Frailty and Changes in Cognitive Function after Kidney Transplantation

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ABSTRACT

Background Restoration of kidney function after kidney transplant generally improves cognitive function. It is unclear whether frail recipients, with higher susceptibility to surgical stressors, achieve such post-transplant cognitive improvements or whether they experience subsequent cognitive decline as they age with a functioning graft.

Methods In this two-center cohort study, we assessed pretransplant frailty (Fried physical frailty phenotype) and cognitive function (Modified Mini-Mental State Examination) in adult kidney transplant recipients. To investigate potential short- and medium-term effects of frailty on post-transplant cognitive trajectories, we measured cognitive function up to 4 years post-transplant. Using an adjusted mixed effects model with a random slope (time) and intercept (person), we characterized post-transplant cognitive trajectories by pretransplant frailty, accounting for nonlinear trajectories.

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Results Of [illegible] recipients (mean age 52.0 years) followed for a median of 1.5 years, 15.0% were frail. After adjustment, pretransplant cognitive scores were significantly lower among frail patients compared with nonfrail patients (89.0 versus 90.8 points). By 3 months post-transplant, cognitive performance improved for both frail (slope =0.22 points per week) and nonfrail (slope =0.14 points per week) recipients. Between 1 and 4 years post-transplant, improvements plateaued among nonfrail recipients (slope =0.005 points per week), whereas cognitive function declined among frail recipients (slope =−0.04 points per week). At 4 years post-transplant, cognitive scores were 5.8 points lower for frail recipients compared with nonfrail recipients.

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Conclusions On average, both frail and nonfrail recipients experience short-term cognitive improvement post-transplant. However, frailty is associated with medium-term cognitive decline post-transplant. Interventions to prevent cognitive decline among frail recipients should be identified.

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Among adults of all ages and older adults, lower kidney function is associated with worse cognitive function.[1–5] However, even with restoration of kidney function, cognitive impairment affects up to 58% of kidney transplant (KT) recipients of all ages.[6] Transplant recipients, in particular, rely on intact cognitive function to maintain overall health. They must adhere to complex medication regimens

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and manage outpatient clinic visits and tests; lack of such adherence is a major contributor to graft loss and other adverse KT outcomes.[7,8] To date, studies that have compared cognitive performance measures pre- and post-KT have been smaller, been cross-sectional, and/or lacked longer-term repeated measures of cognitive function; however, they collectively suggest that cognitive function improves from baseline levels up to 1 year after successful KT.[3,9–14] Cognitive trajectories beyond 1 year are understudied, but they are critical to understanding the balance between restoration of kidney function and aging. As KT recipients age and live longer with a functioning graft,[15] it is unclear whether they experience a decline in cognitive function as observed among older adults.[16–19]

Frailty, a syndrome conceptualized as the body's inability to respond efficiently to chronic and acute stressors, is distinct from but related to disability, comorbidity, and cognitive impairment,[20–27] and it is most widely measured using the physical frailty phenotype (PFP),[28] which was initially described by Fried *et al.*[25] among community-dwelling older adults.[27] In studies of older adults, frailty is associated with worse cognitive function.[23,24] The PFP has since been shown to be an important predictor of adverse outcomes in ESRD and KT populations.[29–33] It occurs in approximately 20% of KT recipients of all ages,[34] and it has been identified as a key risk factor for poor health outcomes, including quality of life, delirium, delayed graft function, hospital length of stay, early hospital readmission, mycophenolate mofetil intolerance, and mortality.[30,31,34–38] One suggested pathway linking frailty to adverse health outcomes is through behavioral and medical care changes affected by poor cognitive function; however, among KT recipients, it remains unclear whether frailty is analogously associated with worse cognitive performance as observed among patients of all ages initiating hemodialysis[35] and older adults generally.[23,25] Additionally, the association between pre-KT frailty and post-KT cognitive trajectory in the short term and beyond 1 year is unknown. Specifically, it remains unclear whether frail recipients, with higher susceptibility to surgical stressors, experience the same post-KT improvements in cognitive function that have been found among KT recipients generally[9–14] and whether they experience cognitive decline observed with aging.[16–19] It is likely that, in facing stressors introduced from surgery and consumption of immunosuppressive medications post-KT, frail recipients experience short-term mitigated improvements and possible cognitive decline as they age with a functioning graft compared with nonfrail recipients.

To better understand post-KT cognitive trajectories among frail and nonfrail recipients, we conducted a longitudinal study of 665 adult KT recipients (≥18 years of age). The goals of this study were to (*1*) assess the short- (intervals ≤1 year) and medium-term (1–4 years) post-KT cognitive trajectories among all adult KT recipients, (*2*) assess whether cognitive performance levels differed by frailty at KT admission, and (*3*) test whether short- and medium-term post-KT cognitive trajectories differed by frailty ascertained at KT admission.

