Impact of Cognitive Function Change on Mortality in Renal Transplant and End-Stage Renal Disease Patients

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Key Words

Kidney transplant · Cognitive function · Mortality

Abstract

Background: Limited evidence from small-scale studies, mainly involving end-stage renal disease (ESRD) patients, suggests that kidney transplantation may improve cognitive function. We examined changes in cognitive function after a kidney transplant and its association with survival in advanced chronic kidney disease (CKD)/ESRD patients. **Methods:** In a prospective study design, cognitive performance of 90 patients (50.6 ± 13.1 years, 66.7% men, 27.8% blacks, 76% CKD stages 4–5) was assessed at the respective patients' residences using established neurocognitive tests. **Results:** Among the 90 patients, 44 received a kidney transplant (KTx group) while 46 did not (no-KTx group). After a mean follow-up of ~19 months, there was no significant change in scores for majority of cognitive tests in either group. Older age, but not diabetes or renal function status (CKD vs. ESRD), was a determinant of poor follow-up cognitive performance. Additionally, poor attention/psychomotor speed and executive performance (as measured by Trails A and Stroop test, respectively) was associated with higher mortality over a mean follow-up of 4.7 years, even after adjustment for age, sex, dia-

betes, CKD or ESRD status and kidney transplant status. **Conclusion:** Overall, cognitive function does not significantly improve after kidney transplant or significantly decline in non-transplanted, advanced CKD/ESRD patients. Poor attention, psychomotor speed and executive performance independent of transplant status were associated with higher mortality over time.

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Introduction

Up to 30–70% of end-stage renal disease (ESRD) and 17–30% of advanced chronic kidney disease (CKD) patients are reported to have significant cognitive deficits [1–4]. Cognitive impairment may affect the patients' daily functioning, independence, social adjustments, employment options, medication adherence, medical decision making [5] and is also an independent predictor of mortality [6, 7]. Although there is a well-established survival benefit of renal transplantation, the evidence of its effect on cognitive function is limited and not entirely consistent.

Previous studies demonstrated that advanced CKD/ESRD patients have significant impairments in verbal

memory and executive functioning [1, 2, 4, 8]. There also appears to be an association between the severity of kidney disease and the degree of cognitive impairment [3, 5, 9]. The etiology of cognitive impairment in this population is multifactorial including high prevalence of cerebrovascular risk factors, cerebrovascular disease and increased exposure to acute changes in metabolic abnormalities/fluid shifts associated with renal replacement therapy (RRT) [10]. Kidney transplantation, perhaps by improving uremic milieu and metabolic abnormalities, may improve cognitive function. However, it is possible that the risk factors contributing to cognitive impairment cannot be corrected or reversed by transplant alone. In fact, cognitive function may worsen after the transplant as an after-effect of immunosuppressive medications.

Early studies demonstrated a beneficial effect of kidney transplantation on cognitive function, specifically on verbal memory [11–13]. More recent studies have revealed improvement in psychomotor speed, abstract thinking, attention and executive functioning with improvements sustaining well past the initial transplantation [14–16]. Although this is encouraging, these studies remain limited by small sample size, lack of non-transplant comparison group and lack of generalizability to the United States CKD/ESRD population. Moreover, almost all of these studies were performed only on patients undergoing hemodialysis (HD), and very limited information is available regarding the outcomes of non-dialysis CKD undergoing renal transplant.

The primary aim of our study was to examine the changes in cognitive function after a kidney transplant in a cohort of patients with advanced CKD/ESRD. We compared changes in cognitive function over time in patients who received a kidney transplant with those who did not. We hypothesized that those receiving the transplant will have improved cognitive function compared to those without a transplant. Finally, we examined whether baseline cognitive tests were associated with mortality in the transplanted (KTx) and non-transplanted (no-KTx) groups.

Subjects and Methods

Study Participants

This cohort comprises data collected as part of a prospective study that investigated memory, sleep and quality of life in adult, English-speaking patients with advanced CKD (dialysis dependent or Modification of Diet in Renal Disease estimated glomerular filtration rate (eGFR) ≤ 30 ml/min/1.73 m²) or ESRD, defined as being on RRT (at least 3 times per week in-center HD

Fig. 1. Flowchart of patient selection for inclusion in the study cohort.

or peritoneal dialysis) for a minimum of 3 months [17]. We approached patients during routine CKD or dialysis clinic visit, or initial evaluation at a kidney transplant clinic in Western Pennsylvania between March 2004 and December 2008. Exclusion criteria included age (<18 or >90 years), craniofacial abnormalities, active malignancy, treated sleep apnea, active infection, active coronary artery disease, advanced cirrhosis, active alcohol abuse, history of head injury or refractory psychiatric disease. Patients with severe cognitive impairment (advanced dementia, clinically confused or those unable to provide basic personal information) were also excluded. Baseline cognitive evaluation was performed shortly after enrollment during initial home visit and patients were followed up prospectively. All participants signed informed consent and the study was approved by the University of Pittsburgh Institutional Review Board (PRO14010028).

