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ORIGINAL ARTICLE

Cognitive impairment burden in older and younger adults across the kidney transplant care continuum

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Abstract

Background: Younger kidney transplant (KT) candidates and recipients may have cognitive impairment due to chronic diseases and reliance on dialysis.

Methods: To quantify cognitive impairment burden by age across the KT care continuum, we leveraged a two-center cohort study of 3854 KT candidates at evaluation, 1114 recipients at admission, and 405 recipients at 1-year post-KT with measured global cognitive performance (3MS) or executive function (Trail Making Test). We also estimated burden of severe cognitive impairment that affects functional dependence (activities of daily living [ADL] < 6 or instrumental activities of daily living [IADL] < 8).

Results: Among KT candidates, global cognitive impairment (18–34 years: 11.1%; 35–49 years: 14.0%; 50–64 years: 19.5%; ≥65 years: 22.0%) and severe cognitive impairment burden (18–34 years: 1.1%; 35–49 years: 3.0%; 50–64 years: 6.2%; ≥65 years: 7.7%) increased linearly with age. Among KT recipients at admission, global cognitive impairment (18–34 years: 9.1%; 35–49 years: 6.1%; 50–64 years: 9.3%; ≥65 years: 15.7%) and severe cognitive impairment burden (18–34 years: 1.4%; 35–49 years: 1.4%; 50–64 years: 2.2%; ≥65 years: 4.6%) was lower. Despite lowest burden of cognitive impairment among KT recipients at 1-year post-KT across all ages (18–34 years: 1.7%; 35–49 years: 3.4%; 50–64 years: 4.3%; ≥65 years: 6.5%), many still exhibited severe cognitive impairment (18–34 years: .0%; 35–49 years: 1.9%; 50–64 years: 2.4%; ≥65 years: 3.5%).

Conclusion: Findings were consistent for executive function impairment. While cognitive impairment increases with age, younger KT candidates have a high burden comparable to community-dwelling older adults, with some potentially suffering from severe forms. Transplant centers should consider routinely screening patients during clinical care encounters regardless of age.

KEYWORDS
age, cognition, epidemiology, kidney disease, transplantation

1 | INTRODUCTION

Patients of all ages with kidney failure are at substantial risk of cognitive decline and subsequent cognitive impairment.[1–5] Causes of cognitive decline among this vulnerable population can be attributed to the presence of chronic disease, as well as buildup of uremic toxins, lack of physical activity, inflammation, cerebral hypotension, and hypoxia during dialysis sessions.[1,3–6] Indeed, adult patients with kidney failure have a high burden of global cognitive impairment, with prevalence ranging anywhere between 10% and 80% due to heterogeneous case mixes and different tests used to identify it.[7–14] Severe forms of cognitive impairment often affect functional dependence, which has also been shown to be common in transplant populations.[15] While cognitive impairment burden and severity likely increases with age among kidney failure patients as in the general population, younger patients (18–64 years) with kidney failure may still have a high burden of impairment given their unique chronic disease and therapeutic profiles.

Maintaining intact cognitive function is particularly critical for KT candidates, regardless of age, as they navigate through the pre-kidney transplant (KT) evaluation.[7] However, candidates of all ages can have unrecognized cognitive impairment at time of admission for KT,[7,16] due to lack of screening for cognitive function before and after referral to a transplant center.[17] While it is well recognized that cognitive impairment is associated with age in the general population[18–20] and among KT recipients who have already undergone KT,[21] less is known about the burden of cognitive impairment by age among candidates at time of evaluation versus admission for KT. Given that cognitive impairment is associated with an increased risk of waitlist mortality[7] and that cognitive function improves post-KT,[8] it is likely that there is a greater burden among KT candidates than among recipients prior to KT or recipients who had already undergone KT.

Older adult patients undergoing dialysis[22] and KT[23] are additionally at higher risk of diagnosed dementia in later-life—a chronic and severe form of cognitive impairment that affects daily function and dependence.[24–27] Diagnosis of dementia is especially challenging due to its complex pathophysiology, slow progression, and heterogeneous clinical manifestations.[26,28] Despite the high prevalence of dementia in the general population, it is often underdiagnosed by clinicians and underreported by patients; only about half of individuals who meet the diagnostic criteria for dementia receive a physician diagnosis of dementia.[29] While dementia is contraindicated for KT, given the difficulty with diagnosis,[29] coupled with the lack of cognitive screening among patients with kidney failure,[17] it is possible that patients of all ages across the KT care continuum have unrecognized, severe forms cognitive impairment, marked by additional manifestation of functional dependence.[7]

In this study, our goal was to estimate and compare the burden of global cognitive impairment and the joint prevalence of functional dependence by age across the KT care continuum, from time of evaluation to admission for KT prior to surgery, and at 1-year post-KT. Additionally, we tested whether differences in burden by age vary by other potential risk factors of cognitive impairment (such as sex, race, education, dialysis type, diabetes status, and donor type). Given potential differences in etiology in cognitive impairment, we also assessed burden of impairment in executive function, a cognitive domain responsible for mental flexibility, set-shifting, and complex problem-solving, that is often impacted by dialysis initiation.[1,3] A better understanding of cognitive impairment burden across the age spectrum at evaluation and admission for KT will allow transplant centers to appropriately target screening in this vulnerable population.