Significance Statement

Frailty is a predictor of adverse outcomes in kidney transplant populations. Although restoration of kidney function after transplant generally improves cognitive function, it seems plausible that, in frail individuals, stressors related to surgery and immunosuppression might mitigate short-term cognitive improvement and contribute to possible subsequent decline. The authors found significantly lower pretransplant cognitive scores in frail kidney transplant recipients compared with nonfrail recipients. Although both groups showed cognitive improvement by 3 months post-transplant, cognitive function plateaued for nonfrail recipients between 1 and 4 years after transplant and declined for frail recipients. By 4 years post-transplant, cognitive scores were significantly lower among frail versus nonfrail recipients. Transplant centers are encouraged to apply available evidence-based strategies to reduce risk of cognitive impairment among frail transplant recipients.

Understanding the relationship between KT, frailty, and cognitive function could provide evidence for developing strategies to mitigate cognitive impairment as part of clinical practice and the decision-making process for KT candidates.

METHODS

Study Design

We leveraged an ongoing two-center cohort study (from December 2008 to March 2017) of KT recipients ages 18 years old and older. Study participants were enrolled in the study at KT admission, where they were assessed for frailty and cognitive performance as well as activities of daily living (ADLs), instrumental activities of daily living (IADLs), health-related quality of life (HRQOL), and Centers for Epidemiologic Studies Depression (CES-D). We followed participants longitudinally as part of routine clinical care at approximately 1, 3, 6, and 12 months and then yearly up to 4 years post-KT. Recipient, donor, and transplant factors were either self-reported and/or abstracted from medical records, including sex, age, race, education, body mass index, history of cardiovascular disease, history of diabetes, the Charlson Comorbidity Index (modified for patients with ESRD),[39,40] cause of ESRD, previous transplant, time on dialysis, type of dialysis, donor type, recipient eGFR, immunosuppressive medications, and whether they experienced acute rejection within 1 year post-KT.

Of the 1101 KT recipients enrolled in the cohort study, we excluded KT recipients with three or more of the five frailty criteria missing at time of admission for KT (*n* excluded =37), consistent with standard practice,[21] as well as those without cognitive performance measures (*n* excluded =399). Our analytic population was composed of 665 recipients from the Johns Hopkins Hospital in Baltimore, Maryland (*n*=594) and the University of Michigan Medical Center in Ann Arbor, Michigan (*n*=71) followed for up to 4 years. Individuals who were included in analyses did not differ significantly from individuals who were excluded by age, sex, race, cognitive impairment status, Modified Mini-Mental State Examination

(3MS) score, frailty status, time on dialysis, self-reported quality of life, ADLs, or IADLs ($P>0.05$).

All clinical and research activities being reported are consistent with the Declaration of Helsinki and the Declaration of Istanbul. The institutional review boards of Johns Hopkins Hospital and the University of Michigan approved this study, and all enrolled participants provided written informed consent.

Frailty

The PFP, a validated tool to measure frailty in ESRD and KT populations,[29–32,37,41] was ascertained at KT admission (pre-KT). The PFP is on the basis of five criteria: shrinking (self-report of unintentional weight loss of >10 pounds [dry weight] in the past year), weakness (grip strength below an established sex- and body mass index–based cutoff using a handheld dynamometer), exhaustion (self-report on the basis of two questions from the CES-D[42]), low activity (kilocalories per week below an established cutoff on the basis of the Minnesota Leisure Time Physical Activity questionnaire), and slowness (walking time of 15 feet below an established sex- and height-based cutoff).[25] Each of the criteria was scored as zero or one, representing absence or presence of that component, respectively, and the scores were summed to create a total score ranging from zero to five. Scores of three to five were defined as frail as previously determined by our group in ESRD and KT populations.[29–31,33–38,43,44]

Global Cognitive Function

We measured global cognitive function using the 3MS.[45,46] The 3MS is a validated verbal test with 15 items spanning multiple domains, including orientation, attention, language, and memory, with scores ranging from zero to 100, where higher scores represent better cognitive function. The 3MS presents an improvement in sensitivity for mild cognitive impairment in community studies over the traditional 30-point Mini-Mental State Examination (MMSE),[45–47] and it has a higher test-retest reliability (between 0.68 and 0.77) compared with the MMSE (between 0.48 and 0.65).[48] Change in cognitive function after KT was the main outcome of interest. Consistent with prior studies, cognitive impairment was defined as a 3MS score <80 (−1 SD).[38,47,49,50]

Statistical Analyses

Differences in participant characteristics and cognitive scores by frailty were tested using *t* tests to compare unadjusted means for normally distributed continuous variables, Kruskal–Wallis tests to compare unadjusted means for non-normally distributed continuous variables, and Fisher exact tests to compare proportions for categorical variables.

