

# Neurocognitive Function Changes Following Kidney Transplant: A Prospective Study

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**Rationale & Objective:** Patients with advanced kidney disease are at risk for cognitive impairment, which may persist after kidney transplantation. We sought to understand changes in neurocognitive function domains utilizing comprehensive cognitive assessments.

**Study Design:** Prospective cohort study.

**Setting & Population:** Single-center study of patients undergoing kidney transplantation.

**Exposure:** Kidney transplantation.

**Outcomes:** Changes in neurocognitive function as measured by the Repeatable Battery for Assessment of Neuropsychological Status (RBANS) and the Trail Making Test Parts A and B (TRAIL A and B) before transplantation (baseline) and compared to 3 months and 12 months posttransplant.

**Analytical Approach:** Wilcoxon signed-rank and linear mixed effect models were utilized to assess changes in neurocognitive scores at 3 months and 12 months compared to baseline.

**Results:** Thirty-two patients were included with a mean age of 45 years, 47% female, 85% White, and 62% with at least some college education.

Hypertension and diabetes were etiologies of kidney disease in 31% and 25% of patients, respectively. Baseline RBANS and TRAIL A and B scores averaged  $84.7 \pm 14$ ,  $40.4 \pm 9.9$ , and  $41 \pm 11.5$ , respectively. Although there were posttransplant improvements in immediate and delayed memory at 3 months, these were not sustained at 12 months. There were no significant differences from baseline at 3 months and 12 months in RBANS index scores for language, visuospatial/constructional abilities, and attention. Compared to baseline, TRAIL A scores were not significantly different at 3 months but were significantly improved at 12 months, whereas TRAIL B scores improved significantly at both 3 months and 12 months.

**Limitations:** Single-center design and small sample size.

**Conclusions:** Utilizing comprehensive cognitive assessments, we found improvements in attention and executive function in the first posttransplant year as measured by TRAIL A and B. However, there was no significant change in global cognition as measured by RBANS. These findings identify cognitive domains for potential intervention in the posttransplant population.

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Kidney Med. XX(XX):100560. Published online month xx, xxxx.

doi: 10.1016/j.xkme.2022.100560

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Q3 Persons with kidney failure and earlier stages of chronic kidney disease are known to be at increased risk for cognitive impairment when compared to the general population.<sup>1-6</sup> The COGNITIVE-HD study showed that up to 71% of patients treated by maintenance hemodialysis

correcting metabolic abnormalities and may contribute to further cognitive decline.<sup>7,8</sup> In fact, the prevalence of cognitive impairment in kidney transplant candidates ranges from 6%-10%.<sup>9-11</sup>

Kidney transplantation can correct the metabolic derangements and eliminate the fluid and osmotic shifts that patients can experience on dialysis; however, cognitive impairments still persist posttransplant.<sup>10</sup> This has important implications for patient and graft survival as cognitive impairment at time of transplantation has been associated with an increased risk of graft loss and mortality in kidney transplant recipients.<sup>9,12</sup> In the current literature, there are mixed findings on the impact of transplantation on global cognitive function and individual cognitive domains.<sup>7,9,12-23</sup> Multiple studies assessing global cognitive function only utilized screening tests such as the Modified Mini-Mental State (3MS) test or Mini-Mental State Examination rather than more comprehensive cognitive assessments.<sup>9,12,17,18,21,23</sup> A limited meta-analysis evaluated the impact of kidney transplant on different cognitive domains and determined that transplant recipients had improved cognitive performance in abilities including processing speed, verbal and visual memory, and spatial reasoning compared to dialysis patients or those

## Editorial, . . .

have impairment in at least 1 cognitive domain, including motor function, executive function, language, learning and memory, orientation, and complex attention.<sup>2</sup> A meta-analysis in 2019 demonstrated that mild cognitive impairment could be overlooked, and some of our traditional methods for screening may not detect mild expressions of impairment in the pre-dialysis and dialysis population, underestimating the significant burden cognitive impairment has on this patient population.<sup>3</sup> Multiple mechanisms have been proposed to account for the increased risk of cognitive impairment because of kidney disease, including increased uremic toxins, hyperparathyroidism, and Klotho deficiency.<sup>7</sup> Unfortunately, the initiation of dialysis in the chronic kidney disease population does not necessarily reverse these deficits despite