2 | MATERIALS AND METHODS

2.1 | Study design

We leveraged a two-center cohort study of 3854 KT candidates at evaluation for KT, 1114 KT recipients at admission for KT, and 405 KT recipients at 1-year post-KT with measured global cognitive performance (3MS) and/or executive function (Trail Making Test [TMT]), as described below. Eligible participants in the study (≥18 years of age and English-speaking) were enrolled at the Johns Hopkins Hospital (1/2009–1/2019) and the University of Michigan Medical Center (6/2014–4/2016) at time of evaluation (candidates) and admission (recipients) for KT prior to surgery; KT recipients were then followed through 1-year post-KT as part of routine clinical visits. Participant characteristics, including age, sex, race, education, household income, smoking status, dialysis type, years on dialysis, diabetes status, and donor type, were self-reported or abstracted from medical records at evaluation (candidates), admission (recipients), or 1-year post-KT (recipients). Additionally, the Charlson Comorbidity Index (CCI), adapted for patients with kidney failure[30] was calculated using comorbidity information abstracted from patient electronic medical records, and supplemented with participant self-report. Frailty status for participants was also measured using the physical frailty phenotype derived by Fried et al.[31] (≥3 of the 5 criteria).

All clinical and research activities being reported are consistent with the Declaration of Helsinki and the Declaration of Istanbul. The Johns Hopkins Institutional Review Board and the University of Michigan Institutional Review Board approved the study, and all participants provided written informed consent.

2.2 | Global cognitive impairment

This study focused on burden of global cognitive impairment using the Modified Mini Mental State Exam (3MS)[32] for KT candidates at evaluation (not during dialysis), KT recipients at admission prior to KT, and KT recipients at 1-year post-KT. The 3MS was administered to patients with diverse age, sex, race, and educational backgrounds in a standardized manner by trained research assistants in a private clinic room. It was collected as part of a larger cohort study of aging and KT, and was solely measured for research purposes. The 3MS is a validated 15-item verbal test assessing multiple components, including psychomotor

skills, memory, identification/association, orientation, and concentration/calculation. 3MS scores range from 0 to 100, where lower scores represent worse cognitive function. The 3MS presents enhanced sensitivity for mild cognitive impairment in community studies over the traditional 30-point Mini-Mental State Examination (MMSE),[32–34] and has a higher test-retest reliability (between .68 and .77) compared to the MMSE (between .48 and .65). Consistent with prior studies, cognitive impairment was defined as a 3MS score less than 80 (−1 SD).[34–37]

2.3 | Executive function impairment

Starting in 2014, we additionally measured the Trail Making Test Part A and Part B (TMT-A and TMT-B respectively) to assess executive function for KT candidates at evaluation (not during dialysis), KT recipients at admission, and KT recipients at 1-year post-KT. The TMT-A and TMT-B measure the time (in seconds) needed to connect a series of sequentially numbered (TMT-A) and numbered/lettered (TMT-B) circles,[38] assessing scanning, speed of processing, attention and concentration, and psychomotor speed; the TMT-B further assesses cognitive shifting and complex sequencing. Scores are based on the total time of test completion without error, where greater time to completion represents worse cognitive function; times were capped at 3 min for TMT-A and 5 min for TMT-B.[38] Impairment in executive function was defined as a time 1.5 SD above the mean from this cohort for the TMT-B minus TMT-A to account for processing speed.

2.4 | Cognitive impairment and functional dependence

Given that severe forms of cognitive impairment, like dementia, are characterized by impaired cognitive abilities that affect daily life and function,[24–27] we estimated the joint prevalence of cognitive impairment (global cognitive function and executive function) and functional dependence. Functional dependence was derived from the National Long Term Care Survey verbally administered by study staff at time of evaluation for KT for candidates, at admission for KT for recipients, and at 1-year post-KT for KT recipients who were followed for routine clinical visits. Participants self-reported whether they needed help with eating, dressing, walking, grooming, toileting, and bathing, which comprised the six self-care activities of daily living (ADL) domains.[39] Participants also self-reported whether they needed help with using a phone, shopping, cooking, housework, washing, using transportation, managing medications, and managing money, which comprised the eight instrumental activities of daily living (IADL) domains.[40] Candidates and recipients were classified as ADL/IADL dependent if they reported difficulty with any of the aforementioned domains.[15] Participants with a joint prevalence of cognitive impairment and functional dependence were classified as having severe cognitive impairment.

2.5 | Descriptive statistics by age

Percentages, means with standard deviations (SD), and medians with interquartile ranges (IQR) were generated for participant characteristics and cognitive scores and differences by dichotomous age groups (older: ≥65 years vs. younger: 18–64 years) were tested using Fisher exact tests, *t* tests, and Kruskal-Wallis tests for categorical, normally, and non-normally distributed continuous variables, respectively.

2.6 | Cognitive impairment burden by age and joint prevalence of functional dependence

We estimated the burden of global cognitive impairment only, impairment in executive function only, and the joint burden of cognitive impairment and functional dependence (ADL/IADL) by age in more refined four-category groupings (18–34, 35–49, 50–64, ≥65 years). We additionally estimated burden of global cognitive impairment and executive function impairment by continuous age using restricted cubic splines with three knots, which were placed at percentiles based on prior recommended approaches.[41] We used logistic regression models to test whether the burden of cognitive impairment is associated with patients' demographic and health characteristics, adjusting for older age, sex, race, education, dialysis type, diabetes, frailty, and donor type (among KT recipients only). Additionally, we tested whether associations between age (≥65 vs. 18–64 years) and cognitive impairment differed by potential risk factors (sex, race, education, dialysis type, diabetes status, frailty, and donor type) by including an interaction term between age and each factor in separate models; a Wald test was used to examine significance.