We tested whether frailty was cross-sectionally associated with cognitive performance scores at KT admission and then compared post-KT cognitive trajectories by pre-KT frailty using a mixed effects model with random slope (time) and intercept (person) to describe repeated measures of cognitive scores. An unstructured correlation structure was selected for the random effects to generate the best possible model fit, allowing the model to directly calculate variance and covariance values reflected by the data. We accounted for nonlinearity using splines to examine changing trajectories over several different time periods: the first 12 weeks (3 months), 12–24 weeks (3–6 months), 24–52 weeks (6 months to 1 year), and 52–208 weeks (1–4 years) post-KT. Intervals were determined on the basis of (*1*) clinically relevant time points and (*2*) knowledge obtained through thorough exploratory data analysis. Between years 1 and 4, overall trajectories and trajectories by frailty status were approximately linear (Supplemental Table 1), and therefore, we chose not to include splines to avoid potential bias introduced by overfitting. We quantified rates of cognitive change (points per week) by pre-KT frailty using interaction terms by follow-up time and each spline term. To test the independent association between frailty and cognitive change, we adjusted for recipient, donor, and transplant factors: age, sex, race, education, HRQOL, time on dialysis, clinical site, donor type (live or deceased), immunosuppressive medications (any induction and triple therapy [tacrolimus/mycophenolate mofetil/steroid]), recipient eGFR at admission and discharge, and the Charlson Comorbidity Index adapted for patients with ESRD at KT admission.[40] As strongly recommended by prior research on cognitive change, we did not control for baseline cognitive performance to avoid potential bias that could erroneously inflate our estimates.[51] Additionally, we divided the frailty-cognitive change coefficient (converted to years) by the years of age coefficient to obtain the effect of frailty in our data in terms of number of years older at baseline. To assess whether the association between pre-KT frailty and post-KT cognitive change was modified by age, sex, race, education, or pre-KT cognitive impairment, we tested for interaction by each of the factors in separate models using a Wald test.

We conducted a sensitivity analysis addressing ceiling effects in cognitive testing by using a random effects Tobit model, a method conceived to estimate linear relationships when there is left or right censoring in the measured outcome.[52] We additionally addressed potential effects of general attrition from those lost to follow-up due to withdrawal as well as those who had a competing risk before the end of follow-up, such as death or graft loss, assuming missingness at random by comparing results from two approaches: (*1*) multiple imputations using chained equations, leveraging auxiliary variables associated with missingness, in conjunction with generalized estimating equations and (*2*) inverse probability weighting in conjunction with generalized estimating equations.[53–58] We also accounted for the potential dynamic relationship between frailty and cognitive decline post-KT by examining frailty as a time-varying factor.

RESULTS

Study Population

Of 665 KT recipients followed for a median of 1.5 years (interquartile range [IQR], 0.7–3.4; total person-years =1437.8)