Out of the 145 patients who met the eligibility criteria and consented to this study, 55 failed to complete follow-up cognitive evaluation (fig. 1). Among the 90 participants who completed a baseline and follow-up cognitive evaluation per study protocol, 44 (15 ESRD and 29 CKD) received a transplantation during study period (KTx group) and completed follow-up cognitive evaluation at least 6 months after transplant. We chose this interval to allow for stabilization of renal allograft function and immunosuppressive medication regimen. The remaining 46 patients (7 ESRD and 39 CKD) did not receive transplantations during study period (no-KTx group; fig. 1).

Data Collection

Baseline data were collected from a standardized health interview and questionnaire that included the assessment of previous medical problems, surgeries and relevant medical procedures. Current medications and anthropometric measurements were ob-

Table 1. Description of cognitive tests used

Cognitive test	Brief description	Measurement criteria
CLOX 1 and 2 [39, 40]	Assesses abstract thinking and visual spatial constructive abilities [39, 40].	Scored based on accuracy. Higher score is better
Controlled Oral Word Association (COWA) [41]	Language assessment test for phonetic/semantic fluency components. Individual required to produce words with a designated first letter and a list of animals each within a 1 min period [41]	Combined score used. Higher score is better; 20 words or less is considered seriously deficient
Digit Span Subtest [42]	Individual is required to repeat increasingly longer number sequences in either forward or reverse order. A subtest from Wechsler Memory Scale [42]	Age-based scaled score generated and used
DSST [42]	Test for visual scanning and rapid response where individual substitutes numbers for symbols based on a learned code. A subtest from the Wechsler Memory Scale [42]	Score equaled total number correct within the given time frame
Wechsler Abbreviated Scale of IQ [42]	Abbreviated IQ scale assessment where 2 of 4 subtests (vocabulary and matrix reasoning) were used to generate age-related IQ score [42]	50% percentile for population is 100. Less than 80 is considered borderline
Logical Memory Subtest [42]	Assessment for verbal memory. Individual is read a story, asked to recall story related details immediately and 30 min post. A subtest of Wechsler Memory Scale [42]	Age-based standard score was used
MMSE [43, 44]	Tests orientation, attention, calculation, recall, language, and visual spatial skills [43, 44]	Raw scores used
RCF Copy Condition test [18, 45]	Assesses visual spatial/constructional abilities. Requires individuals to copy complex figures with immediate spontaneous and delayed (30 min later) recall trial [18, 45]	Each copy is scored for accurate reproduction and placement of specific elements of figure. Higher score is better
Stroop test [46]	Assessment of interference in the reaction time of a task. Test requires individual to read the names of colors, name of the color of an image, and name the color of ink of a printed color word [46]	Age-adjusted color word raw score reported. Higher score is better
Trail-Making Tests Parts A and B [47]	Provides an estimate of attention, psychomotor speed, executive functioning and working memory. Part A requires subjects to connect a series of numbers in sequential order as quickly as possible. Part B requires subjects to connect letters and numbers in sequential order as quickly as possible [47]	Measured as time required completing each task. Quicker (lower) scores are better
WCST [47]	Assessment for problem solving that requires flexibility in the face of changing schedules of reinforcement. Individual is given a set of stimulus cards, instructed to match the cards but not told how, and then told whether correct or not [47]. Computerized version used	Number of completed categories reported. Higher score is better

tained using data regarding the self-reported age, race and socio-economic status. Baseline serum laboratory tests were collected from medical record.

Neurocognitive Assessment

Patients were assessed using a battery of well-validated neurocognitive tests with high inter- and intra-rater reliabilities (table 1). Tests were administered by research assistants trained and supervised by an expert in neuropsychological assessment (C.S.). To ensure a quiet, distraction-free environment, assessments were performed at the

patients' residences. By avoiding assessment during HD, we minimized the effect of rapid fluid/electrolyte shifts during HD on cognitive performance. The tests were administered in a standardized way using the same sequence of tests and on paper except the Wisconsin Card Sorting Test (WCST), which was administered on a laptop.