2.7 | Statistical analyses

For all analyses, *P* value < .05 was considered significant. All analyses were performed using STATA 15.0 software (StataCorp, College Station, TX).

3 | RESULTS

3.1 | KT candidates at evaluation

3.1.1 | Characteristics

Among the 3854 KT candidates with measures of global cognitive impairment, the mean age was 55 years (SD = 13.5), 40.6% were female, and 45.0% were Black. The median number of years on dialysis was .7 (IQR = .0–2.8), and 57.2% of participants were undergoing hemodialysis, while 12.5% were undergoing peritoneal dialysis (PD). In the cohort of KT candidates, 25.8% were older adults aged 65 years or older (Table 1). Demographic and health characteristics for KT

TABLE 1 Demographic and health characteristics by age group for kidney transplant (KT) candidates ($n = 3854$) and KT recipients ($n = 1114$ at admission; $n = 405$ at 1-year post-KT) with measures of global cognitive function (3MS)

	KT candidates at evaluation				KT recipients at admission				KT recipients at 1-year post-KT			
Characteristics	Total ($n = 3854$)	Age 18–64 ($n = 2860$)	Age ≥65 ($n = 994$)	p value	Total ($n = 1114$)	Age 18–64 ($n = 878$)	Age ≥65 ($n = 236$)	p value	Total ($n = 405$)	Age 18–64** ($n = 313$)	Age ≥65 ($n = 92$)	p value
Female sex, %	40.6	42.3	35.6	<.001	39.6	40.5	36.0	.21	43.2	45.0	37.0	.17
Race, %												
White	46.5	42.7	57.6	<.001	52.0	49.5	61.0	.02	57.8	53.7	71.7	.01
Black	45.0	48.0	36.5		38.5	40.2	32.2		35.8	38.7	26.1	
Hispanic	3.0	3.6	1.1		3.2	3.5	2.1		2.5	2.9	1.1	
Other	5.5	5.7	4.8		6.3	6.7	4.7		4.0	4.8	1.1	
Education, %												
Below high school	6.1	5.8	7.0	.015	5.3	5.4	5.1	.32	3.7	4.5	1.1	.07
High school	38.4	39.7	34.7		34.1	35.1	30.1		32.6	34.5	26.1	
Above high school	55.5	54.5	58.3		60.6	59.5	64.8		63.7	61.0	72.8	
Annual household income, %												
< $50000	17.1	17.9	14.9	<.001	36.4	38.2	30.1	.11	32.1	34.8	22.8	.10
$50000-99999	12.6	11.6	15.3		19.1	19.0	19.5		23.0	22.7	23.9	
≥$100000	12.3	11.6	14.4		19.0	18.1	22.5		22.0	19.8	29.3	
Not reported	58.0	58.9	55.4		25.4	24.7	28.0		23.0	22.7	23.9	
Years since dialysis, median (IQR)	.7 (.0, 2.8)	.8 (.0, 3.1)	.5 (.0, 2.0)	**<.001**	2.5 (.5, 5.5)	2.7 (.5, 5.9)	1.9 (.4, 3.9)	**<.001**	2.4 (.5, 5.5)	2.7 (.5, 6.1)	1.7 (.4, 4.0)	**.01**
Type of dialysis, %												
No dialysis	30.3	28.5	35.5	**<.001**	18.2	16.8	23.4	**.02**	17.6	16.0	23.0	.28
Hemodialysis	57.2	58.2	54.4		65.1	65.3	64.4		69.6	70.5	66.7	
Peritoneal dialysis	12.5	13.3	10.1		16.6	17.8	12.2		12.8	13.5	10.3	
Current smoker, %	8.2	9.5	4.3	**<.001**	5.7	6.5	2.6	**.03**	5.4	6.6	1.1	**.04**
Frailty	20.9	19.0	26.1	**<.001**	15.7	14.4	20.9	**.02**	8.9	7.4	13.8	**.07**
Charlson comorbidities index (CCI), median (IQR)	2.0 (.0, 3.0)	2.0 (.0, 3.0)	2.0 (.0, 3.0)	**<.001**	1.0 (.0, 3.0)	0.0 (.0, 2.0)	2.0 (.0, 3.0)	**<.001**	.0 (.0, 2.0)	.0 (.0, 2.0)	2.0 (.0, 3.0)	**<.001**
Comorbidities, %												
Myocardial infarction	9.3	8.1	13.0	**<.001**	5.7	4.8	9.2	**.01**	5.5	4.9	7.7	.30
Peripheral vascular disease	6.2	5.6	8.0	**.01**	5.9	4.7	10.6	**<.001**	5.3	3.9	9.9	**.03**
Cerebral vascular disease	5.6	5.3	6.7	.12	3.6	3.3	4.8	.26	2.3	2.6	1.1	.39
Dementia	.4	.3	.6	.27	.1	.0	.4	.05	.3	.0	1.1	.07
Chronic lung disease	5.9	5.6	6.9	.20	5.0	5.2	3.9	.42	4.0	4.9	1.1	.11