**PLAIN-LANGUAGE SUMMARY**

Patients with advanced kidney disease are at risk for cognitive impairment, which may persist after kidney transplantation. This study measured neurocognitive function in 32 patients before transplant and at 3 and 12 months posttransplant utilizing the Repeatable Battery for Assessment of Neuropsychological Status and the Trail Making Test Parts A and B. The study found that there were improvements in attention and executive function in the first posttransplant year as measured by the Trail Making Test Parts A and B. However, there was no significant change in global cognition as measured by the Repeatable Battery for Assessment of Neuropsychological Status test. These findings identify cognitive domains for potential intervention in the posttransplant population.

with chronic kidney disease; however, they continued to perform below matched controls and did not improve in domains of attention, executive function, and verbal fluency.<sup>15</sup>

Therefore, although it is established that kidney transplant candidates are at risk for pre-existing cognitive impairment, further research is warranted to better understand the impact of kidney transplantation on a wide array of cognitive domains, as previous investigations have largely focused on global cognition using brief screening tools. In this prospective study, we aimed to assess the trajectory of and point-specific change in global cognition, attention, and executive function through comprehensive cognitive assessments that evaluate diverse and clinically relevant cognitive domains in kidney transplant recipients before transplantation and during the first posttransplant year.

**METHODS****Study Setting and Participants**

This was a prospective, single-center study that enrolled patients to undergo neurocognitive performance testing before transplantation and at 3 months and 12 months posttransplant. The study occurred from July 2017 to June 2019. Inclusion criteria were: (1) age greater than or equal to 18 years, (2) eligible for kidney transplantation as determined by the surgical and medical teams, (3) admitted to the hospital for an impending deceased donor kidney transplant or seen in clinic for a pre-operative evaluation before a scheduled living donor kidney transplant, and (4) able to provide informed consent. Patients who were to receive a dual-organ transplant or who were non-English-speaking were excluded. Patients were screened for eligibility through the electronic medical record. The final cohort (N=32) included participants who had baseline data and at least 1 posttransplant observation for the Repeatable Battery for Assessment of Neuropsychological

**Table 1.** Neurocognitive Tests

Neurocognitive Test	Description
TRAIL Making Test A and B	A measurement of attention and executive function. TRAIL A is a test of cognitive flexibility and TRAIL B tests set shifting. Combined, they provide information on visual search, scanning, speed of processing, mental flexibility, and executive functions.
Repeatable Battery for Assessment of Neuropsychological Status (RBANS)	A measurement of global cognition and tests 5 individual domains: attention, language, visuospatial/constructional abilities, and immediate and delayed memory.

Status (RBANS) and/or the Trail Making Test Part A (TRAIL A) and/or Part B (TRAIL B). The study was approved by the Vanderbilt University Institutional Review Board (IRB#170144). The clinical and research activities being reported are consistent with the Principles of the Declaration of Istanbul as outlined in the Declaration of Istanbul on Organ Trafficking and Transplant Tourism.

**Data Collection**

Patient and transplant characteristics were obtained from the electronic medical record. Neurocognitive performance scores were tabulated and computed after completion of testing. Study data were collected and managed using Research Electronic Data Capture hosted at Vanderbilt University.<sup>24,25</sup> Research Electronic Data Capture is a secure, web-based software platform designed to support data capture for research studies.