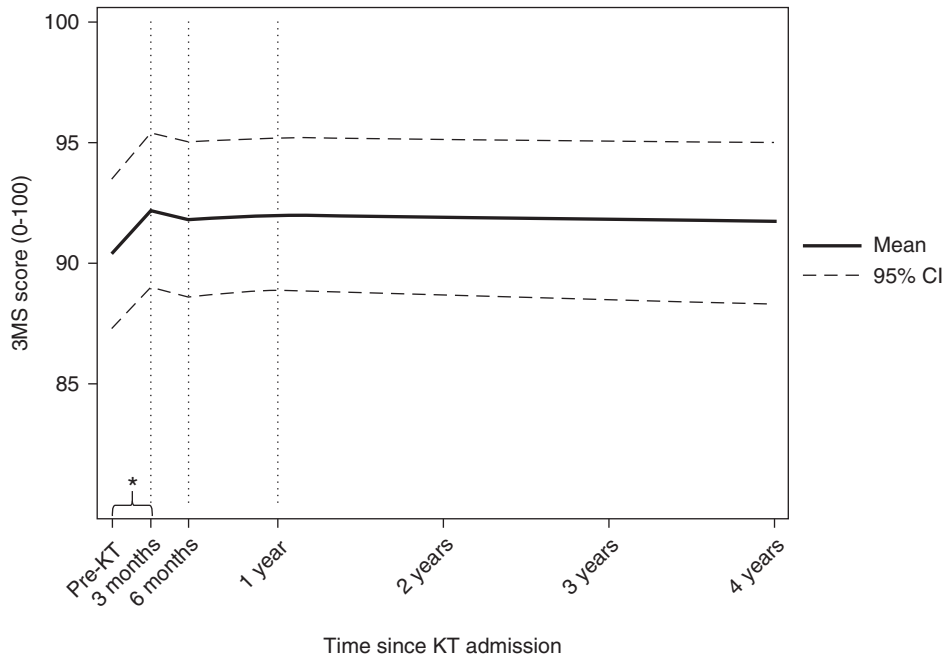

Figure 1. Global cognitive trajectories (Modified Mini-Mental State Examination [3MS] scores) improve among all adult kidney transplant (KT) recipients post-KT (*n*=665) in the short-term. Adjusted trajectories were estimated for 665 KT recipients ages 18+ years old using a mixed effects model with random slope (time) and intercept (person) controlling for baseline age (centered at 55 years old), sex, race, education, self-reported quality of life, donor type (live or deceased), the Charlson Comorbidity Index adapted for patients with ESRD,[39,40] and recipient eGFR at the time of admission and discharge as well as immunosuppressive medications (induction and triple therapy including tacrolimus, mycophenolate mofetil, and steroid). We accounted for nonlinearity by using splines to examine trajectories over several different time periods: the first 3 months, 3–6 months, 6 months to 1 year, and 1–4 years post-KT. Baseline (time 0) represents the time of KT admission or "pre-KT." The thick line represents the average overall global cognitive trajectory across time; thin lines represent the 95% confidence intervals (95% CIs). KT recipients had significant improvements in cognitive performance in the first 3 months post-KT. *Rates of change (points per week) that are statistically significant within the respective interval at a cutoff of *P*=0.05.

and a median of 4.0 visits (IQR, 2.0–5.0), the mean age was 52.0 years old (SD=14.2), 61.2% were men, and 35.8% self-reported as black. Before KT, the median time on dialysis was 2.6 years (IQR, 1.1–5.0). Post-KT, 38 experienced acute rejection within 1 year, 19 experienced graft loss, and 26 died during follow-up.

Cognitive Function among All KT Recipients

Among the 665 KT recipients, 48 (7.2%) had cognitive impairment at KT admission. Before accounting for nonlinearity, the mean score at KT admission was 93.7 (SEM=1.4), and the mean cognitive function improved over the 4-year period (slope =0.01 points per week; 95% confidence interval [95% CI], 0.00 to 0.01) after adjustment for recipient, donor, and transplant factors. However, on exploratory data analysis, there was the suggestion of nonlinearity of the cognitive trajectories present. After additionally accounting for this nonlinearity of cognitive trajectories among all KT recipients, the mean cognitive score at KT admission was 94.1 (SEM=0.9). After adjustment, the mean cognitive function improved in the first 3 months post-KT from baseline levels (slope =0.15 points per week; 95% CI, 0.09 to 0.21) and then, remained stable through the 4 years of follow-up (Figure 1).

Pre-KT Frailty

Among the 665 KT recipients, 15.0% were frail at KT admission. Frail recipients were followed for a median of 1.8 years (IQR, 1.0–3.6; total person-years =242.0), whereas nonfrail recipients were followed for a median of 1.5 years (IQR, 0.6–3.3; total person-years =1195.7). Frail KT recipients were older (mean =55.0 years old, SD=13.7) on average compared with nonfrail recipients (mean =51.4 years old, SD=14.3), and they were significantly more likely than nonfrail KT recipients to have depressive symptoms (26.0% versus 8.5%), disabilities (ADLs: 15.0% versus 3.4%; IADLs: 30.0% versus 12.9%), and poor HRQOL (18.0% versus 7.6%) (Table 1). The proportion of frail recipients who experienced rejection within 1 year post-KT (5.0%) did not differ from that of nonfrail recipients (5.9%; *P*=0.73).

Frailty and Cognitive Function at KT Admission

At time of KT, frail recipients had significantly lower unadjusted cognitive performance (median =93.0; IQR, 87.0–96.5)

Table 1. Characteristics of adult kidney transplant recipients by frailty status at the time of kidney transplant admission (*n*=665)

Characteristic	Nonfrail, *n*=565	Frail, *n*=100	*P* Value
Years on dialysis	2.6 (1.0–4.9)	3.0 (1.1–5.6)	0.55
Age, yr	51.4 (14.3)	55.0 (13.7)	0.02
Women	214 (37.9)	44 (44.0)	0.27
Race			0.10
White	327 (57.9)	47 (47.0)	
Black	193 (34.2)	45 (45.0)	
Other	45 (8.0)	8 (8.0)	
Education			0.44
Grade school	26 (4.6)	7 (7.0)	
High school	186 (32.9)	39 (39.0)	
Technical degree (2 yr)	46 (8.1)	6 (6.0)	
College	175 (31.0)	24 (24.0)	
Graduate school	125 (22.1)	18 (18.0)	
Annual household income			0.13
<$50,000	111 (19.6)	29 (29.0)	
$50,000–$100,000	125 (22.1)	22 (22.0)	
Over $100,000	165 (29.2)	21 (21.0)	
[illegible]ased donor	330 (58.4)	64 (64.0)	0.32
[illegible]	73 (12.9)	30 (30.0)	<0.001
[illegible]	19 (3.4)	15 (15.0)	<0.001
[illegible]ity of life			<0.001
Excellent	42 (7.4)	4 (4.0)	
Very good	112 (19.8)	10 (10.0)	
Good	213 (37.7)	31 (31.0)	
Fair	146 (25.8)	35 (35.0)	
[illegible]or	43 (7.6)	18 (18.0)	
[illegible]essive symptoms	48 (8.5)	26 (26.0)	<0.001
Charlson Comorbidity Index			0.36
0	296 (52.4)	48 (48.0)	
1	79 (14.0)	10 (10.0)	
2	84 (14.9)	15 (15.0)	
3	46 (8.1)	11 (11.0)	
4+	60 (10.6)	16 (16.0)	
Recipient eGFR			
At admission	8.4 (5.8–12.3)	8.3 (6.1–12.5)	0.85
At discharge	43.8 (18.7–65.9)	49.5 (19.2–78.7)	0.28
Immunosuppressive medications			
Induction	510 (90.3)	93 (93.0)	0.46
Triple therapy (TAC/MMF/steroids)	514 (91.0)	91 (91.0)	>0.99
Follow-up, yr	1.5 (0.6–3.3)	1.8 (1.0–3.6)	0.13
Visits	3 (2–5)	4 (3–5)	0.34