(Continues)

TABLE 1 (Continued)

Characteristics	KT candidates at evaluation				KT recipients at admission				KT recipients at 1-year post-KT			
	Total (n = 3854)	Age 18–64 (n = 2860)	Age ≥65 (n = 994)	p value	Total (n = 1114)	Age 18–64 (n = 878)	Age ≥65 (n = 236)	p value	Total (n = 405)	Age 18–64** (n = 313)	Age ≥65 (n = 92)	p value
Rheumatological disease	6.5	6.9	5.2	.09	14.3	13.3	18	.07	12.3	11.4	15.4	.31
Peptic ulcer disease	3.4	3.2	4.2	.18	3.9	3.5	5.3	.22	3.0	2.0	6.6	**.02**
Diabetes	42.5	39.6	50.8	**<.001**	29.5	25.3	45.4	**<.001**	29.8	24.8	46.7	**<.001**
Diabetes with complications	35.5	35.5	35.5	1.00	27.3	24.2	38.2	**<.001**	19.1	15.7	30.4	**.01**
Moderate/severe liver disease	3.5	3.8	2.6	.08	2.6	2.7	2.2	.68	2.3	2.3	2.2	.97
Metastatic cancer	1.0	1.0	1.2	.51	.4	.2	.9	.15	1.0	.7	2.2	.19
Lymphoma or leukemia	1.1	1.0	1.6	.17	.5	.5	.4	.95	.5	.3	1.1	.36
HIV	3.1	4.0	.5	**<.001**	2.1	2.7	.0	**.01**	2.8	3.6	.0	.07
Congestive heart failure	13.9	13.5	15.3	.26	5.9	4.6	10.7	**<.001**	4.6	3.4	8.3	.08
Deceased donor, %	–	–	–		61.8	58.3	74.6	**<.001**	61.7	60.1	67.4	.20

candidates with measures of executive function at evaluation (n = 2129) were similar and are also reported (Table S1).

3.2 | Cognitive impairment burden by age

The proportion of KT candidates with global cognitive impairment at time of KT evaluation increased with age: 18–34 years (11.1%), 35–49 years (14.0%), 50–64 years (19.5%), and ≥65 years (22.0%) (Figure 1A). Across all ages, there was a substantial burden of global cognitive impairment, and this burden increased approximately linearly with age (Figure 2A). Additionally, older candidates aged 65 years or older were more likely to have lower scores in 3MS components including identification/association (23 vs. 24 points), psychomotor skills (20 vs. 21 points), and memory (19 vs. 20 points) (Table 2). Similar results were observed for executive function impairment, such that burden increased with age (18–34: .0%, 35–49: .2%, 50–64: 1.9%, ≥65: 4.2%; Figure 1B) and older candidates were more likely to exhibit worse executive function at time of evaluation (68 vs. 48 s; Table 2). However, burden in executive function impairment at time of evaluation for KT increased approximately linearly starting at the age of 50 years (Figure 2B). Notably, a small proportion with global cognitive impairment (18–34 years: 1.1%, 35–49 years: 2.9%, 50–64 years: 6.0%, ≥65 years: 7.4%) or executive function impairment (18-34 years: .0%, 35–49 years: .2%, 50–64 years: 1.9%, ≥65 years: 4.2%) additionally had functional dependence at time of evaluation for KT (Figure 1A).

Among KT candidates, the characteristics associated with increased odds of global cognitive impairment were older age (adjusted odds ratio [aOR] = 1.45, 95% CI: 1.11, 1.88), male sex (aOR = 1.34, 95% CI: 1.05, 1.69), Black race (aOR = 2.39, 95% CI: 1.85, 3.09), Hispanic race (aOR = 2.15, 95% CI: 1.16, 3.98), other race (aOR = 2.25, 95% CI: 1.40, 3.62), lower education (aOR = 2.42, 95% CI: 1.92, 3.04), and hemodialysis (aOR = 1.44, 95% CI: 1.11, 1.87) (Table 3). Diabetes status (aOR = 1.22, 95% CI: .97, 1.54), frailty (aOR = 1.18, 95% CI: .89, 1.56), and peritoneal dialysis (aOR = 1.01, 95% CI: .68, 1.50) were not associated with global cognitive impairment burden at time of evaluation for KT (Table 3). The association between age and global cognitive impairment only differed by educational attainment (P = .02), such that the association was stronger among those with lower education (aOR = 1.89, 95% CI: 1.34, 2.68) than higher education (aOR = 1.02, 95% CI: .68, 1.53). Results for executive function impairment are also presented (Table S2); the association between age and executive function impairment did not differ by any of the aforementioned characteristics (all P-values > .05).