**Neurocognitive Performance Testing**

We assessed global cognition and attention and executive function before transplantation (baseline) and at 3 and 12 months posttransplant utilizing the RBANS and the TRAIL A and B) (Table 1). The RBANS is a broad-based neuropsychological battery measuring global cognition and tests 5 individual domains: attention, language, visuospatial/constructional abilities, and immediate and delayed memory. It consists of 12 subtests that yield 5 index scores, one for each domain tested, and a total scale score. General population age-adjusted mean and standard deviation (SD) reference values are  $100 \pm 15$  (possible range 40-160), with lower scores indicating worse performance. Scores on the RBANS of  $< 78$  are considered to reflect significant cognitive impairment.<sup>26</sup> The TRAIL A and TRAIL B tests measure attention and executive function, specifically cognitive flexibility and set shifting, respectively. They provide information on visual search, scanning, speed of processing, mental flexibility, and executive functions. T-scores on TRAIL A and TRAIL B tests are adjusted for age, sex, and education and have a mean of 50

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and an SD of 10 (lower scores reflect worse performance). T-scores of  $\leq 35$  are considered to reflect significant cognitive impairment.<sup>27</sup> Tests comprising our battery are psychometrically robust and suitable for use with a broad array of medical populations. All cognitive tests were administered by trained research personnel and took approximately 45-60 minutes to complete.

## Outcome

The primary outcome of interest was change in neurocognitive function as measured by RBANS total and the 5 RBANS index scores and TRAIL A and TRAIL B scores at 3 and 12 months posttransplant in comparison to pretransplant baseline scores.

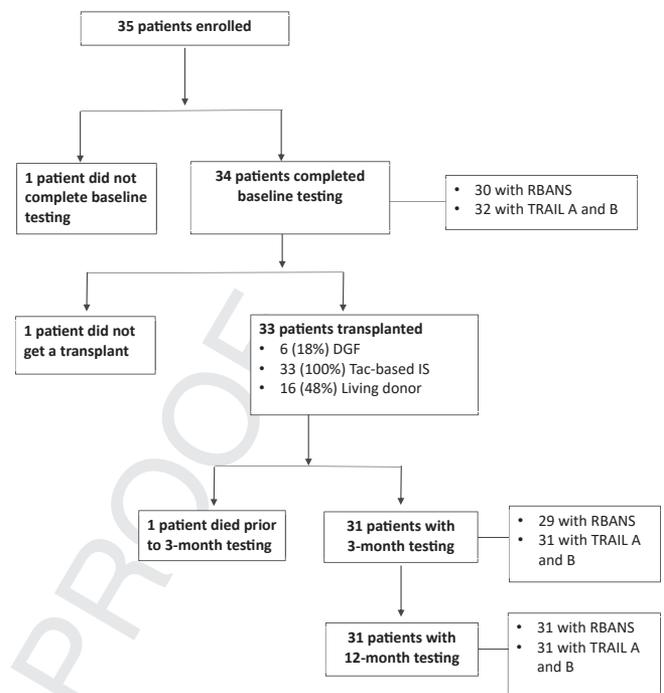
## Statistical Analysis

Summary statistics were computed. Categorical variables were described using frequencies and percentages while continuous variables were expressed as medians (with interquartile ranges) or means (with SDs). Neurocognitive performance scores were referenced to population-based adjusted means. Consistent with the standard convention, cognitive impairment was defined as having a score 1.5 SDs or more below the population mean for each measure.<sup>26</sup> Among patients having data at all 3 time points, differences in median scores at 3 and 12 months posttransplant were assessed for all cognitive function measures as within-subjects planned comparisons versus baseline scores using Wilcoxon signed-rank tests. To comprehensively evaluate outcomes, and to incorporate all available data among patients having baseline and at least 1 posttransplant observation for a given measure, linear mixed effects models were used to assess the effect of posttransplant time point (3 and 12 months; reference pretransplant baseline) for all neurocognitive measures. Data at each posttransplant time point (referenced to pretransplant data) and an intercept were modeled as fixed effects, with a random effect specified at the patient level. To address concerns regarding Type I error, given that analyses were conducted for 8 outcome measures (RBANS total score, 5 RBANS index scores, TRAIL A and TRAIL B), data were evaluated as 2 planned comparisons (3 and 12 months posttransplant versus baseline), and a P value of  $< 0.01$  was considered statistically significant. All analyses were performed using IBM SPSS Statistics for Windows, version 27 (IBM Corp).