Definition of Exposures

Depression was defined as Patient Health Questionnaire-9 score of ≥ 10 , with 5 or more symptoms – including either depressed mood or anhedonia – present for more than half the day

over the prior 2 weeks and/or self-reported treatment with anti-depressants. Diabetes was evaluated by both self-report and/or current use of insulin or hypoglycemic agents. Cardiovascular disease was evaluated by patient self-reporting (of previous myocardial infarction or heart attack, stroke or previous coronary artery bypass/angioplasty). Patient's overall health-related quality of life was assessed using the short-form health survey (SF-36).

Statistical Analysis

Categorical and continuous variables were presented using frequencies with percentages and means with SDs (or medians with IQR for skewed distributions), respectively. Baseline characteristics were compared between KTx and no-KTx groups. Baseline, follow-up and changes in neurocognitive measures were also compared between the 2 groups. Within-group changes in neurocognitive measures from baseline to follow-up were assessed using linear mixed model with random subject intercept. Between-group comparisons used two-sample t test or Wilcoxon rank sum test and chi-square or Fisher exact test for continuous and categorical measures, respectively. Adjusted analyses of change scores of each neurocognitive measure were conducted using linear models that were adjusted for age, gender, baseline cognitive score and intelligence quotient (IQ). IQ score was used as a proxy for education due to limited capture of the education data by the binary 'high school graduate' variable. In multivariable linear regression models stratified by KTx group, we examined the association between select follow-up neurocognitive tests (Mini Mental Status Examination (MMSE), Logical Memory 1 and 2, and Trails A and B) and patient characteristics (age, diabetes, renal function status (CKD vs. ESRD) and IQ score) that may be important determinants of cognitive function after adjusting for the baseline cognitive score. Due to skew, Trails A and B were log-transformed prior to modeling. Within the KTx group, pre- and post-transplant neurocognitive scores were compared between CKD and RRT using 2-sample t test or Wilcoxon rank sum test.

To examine the relationship between cognitive performance (MMSE, Logical Memory 1 and 2, Trails A and B) and overall survival, we fitted Cox proportional hazards model with and without adjusting for age, gender, diabetes, renal function status and a time-dependent covariate, receipt of kidney transplant. Hazards ratio (HR) along with the 95% CIs were reported. National Death Index data until December 31, 2011, were obtained and patients still alive on this date were censored.

For sensitivity analysis, we applied principal component (PC) analysis (PCA) of the neurocognitive measures to reduce the dimensionality. We examined the scree plot, Eigen values and cumulative proportion of variance to determine the number of PCs to keep. Loadings and contributions of the neurocognitive measures were used to characterize the PCs and to examine agreement with the components of commonly presented latent constructs. PC scores were calculated and analyzed using the same methods applied to the original neurocognitive measures. The tests included in PCA analysis were Clock Drawing Test (CLOX 1 and 2), Controlled Oral Word Association, Logical Memory 1 and 2, Trails A and B, Stroop, Digit Span Forward and Backward, Digit Symbol Substitution Subtest (DSST), Rey-Osterrieth Complex Figure (RCF) Copy Condition test and WCST.

All statistical analyses were carried out in R (version 13.2) [18] using the dplyr package [19] for data manipulation, group

comparisons [20] for descriptive tables, ggplot2 [21] for graphics, survival [22] for survival analysis and lme4 for linear mixed modeling.

Results

Baseline characteristics of the KTx and no-KTx group are shown in table 2. Patients who received KTx had significantly lower prevalence of diabetes (27.3 vs. 53.3%, $p = 0.02$) as compared to the no-KTx group. The KTx group had trends toward more patients on RRT and lower eGFR among non-dialysis-dependent CKD ($eGFR\ 16.2 \pm 4.9$ vs. 19.9 ± 8.0 , $p = 0.04$) than the no-KTx group. Except for better self-reported physical health (SF-36 PCS) in the KTx group, both groups were similar in terms of baseline demographics, comorbidities (including history of stroke), cognitive reserve (IQ score), mental health including depression, antidepressant or antihistamine use and biochemical status. Among the KTx group, those with non-dialysis-dependent CKD were more likely to be white, employed, less anemic and have higher cognitive reserve (IQ score) and lower SF-36 mental component summary score as compared to those with ESRD (online suppl. table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000451059). Among the no-KTx group, there were no differences in any demographics, comorbidities or biochemical variables (online suppl. table 2). At CE#1, the KTx and no-KTx group had similar scores for all cognitive tests except CLOX 1 and 2, for which the KTx group performed slightly better (table 3).

In our KTx group, 78% of patients were on a single immunosuppressant, most commonly tacrolimus (95% patients), with an average daily dose of 8.1 mg. CellCept was used in 22%, Rapamune in 4.9% and a combination of one of these with steroids in 2.4% of the patients. The average daily doses of CellCept, Rapamune and steroids were 984, 4 and 30 mg, respectively.