3.3 | KT recipients at admission

3.3.1 | Characteristics

Among the 1114 KT recipients with measures of global cognitive function, the median age was 53 years (SD = 14.0), 39.6% were female, and 38.5% were Black. The median number of years on dialysis was

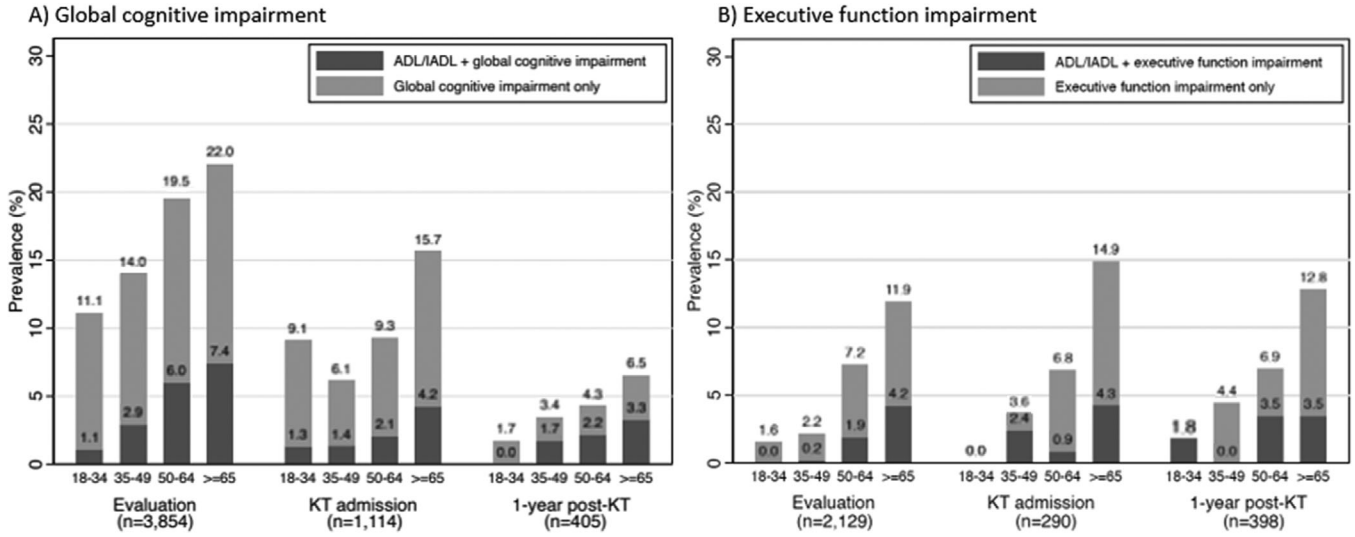

FIGURE 1 Overall burden of (A) global cognitive impairment only versus ADL/IADL dependence + global cognitive impairment and (B) executive function impairment only vs. ADL/IADL dependence + executive function impairment by age group (18–34, 35–49, 50–64, ≥65 years), among kidney transplant (KT) candidates and recipients at KT evaluation, admission, and 1-year post-KT. Age was assessed at time of evaluation for KT candidates, and at KT admission and 1-year post-KT for KT recipients. Global cognitive impairment was defined as a 3MS score less than 80 (−1 SD). Impairment in executive function was defined as a time 1.5 SD above the mean from this cohort for the TMT-B minus TMT-A to account for processing speed.
Abbreviations: ADL, activities of daily living; IADL, instrumental activities of daily living

2.5 (IQR = .5–5.5), 65.1% of participants were undergoing hemodialysis, and 16.6% were undergoing peritoneal dialysis. In this cohort of KT recipients at admission, 21.2% were older adults aged 65 years or older (Table 1). Demographic and health characteristics for KT recipients with measures of executive function at admission (n = 290) were similar and are also reported (Table S1).

3.4 | Global cognitive impairment burden by age

The proportion of KT recipients with global cognitive impairment at time of KT admission increased non-linearly with age: 18–34 years (9.1%), 35–49 years (6.1%), 50–64 years (9.3%), and ≥65 years (15.7%) (Figure 1A). Similar to KT candidates, there was a high burden of global cognitive impairment among KT recipients across all ages; however, burden at KT admission increased exponentially by age those 50 years and older (Figure 2A). Older recipients aged 65 years or older were more likely to have lower scores in 3MS components including identification/association (23 vs. 24 points) and memory (19 vs. 21 points) (Table 2). Similar results were observed for executive function impairment, such that burden increased with age (18–34: .0%, 35–49: 3.6%, 50–64: 6.8%, ≥65:14.9%; Figure 1B), increases were non-linear starting at ages 50 years and older (Figure 2B), and older recipients were more likely to exhibit worse executive function at time of admission (71 vs. 40 s; Table 2). A small proportion of those with global cognitive impairment (18–34 years: 1.3%, 35–49 years: 1.4%, 50–64 years: 2.1%, ≥65 years: 4.2%) or executive function impairment (18–34 years: .0%, 35–49 years: 2.4%, 50–64 years: .9%, ≥65 years: 4.3%) additionally had functional dependence at time of admission for KT (Figure 1A).

Older age (aOR = 2.51, 95% CI: 1.49, 4.22), Black race (aOR = 1.86, 95% CI: 1.07, 3.26), Hispanic race (aOR = 3.44, 95% CI: 1.35, 8.75), other race (aOR = 1.97, 95% CI: .81, 4.77), and lower education (aOR = 2.64, 95% CI: 1.61, 4.33) were all associated with greater global cognitive impairment burden. Male sex (aOR = 1.01, 95% CI: .62, 1.64), dialysis type (hemodialysis vs. no dialysis: aOR = 1.44, 95% CI: .64, 3.22; peritoneal dialysis vs. no dialysis: aOR = .98, 95% CI: .36, 2.65), diabetes status (aOR = .90, 95% CI: .54, 1.49), frailty (aOR = 1.29, 95% CI: .73, 2.27), and donor type (deceased vs. live: aOR = 1.70, 95% CI: .93, 3.09) were not associated with global cognitive impairment burden (Table 3). Results for executive function impairment are also presented (Table S2). The association between age and global/executive function impairment did not differ by any of the aforementioned characteristics (all P-values > .05).