## RESULTS

### Study Cohort

During the study period, 35 patients in total were enrolled. Three were excluded, as indicated (Fig 1). Of the remaining 32 patients, 30 completed baseline RBANS assessment and all 32 completed baseline TRAIL A and TRAIL B tests. Baseline testing was completed within 24 hours for recipients of deceased donor kidneys or at the



**Figure 1.** Patient enrollment and testing. DGF, ; IS, ; RBANS, Repeatable Battery for Assessment of Neuropsychological Status; Tac,; TRAIL A and B, Trail Making Test Parts A and B.

time of standard pre-operative evaluation for living kidney recipients. Repeat testing was conducted at a mean of  $3.5 \pm 0.7$  months posttransplant for the 3-month assessment and at a mean of  $12.5 \pm 1.3$  months for the 12-month assessment. Twenty-nine patients completed RBANS testing at 3 months posttransplant and 31 patients completed RBANS testing at 12 months. Thirty-one patients completed follow-up testing for TRAIL A and TRAIL B at 3 and 12 months. Table 2 outlines the characteristics of the 32 patients included in the study. The cohort had an average age of 45 years, 47% were female, and 87% were White. Sixty-two percent of patients had, at minimum, some college education, and 29% completed their education as high school graduates. Twenty-five percent of patients had preemptive transplants. Hypertension and diabetes represented the predominant etiologies of kidney failure at 31% and 25%, respectively.

### Cognitive Function Pretransplant

Using all available data, RBANS scores at baseline averaged  $84.7 \pm 14$ . TRAIL A and TRAIL B scores averaged  $40.4 \pm 9.9$  and  $41 \pm 11.5$  at baseline, respectively. Seventeen persons (53%) had impaired pretransplant cognitive function based on one or more metrics including the RBANS total score, TRAIL A, and TRAIL B. Among those with any baseline cognitive impairment, 8 of 17 (47%) were impaired on 1 measure, 3 of 17 (18%) were impaired on 2 measures, and 6 of 17 (35%) had impaired pretransplant cognitive function on all 3 measures. Among

**Table 2.** Baseline Patient Characteristics

Characteristics	All Patients <sup>a</sup> N=32	RBANS <sup>b</sup> Score <78 <sup>c</sup> N=10	RBANS <sup>b</sup> Score ≥78 <sup>c</sup> N=20
Age (y)	44.9 ± 12.1	41.1 ± 14.2	47.3 ± 11.2
Sex			
Female	15 (47%)	3 (30%)	11 (55%)
Male	17 (53%)	7 (70%)	9 (45%)
Race			
Black	4 (13%)	3 (30%)	1 (5%)
White	28 (87%)	7 (70%)	19 (95%)
Marital status			
Single	9 (28%)	2 (20%)	6 (30%)
Married	21 (66%)	8 (80%)	13 (65%)
Divorced	2 (6%)	0 (0%)	1 (5%)
Insurance			
Medicare only	9 (28%)	1 (10%)	6 (30%)
Medicare and Medicaid	3 (9%)	1 (10%)	3 (15%)
Medicare and private	14 (44%)	7 (70%)	6 (30%)
Private only	6 (19%)	1 (10%)	5 (25%)
Education			
Some high school	1 (3%)	1 (10%)	0 (0%)
High school graduate	8 (25%)	3 (30%)	5 (25%)
Some college	12 (37%)	3 (30%)	8 (40%)
College graduate	6 (19%)	3 (30%)	3 (15%)
Postgraduate degree	5 (16%)	0 (0%)	4 (20%)
Dialysis modality			
Hemodialysis	18 (56%)	7 (70%)	10 (50%)
Peritoneal dialysis	6 (19%)	1 (10%)	4 (20%)
Not on dialysis	8 (25%)	2 (20%)	6 (30%)
Dialysis duration (y) <sup>d</sup>	2.5 ± 2.0	2.0 ± 1.3	2.7 ± 2.4
Prior kidney transplant	5 (16%)	2 (20%)	2 (10%)
Cause of kidney disease			
Diabetes	7 (22%)	(30%)	4 (20%)
Hypertension	11 (34%)	4 (40%)	6 (30%)
Glomerular disease	7 (22%)	1 (10%)	5 (25%)
Polycystic kidney disease	5 (16%)	1 (10%)	4 (20%)
Other	2 (6%)	1 (10%)	1 (5%)

Note: Table entries are mean ± standard deviation or frequency (%).