Longitudinal Change in Cognitive Function

The time interval between the first (CE#1) and the final (CE #2) cognitive evaluation for the entire cohort was 19.1 ± 9.0 months and was comparable between the KTx and no-KTx groups (table 1). For KTx group, the mean time interval from kidney transplant to CE #2 was 8.3 ± 5.2 months. Table 4 shows the longitudinal changes in cognitive scores for both the groups. In the KTx group, there was no significant change in cognitive scores for all tests except slight improvement in RCF delayed recall testing (19.1 ± 8.4 vs. 17.0 ± 7.8 , $p = 0.02$) compared to

Table 2. Baseline characteristics comparing KTx vs. no-KTx group

Characteristics	All (n = 90)	KTx group (n = 44)	No-KTx group (n = 46)	p value ^a
Age, years	50.6 (13.1)	48.0 (13.9)	53.0 (11.8)	0.07
Gender, male	60 (66.7)	33 (75.0)	27 (58.7)	0.16
Race				0.08
White	63 (70.0)	35 (79.5)	28 (60.9)	
Black	25 (27.8)	9 (20.5)	16 (34.8)	
Others	2 (2.2)	0 (0.0)	2 (4.4)	
High school graduate	83 (92.2)	42 (95.5)	41 (89.1)	0.44
Married	55 (61.1)	29 (65.9)	26 (56.5)	0.49
Employed	35 (38.9)	20 (45.5)	15 (32.6)	0.30
Ever smoker	47 (52.2)	25 (56.8)	22 (47.8)	0.52
Cardiovascular disease	16 (17.8)	5 (11.4)	11 (23.9)	0.20
Diabetes	36 (40.4)	12 (27.3)	24 (53.3)	0.02
Hypertension	75 (89.3)	39 (90.7)	36 (87.8)	0.74
Stroke	5 (5.75)	1 (2.38)	4 (8.89)	0.36
Depression	8 (8.99)	2 (4.55)	6 (13.3)	0.27
Renal function status				0.07
CKD	68 (75.6)	29 (65.9)	39 (84.8)	
HD	20 (22.2)	14 (31.8)	6 (13.0)	
PD	2 (2.22)	1 (2.27)	1 (2.17)	
Dialysis vintage ^c , months	9.0 (4.5–19.0)	5.0 (3.5–11.5)	15.0 (10.5–40.2)	0.07
Cognitive reserve (IQ score)	101 (15.6)	103 (16.2)	99.4 (14.9)	0.33
Anti-depressant use	15 (16.7)	9 (20.5)	6 (13.0)	0.51
Anti-histamine use	2 (2.2)	1 (2.3)	1 (2.2)	1.00
SF36 Physical Component Summary score	41.4 (6.6)	43.0 (6.0)	40.0 (6.8)	0.04
SF 36 Mental Component Summary score	44.5 (7.5)	44.8 (6.8)	44.2 (8.2)	0.73
Systolic blood pressure ^b	147 (23.2)	147 (19.5)	146 (26.7)	0.79
Diastolic blood pressure ^b	83.6 (13.6)	85.7 (13.1)	81.4 (13.9)	0.14
Serum creatinine, mg/dl	5.0 (2.3)	5.5 (2.4)	4.4 (2.0)	0.04
eGFR (Modification of Diet in Renal Disease) ^d , ml/min/1.73 m ²	18.2 (7.0)	16.2 (4.9)	19.9 (8.0)	0.04
Hemoglobin, g/dl	11.8 (1.4)	11.7 (1.2)	11.9 (1.5)	0.56
Albumin, g/dl	3.8 (0.6)	3.9 (0.5)	3.8 (0.6)	0.24
Phosphorus, mg/dl	4.8 (1.4)	4.9 (1.4)	4.7 (1.5)	0.69
Bicarbonate, mEq/l	23.5 (3.3)	22.9 (3.0)	24.1 (3.5)	0.12
Parathyroid hormone, pg/ml	176 (108–310)	227 (124–263)	156 (104–320)	0.68
Time from 1st to 2nd cognitive evaluation, months	19.1 (9.0)	17.7 (8.8)	20.4 (9.0)	0.15
Time from 1st cognitive evaluation to KTx, months		9.3 (7.7)		
Time from KTx to 2nd cognitive evaluation, months	–	8.3 (5.2)	–	–

Data are presented as percentage n (%), mean (SD) or median (Q1–Q3) where Q1 is the 25th percentile and Q3 is the 75th percentile.