3.5 | KT recipients at 1-year post-KT

3.5.1 | Characteristics

Among the 405 KT recipients with measures of global cognitive function at 1-year post-KT, the median age was 52 years (SD = 14.1), 43.2% were female, and 35.8% were Black. The median number of years on dialysis was 2.4 (IQR = .5–5.5), 69.6% of participants were undergoing hemodialysis, and 12.8% were undergoing peritoneal dialysis. In this cohort of KT recipients at 1-year post-KT, 22.7% were older adults aged 65 years or older (Table 1). Demographic and health characteristics for KT recipients with measures of executive function at admission (n = 290) were similar and are also reported (Table S1).

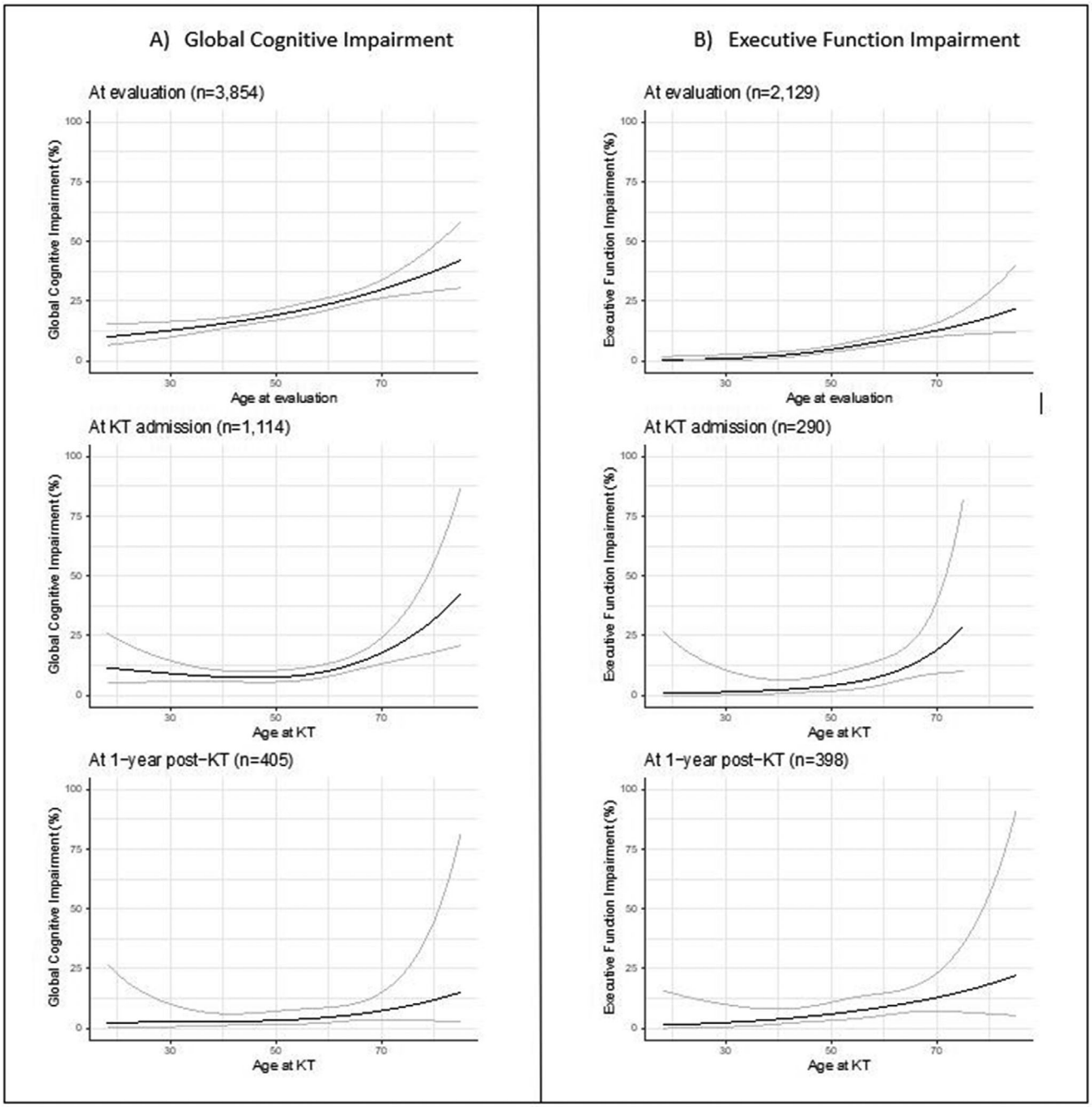

FIGURE 2 Prevalence of (A) global cognitive impairment by age and (B) impairment in executive function by age among kidney transplant (KT) candidates and recipients at KT evaluation, admission, and 1-year post-KT. Age was treated as a continuous variable at time of evaluation for kidney transplant (KT) candidates, and at KT admission and 1-year post-KT for KT recipients. Restricted cubic splines were used. 95% confidence intervals are depicted as the grey colored region