<sup>a</sup>Patients with baseline RBANS or TRAIL A or B testing and at least one posttransplant observation (N=32)

<sup>b</sup>RBANS, Repeatable Battery for Assessment of Neuropsychological Status

<sup>c</sup>Patients with baseline RBANS and at least one posttransplant observation (N=30)

<sup>d</sup>Patients on hemodialysis or peritoneal dialysis with available data (n=20)

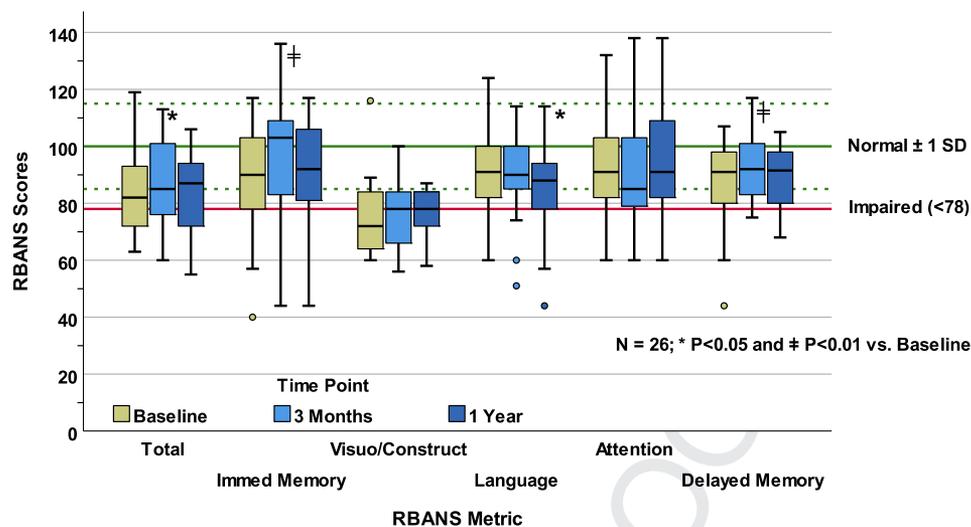
all patients, 33% (10 of 30) had cognitive impairment before transplantation based on the RBANS total score, 41% (13 of 32) had impairment based on TRAIL A and 28% (9 of 32) were cognitively impaired based on TRAIL B scores.

### Global Cognitive Function Posttransplant (RBANS)

Using all available data, RBANS scores at 3 months and 12 months posttransplant averaged  $87.5 \pm 14.3$  and  $85.06 \pm 14.2$ , respectively. Twenty-six patients completed RBANS testing at all 3 time points. Paired comparisons of median RBANS total scores demonstrated no significant improvement from baseline at 3 months or at 12 months posttransplant (all  $P > 0.01$ ; Fig 2). Paired comparisons among RBANS index scores showed statistically significant

improvement from baseline in immediate memory ( $P = 0.005$ ) and delayed memory ( $P = 0.008$ ) at 3 months, but these changes were not sustained at month 12 (both  $P > 0.75$  versus baseline). There were no significant differences from baseline in the index scores for language, visuospatial/constructional abilities, and attention at 3 months or at 12 months (all  $P > 0.02$ ).

Findings from the linear mixed effects models aligned with the paired, nonparametric analyses and are outlined in Table 3, with time-specific contrasts referenced to pretransplant baseline scores. There were no significant differences from baseline in RBANS total scores at 3 or 12 months posttransplant (both  $P > 0.06$ ). On average, immediate memory index scores improved by 8.8 points at 3 months ( $P = 0.003$ ), but this was not sustained at month 12 ( $P = 0.89$ ). No other RBANS index



**Figure 2.** RBANS scores and paired tests. This figure shows longitudinal summary data for persons having RBANS scores at all 3 measurement points. The general population norm  $\pm 1$  SD, which pertains to all metrics, is indicated in green by the solid and dashed reference lines, respectively. The solid red line indicates the threshold below which scores are considered impaired. RBANS, Repeatable Battery for Assessment of Neuropsychological Status; SD, standard deviation.

scores demonstrated statistically robust effects in comparison to baseline (all  $P \geq 0.013$ ).