^a p values use analysis of variance or Kruskal–Wallis for continuous variables and Fisher exact or chi-square for categorical variables.

^b Blood pressure was measured during home visit at the time of cognitive evaluation.

^c Dialysis vintage missing for 1 patient.

^d For non-dialysis-dependent CKD only.

pre-transplant score. We also tested whether the patients' post-transplant scores were different based on patients' CKD or ERSD status at baseline and found no significant difference (online suppl. table 3). Similarly, in the no-KTx group, there was no change in cognitive scores over a period of 20.4 ± 9.0 months. Figure 2 displays unadjusted and adjusted (for age, sex, baseline IQ (as proxy for edu-

cation) and baseline cognitive score) mean difference of longitudinal changes in cognitive scores between KTx and no-KTx groups. Overall, there was no significant difference in the change of cognitive function over time in the 2 groups except for greater improvement in Logical Memory 2 within KTx group (adjusted HR 1.08 (95% CI 0.20–1.96); $p = 0.02$).

Table 3. Baseline cognitive scores (CE#1) comparing KTx vs. no-KTx group

Neurocognitive test	All (n = 90)	KTx group (n = 44)	No-KTx group (n = 46)	p value
MMSE	27.7 (2.1)	28.0 (2.0)	27.4 (2.1)	0.20
CLOX 1	12.9 (2.2)	13.5 (2.1)	12.4 (2.2)	0.02
CLOX 2	14.5 (0.9)	14.7 (0.5)	14.3 (1.1)	0.03
Controlled Oral Word Association total	35.3 (13.0)	36.2 (12.9)	34.5 (13.2)	0.53
Digit Span Forward	10.1 (2.3)	10.2 (2.5)	9.9 (2.0)	0.46
Digit Span Backward	6.8 (2.5)	7.2 (2.5)	6.4 (2.4)	0.15
DSST	49.0 (14.5)	51.3 (16.1)	46.7 (12.5)	0.14
Logical Memory 1	8.0 (3.1)	8.3 (2.8)	7.8 (3.3)	0.45
Logical Memory 2	8.9 (2.7)	9.1 (2.7)	8.7 (2.8)	0.49
RCF copy	31.6 (5.0)	32.2 (4.2)	31.1 (5.7)	0.29
RCF delayed recall	16.1 (7.2)	17.0 (7.8)	15.1 (6.5)	0.22
Stroop	41.5 (10.0)	42.2 (11.7)	40.9 (8.3)	0.55
Trails A time, s	31.5 (26.0–39.8)	29.0 (26.5–39.0)	33.0 (26.0–41.8)	0.18
Trails B time, s	79.0 (54.0–105)	69.0 (53.0–95.8)	87.0 (59.0–116)	0.13
WCST	2.2 (1.6)	2.4 (1.8)	1.9 (1.4)	0.15

Data are presented as percentage n (%), mean (SD) or median (Q1–Q3) where Q1 is the 25th percentile and Q3 is the 75th percentile.

Determinants of Cognitive Function

We conducted multivariable analysis of association of CE#2 with select patient characteristics that may be important determinants of cognition (age, baseline IQ (as proxy for education), diabetes, renal function status (CKD vs. ESRD)) after adjusting for baseline score and stratification by transplant status. For both the KTx and no-KTx groups, lower IQ was associated with lower MMSE score but did not associate with Trails A or B or Logical Memory 1 or 2. Within the no-KTx group, increasing age was associated with poorer performance on MMSE, Trails A, Logical Memory 1 and 2. Diabetes and renal function status were not significant determinants of cognitive function for either of the group (online suppl. fig. 1).

Association of Cognitive Function with Survival

For survival analysis, our cohort included all subjects who had completed a baseline cognitive evaluation (n = 145). There were 35 deaths over a mean follow-up period of 4.7 ± 1.8 years. Association of baseline cognitive scores with mortality was assessed by adjusting for transplant status as a time-dependent variable. In unadjusted analysis, poor performances on Trails A, Trails B, DSST and Stroop test were associated with higher mortality (unadjusted HR 3.03 (95% CI 1.53–6.02); $p = 0.002$ for Trails A; 3.25 (95% CI 1.60–6.61); $p = 0.002$ for Trails B, 0.97 (95% CI 0.94–0.99); $p = 0.016$ for DSST; 0.94 (95% CI 0.90–

0.98); $p = 0.002$ for Stroop; fig. 3). However, after adjustment for age, sex, diabetes, CKD or ESRD status and kidney transplant status, only poor performance on Trails A and Stroop were significantly associated with mortality (adjusted HR 3.47 (95% CI 1.19–10.1); $p = 0.02$ and 0.93 (95% CI 0.88–1.00); $p = 0.04$, respectively). There was no association of baseline MMSE, CLOX 1 or 2, Logical Memory 1 or 2, RCF copy, RCF delayed recall, Digit Span Forward or Backward with mortality.