N (%) for categorical characteristics and mean (SD) for continuous characteristics are presented. For years on dialysis, years of follow-up, and number of visits, median and IQR are presented. Frailty is defined by the Fried frailty phenotype. Education refers to the highest education level attained. Charlson Comorbidity Index refers to the index that was modified for patients with ESRD.[39,40] IADL, instrumental activity of daily living; ADL, activity of daily living; TAC, tacrolimus; MMF, mycophenolate mofetil.

compared with nonfrail recipients (median =96.0; IQR, 91.0–98.0). However, the proportion of frail recipients with cognitive impairment (11.0%) at baseline did not differ from that of nonfrail recipients (6.6%; *P*=0.14). Distributions across the 3MS score components, including psychomotor skills, memory, and identification/association, also differed by frailty status (Table 2). On the basis of exploratory data analysis, we decided to examine differences by frailty status, accounting for nonlinear trajectories. After accounting for nonlinear cognitive trajectories and adjusting for recipient, donor, and transplant factors, frail recipients had lower mean cognitive scores (mean =89.0) compared with nonfrail recipients (mean =90.8) at KT admission (difference =−1.8 points; 95% CI, −3.3 to −0.3) (Table 3).

Pre-KT Frailty and Short-Term Cognitive Trajectory 1 Year Post-KT

After accounting for nonlinear cognitive trajectories and adjusting for recipient, donor, and transplant factors, improvements in cognitive scores in the first 3 months post-KT were evident for both frail (slope =0.22 points per week; 95% CI, 0.05 to 0.29) and nonfrail recipients (slope =0.14 points per week; 95% CI, 0.08 to 0.21), and these rates of improvement did not differ from each other (difference =0.08 points; 95% CI, −0.10 to 0.26). By 3 months post-KT, cognitive performance levels did not differ by frailty (difference =−0.9 points; 95% CI, −3.0 to 1.2). The same was true by 6 months post-KT (difference =−1.5 points; 95% CI, −3.8 to 0.8) and 1 year post-KT (difference =0.5 points; 95% CI, −1.3 to 2.3), because both frail and nonfrail recipients remained stable through the end of the first year post-KT (difference =0.07 points per week; 95% CI, −0.03 to 0.17).

Frailty and Medium-Term Cognitive Trajectory 1–4 Years Post-KT

After accounting for nonlinear cognitive trajectories and adjusting for recipient, donor, and transplant factors, rates of cognitive change differed between frail and nonfrail participants after 1 year of follow-up post-KT (Figure 2). Specifically, frail recipients experienced steeper decline in cognitive function compared with nonfrail recipients after 1 year post-KT (difference =−0.04 points per week; 95% CI, −0.06 to −0.01) (Table 3). Among nonfrail recipients, mean cognitive trajectories remained stable after 1 year post-KT (slope =0.005 points per week; 95% CI, −0.01 to 0.02); converted to points per year, this slope equates to an average of +0.3 points per year over the course of a 3-year period from 1 to 4 years post-KT. In contrast, frail recipients had declines in mean cognitive scores after 1 year post-KT (slope =−0.03 points per week; 95% CI, −0.06 to −0.01); converted to points per year, this slope equates to an average

Table 2. Unadjusted cognitive performance scores by frailty status at the time of admission for kidney transplant

Cognitive Function	Overall, *n*=665	Nonfrail, *n*=565	Frail, *n*=100
Cognitive impairment (3MS<80), *n* (%)	48 (7.2)	37 (6.6)	11 (11.0)
3MS total score	95.0	96.0[a]	93.0[a]
Psychomotor skills	21.0	21.0[a]	21.0[a]
Memory	21.0	21.0[a]	20.0[a]
Identification/association	24.0	24.0[a]	23.0[a]
Orientation	25.0	25.0	25.0
Concentration/calculation	7.0	7.0	7.0