3.6 | Global cognitive impairment burden by age

The proportion of KT recipients with global cognitive impairment at 1-year post-KT increased non-linearly with age: 18–34 years (1.7%), 35–49 years (3.4%), 50–64 years (4.3%), and ≥65 years (6.5%) (Figure 1A). Similar to KT candidates at evaluation and recipients at admission, there was a high burden of global cognitive impairment among KT recipients across all ages; however, burden at 1-year post-KT increased linearly by age, particularly among those aged 50 years and older (Figure 2A). Similar results were observed for executive function impairment, such that burden increased approximately linearly with age (18-34: 1.8%, 35–49: 4.4%, 50–64: 6.9%, ≥65:12.8%; Figures 1B and 2B), and older recipients were more likely to exhibit worse executive function at 1-year post-KT (55 vs. 37 s; Table 2). A small proportion

TABLE 2 Cognitive impairment and performance scores by age group among kidney transplant (KT) candidates and recipients

	Global cognitive function								
	KT candidates at evaluation			KT recipients at admission			KT recipients at 1-year post-KT		
	Total ($n = 3854$)	Age 18–64 ($n = 2860$)	Age ≥65 ($n = 994$)	Total ($n = 1114$)	Age 18–64 ($n = 878$)	Age ≥65 ($n = 236$)	Total ($n = 405$)	Age 18–64 ($n = 313$)	Age ≥65 ($n = 92$)
Global cognitive impairment, *n* (%)	695 (18.0)	476 (16.6)	219 (22.0)	109 (9.8)	72 (8.2)	37 (15.7)	17 (4.2)	11 (3.5)	6 (6.5)
3MS total score, median (IQR)	92 (83, 97)	92 (83, 97)	89 (81, 95)	95 (90, 98)	95 (90, 98)	93 (85, 97)	97 (93, 99)	97 (93, 99)	96 (91, 99)
Orientation	25 (22, 25)	25 (22, 25)	25 (22, 25)	25 (25, 25)	25 (25, 25)	25 (25, 25)	25 (25, 25)	25 (25, 25)	25 (25, 25)
Concentration/Calculation	7 (7, 7)	7 (7, 7)	7 (6, 7)	7 (7, 7)	7 (7, 7)	7 (6, 7)	7 (7, 7)	7 (7, 7)	7 (7, 7)
Identification/Association	24 (21, 25)	24 (21, 25)	23 (20, 25)	24 (22, 26)	24 (22, 26)	23 (20, 25)	25 (24, 26)	25 (24, 26)	25 (23, 26)
Psychomotor skills	21 (19, 21)	21 (19, 21)	20 (19, 21)	21 (19, 21)	21 (19, 21)	21 (19, 21)	21 (19, 21)	21 (19, 21)	21 (19, 21)
Memory	20 (17, 21)	20 (17, 21)	19 (15, 21)	21 (18, 21)	21 (18, 21)	19 (17, 21)	21 (20, 21)	21 (20, 21)	21 (18, 21)
	Executive function								
	Total ($n = 2129$)	Age 18–64 ($n = 1583$)	Age ≥65 ($n = 546$)	Total ($n = 290$)	Age 18–64 ($n = 243$)	Age ≥65 ($n = 47$)	Total ($n = 398$)	Age 18–64 ($n = 312$)	Age ≥65 ($n = 86$)
Executive function impairment, *n* (%)	143 (6.7)	78 (4.9)	65 (11.9)	18 (6.2)	11 (4.5)	7 (14.9)	27 (6.8)	16 (5.1)	11 (12.8)
Executive function, median (IQR)	52 (33, 84)	48 (31, 75)	68 (42, 105)	46 (30, 66)	40 (28, 59)	71 (48, 91)	40 (26, 71)	37 (25, 59)	55 (38, 93)

Median unadjusted scores (IQR) are presented for the Modified Mini-Mental State Exam (3MS) score components, including orientation (range 0–25), concentration/calculation (range 0–7), identification/association (range 0–26), psychomotor skills (range 0–21), and memory (range 0–21). Lower 3MS scores indicate worse cognitive function. Executive function is defined by the time (in seconds) it takes to complete the Trail Making Test (TMT) Part B minus the time it takes to complete TMT Part A, which accounts for processing speed. Median unadjusted time (IQR) are presented. Longer times to complete TMT Part A and TMT Part B represent worse cognitive function. Bolded scores represent statistically significant differences by age group.

of those with global cognitive impairment (18–34 years: .0%, 35–49 years: 1.7%, 50–64 years: 2.2%, ≥65 years: 3.3%) or executive function impairment (18–34 years: 1.8%, 35–49 years: .0%, 50–64 years: 3.5%, ≥65 years: 3.5%) additionally had functional dependence at 1-year post-KT (Figure 1A).