Sensitivity Analysis Using PCA

We employed PCA to derive a composite score of cognition. The number of PCs to keep, however, was not consistent among the different criteria. The scree plot showed that 1 component is sufficient, but only 36% of the variance would be accounted for. The criterion of Eigen value >1 would keep 5 components, which would account for about 70% of the variance. We would have to keep 7 components in order to account for at least 80% of the variability. These findings suggest that PCA was not very effective for this data set. Nevertheless, we chose to keep 5 components. Based on the neurocognitive loadings and contributions, these components represent (1) executive functioning, (2) logical memory, (3) digit span, (4) RCF and (5) CLOX. There was no significant difference between the KTx and no-KTx groups' baseline or follow-up cognitive functioning. In the KTx group, the only significant change was a slight improvement in CLOX (post-pre

Table 4. Raw score comparison for cognitive tests pre vs. post kidney transplant in the KTx and no-KTx group

Neurocognitive test	KTx group		No-KTx group		p value ^a	difference (post-pre)	p value ^a	follow-up score ^c	difference (follow-up-baseline)	p value ^a
	pre KTx score ^b	post KTx score ^b	pre KTx score ^b	post KTx score ^b						
MMSE	28.0 (2.0)	28.1 (2.1)	27.4 (2.1)	27.7 (1.9)	0.60	0.1 (1.7)		27.7 (1.9)	0.3 (2.0)	0.39
IQ	102.6 (16.2)	103.9 (16.0)	99.4 (14.9)	99.7 (17.8)	0.30	1.3 (8.1)		99.7 (17.8)	0.3 (10.0)	0.86
CLOX 1	13.5 (2.1)	13.1 (1.9)	12.4 (2.2)	12.1 (3.0)	0.34	-0.4 (2.9)		12.1 (3.0)	-0.3 (3.2)	0.59
CLOX 2	14.7 (0.5)	14.5 (0.8)	14.3 (1.1)	13.8 (1.6)	0.06	-0.3 (0.9)		13.8 (1.6)	-0.5 (1.4)	0.01
Controlled Oral Word Association total	36.2 (12.9)	37.7 (12.4)	34.5 (13.3)	34.9 (12.9)	0.32	1.5 (9.6)		34.9 (12.9)	0.4 (7.1)	0.73
Digit Span Forward	10.3 (2.5)	10.6 (2.4)	9.9 (2.0)	10.2 (1.9)	0.41	0.3 (2.5)		10.2 (1.9)	0.3 (1.6)	0.28
Digit Span Backward	7.2 (2.5)	7.3 (2.7)	6.4 (2.4)	6.2 (2.6)	0.61	0.2 (2.4)		6.2 (2.6)	-0.2 (1.9)	0.43
DSST	51.3 (16.1)	52.1 (17.7)	46.7 (12.5)	45.4 (13.4)	0.36	0.9 (6.2)		45.4 (13.4)	-1.4 (7.0)	0.20
Logical Memory 1	8.3 (2.8)	8.6 (3.4)	7.8 (3.3)	7.5 (2.9)	0.50	0.3 (2.7)		7.5 (2.9)	-0.3 (2.3)	0.38
Logical Memory 2	9.1 (2.7)	9.7 (2.9)	8.7 (2.8)	8.4 (2.7)	0.09	0.6 (2.3)		8.4 (2.7)	-0.4 (2.1)	0.23
RCF copy	32.2 (4.2)	32.6 (3.9)	31.1 (5.7)	31.3 (5.3)	0.60	0.3 (4.3)		31.3 (5.3)	0.5 (4.7)	0.58
RCF delayed recall	17.0 (7.8)	19.1 (8.4)	15.1 (6.5)	16.6 (8.3)	0.02	2.1 (5.7)		16.6 (8.3)	1.2 (5.3)	0.13
Stroop	42.2 (11.7)	43.3 (11.9)	40.9 (8.3)	41.3 (9.0)	0.14	1.8 (7.2)		41.3 (9.0)	0.3 (7.9)	0.77
Trails A time, s	29.0 (26.5–39.0)	27.5 (20.8–35.3)	33.0 (26.0–41.8)	34.0 (26.0–43.5)	0.16	-1.5 (-7.3 to 1.5)		34.0 (26.0–43.5)	0.0 (-4.8 to 6.8)	0.43
Trails B time, s	69.0 (53.0–95.8)	61.0 (43.8–99.5)	87.0 (59.0–116.0)	78.0 (57.3–123.3)	0.84	-2.5 (-13.3 to 9.3)		78.0 (57.3–123.3)	-4.0 (-25.0 to 8.0)	0.60
WCST	2.4 (1.8)	2.6 (1.6)	1.9 (1.4)	2.3 (1.7)	0.49	0.3 (2.0)		2.3 (1.7)	0.4 (1.5)	0.10