Median scores are presented for the 3MS total score (range, 0–100) and the 3MS score components, include psychomotor skills (range, 0–21), memory (range, 0–21), identification/association (range, 0–26), orientation (range, 0–25), and concentration/calculation (range, 0–7). 3MS, Modified Mini-Mental State Examination.
[a]Statistically significant difference by frailty status at a level of 0.05.

of −1.6 points per year over the course of 3 years from 1 to 4 years post-KT. This effect of being frail is approximately equivalent in our data to being 26.0 years older at time of KT. By 4 years post-KT, frail recipients had lower cognitive scores compared with nonfrail recipients (difference =−5.5 points; 95% CI, −8.7 to −2.4) (Table 3). Age, sex, race, education, and pre-KT cognitive impairment did not modify the association between pre-KT frailty and post-KT cognitive change (*P* value for interactions for each time interval >0.05).

Sensitivity Analyses

For all sensitivity analyses, inferences remained relatively consistent on the basis of the magnitude and direction of the estimates. Specifically, when we (*1*) addressed potential bias introduced by cognitive score ceiling effects, (*2*) addressed concerns related to general attrition (including loss to follow-up and loss due to competing risks, such as mortality and graft loss), or (*3*) accounted for dynamic frailty (as a time-varying factor), both frail and nonfrail recipients improved in cognitive function in the short term between time of admission and 1 year post-KT. Consistent with primary analyses, sensitivity analyses showed that nonfrail recipients either plateaued or even increased through the rest of the 4-year period, whereas frail recipients experienced declines in cognitive function on the basis of magnitude and direction of estimates (Supplemental Tables 1–6).

DISCUSSION

In this cohort of KT recipients of all ages, after accounting for nonlinear trajectories, those who were frail had worse cognitive function (mean =89.0) compared with nonfrail recipients (mean =90.8) at KT admission (difference =−1.8 points; 95% CI, −3.3 to −0.3). Both frail and nonfrail recipients experienced short-term improvements in cognitive function post-KT. By 3 months post-KT, cognitive scores did not differ by frailty (difference =−0.9 points; 95% CI, −3.0 to 1.2). Although nonfrail recipients showed stable cognitive performance scores thereafter through the end of the study period, frail recipients experienced cognitive decline between 1 and 4 years post-KT (slope =−0.04 points per week; 95% CI, −0.06 to −0.01); this difference by frailty status in this study is approximately equivalent to being 26.0 years older at the time of KT. By 4 years post-KT, frail recipients had a mean cognitive score of 5.5 points lower than nonfrail recipients (95% CI, −8.7 to −2.4). This association between frailty and cognitive trajectories did not differ by age, sex, race, education, and cognitive impairment at KT admission.

Our results highlight the importance of accounting for nonlinearity when studying cognitive function among KT recipients; modeling trajectories otherwise can miss important nuances. After accounting for nonlinearity, our results are consistent with previous findings from smaller studies with shorter-term follow-up that suggest that , restoration of kidney function, recipients may experience improvements in cognitive function.[9–14] Although frailty represents a vulnerability to stressors, our findings suggest that benefits that come with restoration of kidney function may outweigh negative effects of frailty in the short term post-KT.

However, between 1 and 4 years of follow-up post-KT, frail recipients experienced cognitive decline, whereas nonfrail recipients remained stable. These findings support our hypothesis that the PFP represents a distinct vulnerability to stressors.[25] Although we do not fully understand the mechanisms driving this association between frailty and cognition among adult KT recipients, recent reviews of frailty and cognition in older adults suggested potential effects of inflammation, cardiovascular disease, nutrition, and neuropathology.[23,24] Among KT recipients especially, consumption of immunosuppressive medications may potentially serve as a chronic stressor. As shown by prior research, frail recipients may not recover from the physiologic stress of their immunosuppressive regimens as efficiently as nonfrail recipients; in theory, their underlying multisystem dysfunction hinders their ability to reach homeostasis in the face of stressors introduced by such medications with dose-dependent adverse events, putting them at higher risk of poor KT outcomes.[32] This may serve as one potential explanation linking frailty, cognitive impairment, and dementia among KT recipients; however, additional research is needed to thoroughly explore the longitudinal role of immunosuppression regimens on frailty and cognitive function among KT recipients.

This study was not without limitations. In this study, measurements were ascertained at clinical follow-up, and not all participants completed follow-up. However, the KT recipients with and without longitudinal measurements of cognitive function did not differ significantly by age, sex, race, cognitive impairment, cognitive score, frailty, or time on dialysis.