### Executive Function Posttransplant (TRAIL A & B)

Using all available data, TRAIL A scores averaged  $44.7 \pm 11$  at 3 months and  $45.6 \pm 11.9$  at 12 months. Average TRAIL B scores were  $48.4 \pm 12.2$  at 3 months and  $46.6 \pm 11.3$  at 12 months. Thirty persons completed TRAIL A and B tests at all 3 time points (Fig 3). Paired comparisons of median scores for the TRAIL A test demonstrated no significant difference from baseline at 3 months posttransplant ( $P = 0.02$ ); however, there was a significant improvement at 12 months posttransplant compared to baseline ( $P = 0.002$ ). Paired comparisons demonstrated that TRAIL B scores improved from baseline at 3 months posttransplant ( $P = 0.001$ ) and remained improved at 12 months posttransplant ( $P < 0.001$ ).

Linear mixed effects model analyses for TRAIL A and TRAIL B tests aligned with the paired, nonparametric analyses and are outlined in Table 3. At 3 months, scores on the TRAIL A test were not significantly different from baseline ( $P = 0.01$ ), but TRAIL B scores had improved by approximately 7.6 points ( $P < 0.001$ ). There was a statistically significant improvement from baseline, of approximately 6 points, in TRAIL A and TRAIL B scores at 12 months posttransplant (both  $P = 0.002$ ).

**Table 3.** ...

	Baseline	3 months	12 months
TRAIL A	$40.38 \pm 9.99$ (N=32)	$44.68 \pm 11.03$ (N=31)	$45.61 \pm 11.89$ (N=31)
TRAIL B	$41.00 \pm 11.46$ (N=32)	$48.35 \pm 12.16$ (N=31)	$46.61 \pm 11.32$ (N=31)
RBANS	$84.77 \pm 14.08$ (N=30)	$87.48 \pm 14.27$ (N=29)	$85.06 \pm 14.16$ (N=31)

## DISCUSSION

In this study we found an improvement in attention and executive function 12 months posttransplant based on TRAIL A and TRAIL B tests, respectively. Improvements on these measures were not only statistically significant but clinically significant as well, reflecting changes of over half a SD, likely significant enough to have actual impacts on a patient's daily life. There was not significant improvement in global cognition, as reflected by the RBANS. However, it is worth noting that in our cohort, the average total RBANS score at baseline was comparable to patients with mild cognitive impairment, further reinforcing the cognitive deficits seen in this population.<sup>26</sup>

The current literature is inconclusive with regard to the impact of transplantation on cognitive function, with studies reporting highly variable findings. In contrast to our findings, prior studies do not support improvement in executive function, assessed by TRAIL A and/or TRAIL B, at 6-12 months posttransplant in comparison to patients with kidney failure treated by hemodialysis.<sup>12,16,19,20</sup> Other studies do suggest improvement in executive function based on various measurements in addition to TRAIL A and TRAIL B such as P300 latencies and components of the Complex Reactionmeter Drenovac series.<sup>14,17,18,21,22</sup> Consistent with our results, most studies have not shown clear improvement in global cognition 3-19 months



with improved functional connectivity in several resting-state subnetworks, including the central executive network. The improved connectivity seen in the central executive function network was no longer different from functional activity when compared to controls at 6 months. There has also been evidence of changes in cerebral blood flow, neurochemical concentrations, and white matter integrity in kidney transplant recipients that suggests some reversibility to brain abnormalities seen in kidney failure patients treated by hemodialysis.<sup>18,35-37</sup>