Tx 0.3 (1.0); $p = 0.04$). For survival analysis using PCA, we found that worse performance on PC Executive functioning was associated with mortality in unadjusted analysis (HR 0.82 (95% CI 0.68–0.99); $p = 0.04$); however, this became insignificant when adjusted for age, sex, diabetes, CKD or ESRD status and KTx status.

Selection Bias Analysis

To rule out the selection bias, we compared the characteristics of the study cohort for patients who had 2 cognitive evaluations ($n = 90$) with patients who completed only baseline cognitive evaluation ($n = 55$) and subsequently dropped out. The groups were similar in terms of demographics, comorbidities and renal function status, with the only significant difference being dialysis vintage duration (median 9.0 (4.5–19.0) months for study cohort vs. 45.0 (11.0–61.0) months, $p = 0.01$ for the drop-outs; online suppl. table 4). There was no significant difference in any of the baseline cognitive scores among the 2 groups (online suppl. table 5).

Discussion

Our prospective study demonstrated that kidney transplantation was not associated with significant improvement in cognitive function among patients with advanced CKD/ESRD. In patients with advanced CKD/ESRD who had not received a transplant, cognitive function remained stable over a mean follow-up of about 20 months. Multivariable stratified analysis demonstrated that diabetes and renal function status (CKD vs. ESRD) were not associated with changes in cognitive performance over time, but lower age was associated with better performance on certain tests. We also found that poor attention/psychomotor speed and executive performance (as measured by Trails A and Stroop test, respectively) were significantly associated with higher mortality over a

(footnote to table 4)

Data are presented as mean (SD) or median (Q1–Q3) where Q1 is the 25th percentile and Q3 is the 75th percentile.

^a p value obtained from unadjusted random intercept model.

^b In KTx group, for baseline (pre KTx score)-Stroop and WCST missing for 2 subjects. For post-KTx score, CLOX-1 and CLOX-2 scores missing for 1 subject and WCST missing for 3 subjects.

^c In no-KTx group, for baseline scores – Trail B missing for 1 subject, WCST missing for 2 subjects, Stroop missing for 1 subject. For follow-up scores, RCF copy missing for 6 subjects, RCF delayed recall missing for 1 subject, WCST missing for 2 subjects, Stroop missing for 3 subjects.

Fig. 2. Mean difference in the longitudinal change in cognitive scores (post-pre) in KTx vs. no-KTx group. Adjusted for age, sex and baseline cognitive score. * Effect per 5 unit increase.

mean follow-up of 4.7 years, even after adjustment for age, sex, diabetes, CKD or ESRD status and kidney transplant status.

Our study adds to the existing literature by examining the effect of transplant on cognitive function in a representative US CKD/ESRD population. While most studies have evaluated the effect of transplant only in HD patients, we extend these findings to non-dialysis-dependent CKD patients, which comprised 76% of our cohort. A unique strength of our study was that both baseline and follow-up cognitive assessments were performed in the patients' residences, away from distractions and acute effect of HD, as opposed to during HD or in a research office in prior studies, which by itself may have introduced bias [13–16]. There is emerging evidence that, in addition to the uremic milieu, HD procedure it-

self poses significant circulatory stress and causes irreversible ischemic brain injury in this population that is having already-existing vascular diseases [23]. The longer dialysis vintage in our cohort compared to most other studies (median 5 years compared to mean 2.9 ± 2.5 years in Gelb et al., 2.6 ± 2.7 years in Griva et al. [13] and 3.6 ± 3.6 years in Harciarek et al. [14]) may have contributed to lack of improvement in cognitive performance in our study [24]. Another possible explanation may be the patient characteristics of our cohort, which was slightly older than in most other studies and may have chronic aging-related changes in cerebrovascular structure/function that are not reversed by transplantation. We did find that older age was strongly associated with diminished cognitive performance. Our patients also had a higher prevalence of diabetes, which is a risk factor for micro-

Fig. 3. Association of baseline cognitive function with survival. * HR per 0.25 unit increase.

vascular changes, although we did not see any differences in our stratified analysis, which was underpowered. Although the KTx group had more ESRD patients (34%) than the no-KTx group (15%), we do not feel that this affected our results. It may be argued that cognitive function may be directly correlated with the severity of kidney disease. However, the baseline cognitive scores for the KTx and no-KTx groups were similar for all cognitive tests except CLOX 1 and 2, for which the KTx had slightly better scores. Moreover, there was no significant difference in post-transplant scores for any of the tests based on the patients' pre-transplant renal function status or association of CE#2 with renal function status in multivariable analysis.

