al., 2012; Dolansky et al., 2016), hypertension (Cho et al., 2018; Chudiak et al., 2018), and type 2 diabetes (Świątoniowska-Lonc et al., 2021), have found positive relationships between cognitive function and treatment adherence. Findings in the current study therefore align with these previous studies and provide further evidence that these associations may be stable across time and may translate into key clinical outcomes.

Taken together, our findings have several important clinical implications. First, screening of SCCs on a regular basis using a simple and quick self-reported measure (i.e., KDQOL-CF) could help identifying patients with persistent SCCs or deteriorating cognitive function who may be at risk of developing objective CIs and at risk of low self-efficacy, poor self-management skills, and nonadherence. CIs are underdiagnosed in ESRD patients (Murray, 2008; Sehgal et al., 1997), which may be due in part to the lack of a gold standard cognitive screener that is sensitive, efficient, and easily accessible. There is currently no established protocol or guideline to screen for CIs in the ESRD population. Neuropsychological tests, albeit sensitive in detecting objective CIs, are usually time-consuming and labour-intensive, and may not be able to identify at-risk patients who report some SCCs yet perform normally on objective tests (Crowe et al., 2021; Kurella et al., 2004). Brief self-reports may be feasible alternatives in busy dialysis settings although their diagnostic ability needs further study. Second, SCCs emerged as a potentially modifiable risk factor for poor patient outcomes. Research in the Alzheimer’s disease literature has started to examine the effects of various types of interventions including mindfulness, exercise, cognitive training, and psychoeducation on SCCs (Ayda et al., 2022; Bhome et al., 2018). Besides the need for further research on these interventions in the dialysis population, it is also important to consider strategies that mitigate/compensate for patients’ everyday cognitive lapses and consequences associated with these lapses (e.g., nonadherence). For example, for patients who report adherence difficulties due to memory issues, strategies such as text message reminders, medication management plans, and medication mobile apps may be helpful.

The present study has several limitations. First, only two time points were included in the present study, which precludes us from conducting growth mixture modelling to identify trajectory groups in a data-driven fashion. Second the observed prevalence rates of probable CIs and persistent cognitive complaint trajectory reported in this study are likely to be underestimates since the KDQOL-CF only contains three items (i.e., slow reaction time, concentration difficulty, and confusion) which do not capture important domains such as memory and executive function that have been shown to be most impaired in ESRD patients (Joshee et al., 2018; O’Lone et al., 2016). Therefore, a score higher than 60 on this scale may not necessarily indicate intact cognitive function and absence of CI (Sorensen et al., 2012). Revision to the KDQOL-CF scale may be needed for a more accurate estimate of the extent of SCCs in the dialysis population.

as mentioned the KDQOL-CF measure is not a comprehensive measure of SCCs. To obtain a better understanding of these complaints in HD patients, more lengthy questionnaires can be used in future studies. Also, the use of binary classification of the KDQOL-CF scores may have resulted in loss of information as it fails to capture longitudinal changes in continuous scores in each trajectory group. Despite the limitations, the current study adopted a prospective design and demonstrated the longitudinal associations of SCCs with clinical, behavioural, and psychosocial outcomes in dialysis patients. SCCs may be a risk factor for poor prognosis in HD patients and therefore screening for SCCs may allow for early identification of those at higher risks of cognitive decline and nonadherence. SCCs may also be a potential target in future intervention studies that aim to prevent exacerbation of cognitive decline and promote self-care behaviour in this population. Research on SCCs in ESRD patients is still in its infancy. A better understanding of this problem based on both quantitative and qualitative evidence is expected to improve future renal care services.

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