Table 3. Adjusted estimates of global cognitive trajectories among kidney transplant recipients overall and by frailty status (*n*=665)

Time of Assessment	Estimated Score Points			Difference in Estimated Score (95% Confidence Interval), Points		Estimated Rate of Change during Interval (95% Confidence Interval), Points per Week		
	Overall	Frail	Nonfrail	Absolute Difference	Net Effect	Frail	Nonfrail	Difference
Pre-KT	90.4	89.0	90.8	−1.8[a]	—	—	—	—
Post-KT, wk								
≤12	91.2	91.6	92.5	−0.9	−0.91 (−3.06 to 1.23)	0.22 (0.05 to 0.29)[a]	0.14 (0.08 to 0.21)[a]	0.08 (−0.10 to 0.26)
12–24	91.8	90.8	92.3	−1.5	−0.30 (−2.55 to 1.95)	−0.07 (−0.29 to 0.14)	−0.02 (−0.11 to 0.06)	−0.05 (−0.29 to 0.18)
24–52	92.0	92.6	92.1	0.5	−2.30 (−4.23 to −0.36)[a]	0.07 (−0.03 to 0.16)	−0.01 (−0.04 to 0.03)	0.07 (−0.03 to 0.17)
52–208	91.7	87.4	92.9	−5.5[a]	3.70 (0.20 to 7.20)[a]	−0.03 (−0.06 to −0.01)[a]	0.01 (−0.01 to 0.02)	−0.04 (−0.06 to −0.01)[a]

The model was adjusted for baseline age (centered at 55 years old), sex, race, education, self-reported quality of life, donor type (live or deceased), the Charlson Comorbidity Index adapted for patients with ESRD,[39,40] and recipient eGFR at the time of admission and discharge as well as immunosuppressive medication (induction and triple regimen including tacrolimus, mycophenolate mofetil, and steroid). Frailty is defined by the Fried frailty phenotype. The estimated score is for the last day for the time interval. The absolute difference is the difference in estimated scores comparing frail recipients with nonfrail recipients at the end of the period. The net effect refers to the difference in absolute value comparing each respective post-KT interval with pre-KT. KT, kidney transplant; —, not applicable for the respective analyses.

[a]Statistical significance at a cutoff of *P*=0.05.

Sensitivity analyses accounting for attrition confirmed robustness of our inferences; thus, effects of selection bias are likely minimal. Another limitation is the use of a single measure of cognitive function (the 3MS). As a tool that measures global cognitive function, it may be less sensitive to cognitive changes and unable to pinpoint domain-specific effects compared with comprehensive neuropsychologic batteries; however, it is an appealing instrument for a variety of evaluation settings where speed and ease of repeated assessments are needed. Although studies among adults with ESRD[35] and older adults[23,59] have shown positive findings for specific cognitive domains, with the strongest associations for executive function[23,35,59,60]—a critical domain that deteriorates with onset of vascular dementia[61]—additional research is needed to assess the association with specific cognitive domain for a better understanding of underlying mechanisms among KT recipients. Additionally, clinical complications post-transplant not captured in this study, such as infection, acute rejection, and metabolic derangements, may also influence cognitive function post-KT and should be investigated in subsequent analyses.

Notwithstanding these limitations, there were several strengths of this study. This study incorporates repeated measures of carefully collected data up to 4 years, with availability of both pre- and post-KT cognitive tests as well as a validated measure of frailty. Furthermore, this large, diverse, multicenter study provided the unique opportunity to examine the frailty-cognition relationship across all ages and explore differences by age, race, and sex in the face of an acute stressor (KT).

Although both frail and nonfrail recipients experienced improvements in cognitive function by 3 months post-KT, between 1 and 4 years post-KT, nonfrail recipients maintained higher levels of cognitive function, whereas frail recipients experienced cognitive decline and failed to recover to baseline levels. Clinicians may consider regularly monitoring cognitive function and mitigating cognitive decline among frail recipients as part of clinical practice for KT candidates to prevent cognitive impairment and dementia—a state of chronic and severe cognitive impairment more common among KT recipients aged 55+ years old than older adults generally.[62] Among identified interventions that address cognitive decline, cognitive training remains one of the three most promising along with physical exercise and BP management,[63] and its benefits may extend to cognitive tasks of activities of daily life.[64–66] Additionally, transplant centers may consider targeting frailty among candidates before KT with interventions, such as exercise and resistance training, nutrition, geriatric assessment/management, and prehabilitation, to optimize recovery from surgical stressors.[67] Targeting frail KT recipients for outpatient monitoring and intervention may mitigate adverse KT outcomes among a highly vulnerable population.[30,32,36,37,44]