The high prevalence of traditional vascular risk factors, such as hypertension and diabetes in CKD/ESRD patients, may contribute to the high prevalence of clinical

and subclinical cerebrovascular disease leading to abnormalities such as cerebral atrophy, silent brain infarcts and white matter hyper intensities [25–29]. Studies indicate that cognitively impaired ESRD patients have more frequent and severe multiple infarct dementia, vascular dementia and cerebrovascular lesions even in the absence of clinical stroke [30–33]. Such findings suggest that cerebrovascular disease is the primary cause of cognitive impairment in this population [23], thus not likely to be corrected or reversed by kidney transplant.

An interesting finding in our study was stable cognitive function in no-KTx advanced CKD/ESRD patients over time, contrary to some studies suggesting decline in cognition in ESRD patients over a period of 2 years [15]. It may be that cognitive function is better preserved over time in non-dialysis CKD patients, which was the majority of our cohort. Additionally, the mean

baseline IQ our cohort was 101 ± 15.6 (near average per normative data), which may have contributed to better cognitive preservation or test performance over time. Alternatively, we might have selected a group of patients who are more cognitively intact, although we did not find any evidence of selection bias when compared to patients who had completed only baseline evaluation.

To our knowledge, none of the prior studies assessing cognitive function and mortality in CKD accounted for transplant status [27]. We found that poor baseline cognitive function, especially attention, psychomotor speed and executive functioning was independently associated with higher mortality. Despite reaching statistical significance, our results should be interpreted cautiously given the limited sample size and multiple testing in our study. Nevertheless, our findings are consistent with and add to prior literature, and may have important clinical implications in identifying high-risk patients [7].

Our study has several areas of strength. Ours is the largest study evaluating the effect of kidney transplant using a prospective study design. Moreover, the inclusion of a CKD/ESRD control group of patients who did not receive kidney transplant allows for better comparison between the KTx and no-KTx groups and assessment of longitudinal changes in the no-KTx group over time. Additionally, unlike most prior studies, we administered in-home cognitive tests both times, thus minimizing the effect of rapid fluid/electrolyte shifts and hemodynamic changes during HD on cognitive function as well providing a consistent testing environment across the 2 tests. Lastly, we accounted for depression and medications that may impair cognition, both of which may be important confounders in this patient population [34].

Our study has some limitations. We did not have longer term cognitive follow-up to evaluate the effect of transplant on cognition. However, the mean time from kidney transplant to follow-up evaluation in our study was 8.5 ± 5.3 months, which should have allowed adequate time for stabilization of renal function and immunosuppressive drug levels after the transplant. Moreover, prior studies have demonstrated changes in cognitive function over a similar follow-up time interval [13, 14, 35]. Thus, longer follow-up would not be expected to change our results. Second, although a large number of patients who initially enrolled in the study failed to complete follow-up testing, we did not find any evidence of selection bias in terms of demographics, comorbidities, renal function status or baseline cognitive function. How-

ever, it is possible that there may be differences in other variables that were not captured in our study, thus limiting the generalizability of our findings. Third, the transplant allocation was non-random, and one could posit that those who had received a transplant had higher baseline and follow-up cognitive performance and may be more likely to have a ceiling effect. However, we did not find any significant differences in baseline cognitive scores or follow-up scores for any of the measured domains in our cohort. Fourth, although we did not adjust for the effect of immunosuppressive medications on cognitive performance, a contemporary lower immunosuppression protocol was the approach at our transplant center during the time period of this study. Lastly, because of the small number of deaths in our cohort, especially in the KTx group, we were not able to adjust for variables that may affect patient survival.

In conclusion, in a prospective study of CKD/ESRD patients receiving a kidney transplant compared with those who did not receive a transplant, we observed no significant improvement in cognitive function post the transplant. Moreover, we did not find any significant decline in cognitive function over time in those CKD/ESRD patients who did not receive a transplant. We did find poor that cognitive function, especially attention, psychomotor speed and executive functioning, was independently associated with increased mortality. More studies are needed to investigate the determinants of cognitive function in this population and long-term effects on cognitive function post the kidney transplant.

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Disclosure Statement

The authors of this manuscript have no conflicts of interest to disclose.

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