Previous findings of improvement in the initial transplant period and then sustained at 1 year are consistent with aspects of our findings. The slight increase in 3MS scores seen in Chu et al<sup>23</sup> occurred at 3 months, and then cognitive function remained stable in nonfrail patients over the 4-year follow-up period. This finding of initial improvement at 3 months with sustained improvement at 12 months was also shown by Gupta et al.<sup>18</sup> This persistent cognitive impairment in kidney transplant recipients could be due to neurotoxicity secondary to immunosuppressive medications.<sup>7</sup>

There are several strengths to our study. Compared to other studies of similar populations, we moved beyond the use of simple screening tools and incorporated a battery, the RBANS, coupled with brief but sensitive measures of attention and executive function (TRAIL A and TRAIL B). In doing so, we created a comprehensive set of cognitive outcomes allowing us to identify even subtle deficits across a wide range of abilities. Second, despite being a small sample size, we did have a good distribution of patients on hemodialysis, peritoneal dialysis, or patients who had a preemptive transplant. We also did not exclude patients with diabetes or hypertension, allowing our findings to be more generalizable to transplant patients.

Our study does have limitations. It is a small sample size and was conducted at a single center. The majority of our study participants completed some college education, and this could limit the generalizability to the general population. We did not compare our findings to a cohort of patients with kidney failure who remained on dialysis and rather used the reported adjusted population means of the assessments for comparison. Although the RBANS assesses 5 domains over the course of approximately 45 minutes (when used with medical populations) and is significantly more comprehensive than simple screening tests such as the Montreal Cognitive Assessment or the 3MS, it is not as definitive or broad in scope as a clinical neuropsychological battery. Although there are obvious advantages to conducting a lengthier assessment, we concluded that this was likely not feasible because of the nature of the postoperative evaluation for recipients of deceased donor kidney transplants; therefore, longer evaluation may not be feasible in this setting. The performance on the neurocognitive tests could have been affected because of the stress of being called in for possible transplantation as well as not being well rested at the time of evaluation as many patients travel long distances.

In conclusion, utilizing relatively comprehensive cognitive assessments in a small number of patients, we found improvements in attention and executive function in the first posttransplant year as measured by TRAIL A and B. However, there was no significant improvement in global cognition as measured by the RBANS. Although there may be a natural trend toward improvement in domains like attention and executive functioning after transplant, our study serves as a reminder of the importance of fostering enhanced ability in these domains. Although our investigation was not interventional, future research may include the integration of approaches like cognitive rehabilitation or computerized brain training, both of which may be effective in improving neuropsychological ability and functioning.<sup>38</sup> Cognitive impairment is also a barrier for patients to be listed for a kidney transplant.<sup>39</sup> Transplant teams should be mindful that some domains of cognitive function improve after transplantation, and as such, cognitive impairment should not necessarily be used as an exclusion criteria for transplantation. Domain-based assessments as performed in this study will be useful in identifying patients who will benefit from a kidney transplant despite cognitive impairment pretransplant.

Additional research is warranted to further assess the impact of transplant and the durability of any cognitive improvement seen in the initial posttransplant period. It would be beneficial to further expand on our findings by including other validated assessments of the different subdomains of executive function, as this could have important implications for transplant recipients' post-transplant care. The majority of studies have had up to 1 year as the outcome time point, and more longitudinal studies would help to strengthen our current understanding on the long-term effect transplantation can have on cognitive function.

## ARTICLE INFORMATION

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**Support:** Grant funding for this study was provided by Dialysis Clinic, Inc. The funders of this study did not have a role in study design; collection, analysis, and interpretation of data; writing the report; and the decision to submit the report for publication.

**Financial Disclosure:** The authors declare that they have no relevant financial interests.

**Acknowledgements:** This project was also supported by award No. UL1TR000445 from NCATS/NIH. Its contents are solely the responsibility of the authors and do not necessarily represent official views of the National Center for Advancing Translational Sciences or the National Institutes of Health.

**Peer Review:** Received April 9, 2022. Evaluated by 1 external peer reviewer, with direct editorial input from the Statistical Editor, an Associate Editor, and the Editor-in-Chief. Accepted in revised form August 28, 2022.

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