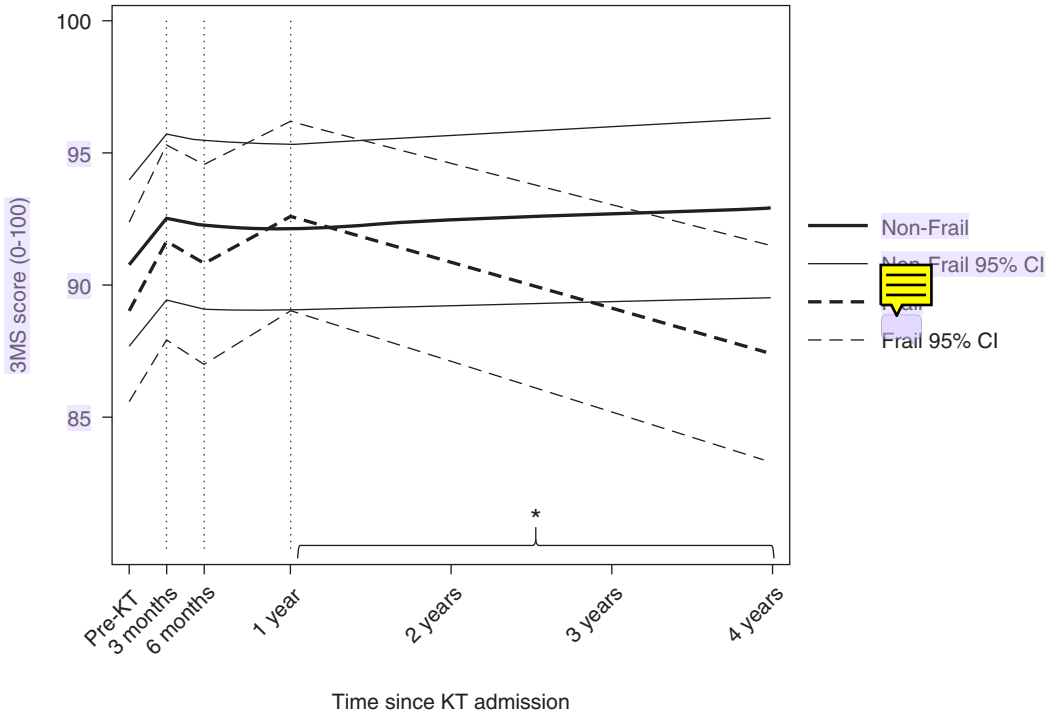

Figure 2. Global cognitive trajectories (Modified Mini-Mental State Examination [3MS] scores) vary by frailty status among adult kidney transplant (KT) recipients post-KT (n=665). Adjusted trajectories were estimated for 565 nonfrail and 100 frail KT recipients ages 18+ years old using a mixed effects model with random slope (time) and intercept (person) controlling for baseline age (centered at 55 years old), sex, race, education, self-reported quality of life, donor type (live or deceased), the Charlson Comorbidity Index adapted for patients with ESRD,[39,40] and recipient eGFR at the time of admission and discharge as well as immunosuppressive medications (induction and triple therapy including tacrolimus, mycophenolate mofetil, and steroid). We accounted for nonlinearity to examine trajectories over different time periods: the first 3 months, 3–6 months, 6 months to 1 year, and 1–4 years post-KT. Baseline (time 0) represents pre-KT. Both frail and nonfrail recipients improved in cognitive function within 3 months post-KT. However, between 1 and 4 years post-KT, frail recipients experienced declines in cognitive function, whereas nonfrail KT recipients plateaued; those cognitive trajectories significantly differed. *Significantly different rates of change (points per week) comparing frail with nonfrail within the respective interval ($P<0.05$).

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DISCLOSURES

None.

SUPPLEMENTAL MATERIAL

This article contains the following supplemental material online at http://jasn.asnjournals.org/lookup/suppl/doi:10.1681/ASN.2018070726/-/DCSupplemental.

Supplemental Table 1. Adjusted estimates of global cognitive trajectories among kidney transplant (KT) recipients by baseline frailty incorporating spline terms at 3 months, 6 months, 1 year, 2 years, and 3 years post-KT (n=665).

Supplemental Table 2. Full multivariate model output for primary analysis assessing post-KT cognitive trajectories (3MS score) by pre-KT frailty status at different time intervals post-KT.

Supplemental Table 3. Sensitivity analysis: adjusted estimates of global cognitive trajectories among kidney transplant (KT) recipients by baseline frailty status using a random effects Tobit model (n=665).

Supplemental Table 4. Sensitivity analysis: adjusted estimates of global cognitive trajectories among kidney transplant (KT) recipients by baseline frailty status accounting for attrition assuming a mortal cohort using MI-GEE (n=665).

Supplemental Table 5. Sensitivity analysis: adjusted estimates of global cognitive trajectories among kidney transplant (KT) recipients by baseline frailty status accounting for attrition assuming an immortal cohort using WGEE (n=665).

Supplemental Table 6. Sensitivity analysis: adjusted estimates of global cognitive trajectories among kidney transplant (KT) recipients by frailty status accounting for time-varying frailty (n=665).

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