After adjustment, none of the characteristics were associated with global cognitive impairment at 1-year post-KT (Table 3), including age (aOR = 2.70, 95% CI: .76, 9.55), sex (aOR = 1.26, 95% CI: .38, 4.12), Black race (aOR = .98, 95% CI: .27, 3.62), education (aOR = 3.21, 95% CI: .98, 10.46), dialysis type prior to KT (hemodialysis vs. no dialysis: aOR = 2.97, 95% CI: .36, 24.57), diabetes (aOR = .87, 95% CI: .26, 2.98), frailty (aOR = 3.42, 95% CI: .89, 13.21), and donor type (deceased vs. living: aOR = 1.04, 95% CI: .27, 4.05) were not associated with global cognitive impairment burden at 1-year post-KT. Results for executive function impairment are also presented (Table S2). The association between age and global/executive function impairment did not differ by any of the aforementioned characteristics (all *P*-values > .05).

4 | DISCUSSION

Among candidates undergoing evaluation for KT and recipients being admitted for KT, cognitive impairment is common across all age groups, including among youngest adults aged 18–50 years. As expected, global cognitive impairment burden was higher among older compared to younger KT candidates at evaluation (18–34 years: 11.1%, 35–49 years: 14.0%, 50–64 years: 19.5%, ≥65 years: 22.0%), KT recipients at admission (18–34 years: 9.1%, 35–49 years: 6.1%, 50–64 years: 9.3%, ≥65 years: 15.7%), and KT recipients at 1-year post-KT (18–34 years: 1.7%, 35–49 years: 3.4%, 50–64 years: 4.3%, ≥65 years: 6.5%). These patterns were consistent for burden of executive function impairment. While global cognitive impairment burden increased linearly with age for KT candidates aged 18 years and older, global cognitive impairment burden among KT recipients at admission and 1-year post-KT increased linearly starting at ages 50 years and older. Notably, across all three cohorts, a small proportion who had global cognitive impairment or executive function impairment additionally had functional dependence, even among younger age groups. For KT candidates at evaluation and recipients at admission, older age, non-White race, and education were associated with increased burden of global cognitive impairment. For KT candidates at evaluation, hemodialysis was additionally associated with global cognitive impairment burden. None of the characteristics were associated with cognitive impairment burden among KT recipients at 1-year post-KT. The association between age and global cognitive impairment only differed by educational attainment for candidates ($P = .02$) at evaluation.

Our findings highlight the substantial burden of cognitive impairment experienced by patients with kidney failure from KT evaluation through KT admission prior to surgery, and extend those findings by examining the burden among younger age groups. Similar to studies

TABLE 3 Associations between socio-demographic characteristics and global cognitive impairment burden among kidney transplant (KT) candidates ($n = 3854$) and KT recipients ($n = 1114$ at admission; $n = 405$ at 1-year post-KT)

Characteristics	KT candidates at evaluation		KT recipients at admission		KT recipients at 1-year post-KT	
	cOR (95% CI)	aOR (95% CI)	cOR (95% CI)	aOR (95% CI)	cOR (95% CI)	aOR (95% CI)
Age						
18–64 years	Ref	Ref	Ref	Ref	Ref	Ref
≥65 years	1.42 (1.18, 1.69)	1.45 (1.11, 1.88)	2.08 (1.36, 3.19)	2.51 (1.49, 4.22)	1.92 (.69, 5.33)	2.70 (.76, 9.55)
Sex						
Female	Ref	Ref	Ref	Ref	Ref	Ref
Male	1.29 (1.09, 1.53)	1.34 (1.05, 1.69)	.96 (.64, 1.44)	1.01 (.62, 1.64)	1.41 (.51, 3.90)	1.26 (.38, 4.12)
Race						
White	Ref	Ref	Ref	Ref	Ref	Ref
Black	2.73 (2.27, 3.28)	2.39 (1.85, 3.09)	2.06 (1.33, 3.21)	1.86 (1.07, 3.26)	1.14 (.42, 3.05)	.98 (.27, 3.62)
Hispanic	2.04 (1.26, 3.29)	2.15 (1.16, 3.98)	3.54 (1.45, 8.61)	4.75 (1.78, 12.68)	–	–
Other	1.97 (1.35, 2.85)	2.25 (1.40, 3.62)	3.03 (1.50, 6.13)	2.60 (1.03, 6.52)	–	–
Education						
Above High School	Ref	Ref	Ref	Ref	Ref	Ref
High School or below	2.87 (2.41, 3.42)	2.42 (1.92, 3.04)	2.16 (1.45, 3.23)	2.64 (1.61, 4.33)	3.40 (1.23, 9.39)	3.21 (.98, 10.46)
Dialysis type						
No dialysis	Ref	Ref	Ref	Ref	Ref	Ref
Hemodialysis	2.23 (1.79, 2.77)	1.44 (1.11, 1.87)	1.30 (.72, 2.33)	1.44 (.64, 3.22)	3.96 (.51, 30.56)	2.97 (.36, 24.57)
Peritoneal dialysis	1.24 (.89, 1.73)	1.00 (.67, 1.49)	.95 (.44, 2.05)	.98 (.36, 2.65)	1.38 (.08, 22.68)	–
Diabetes status						
No diabetes	Ref	Ref	Ref	Ref	Ref	Ref
Diabetes	1.47 (1.19, 1.82)	1.22 (.97, 1.54)	1.26 (.83, 1.91)	.90 (.54, 1.49)	1.00 (.34, 2.91)	.87 (.26, 2.98)
Frailty						
Not frail	Ref	Ref	Ref	Ref	Ref	Ref
Frail	1.56 (1.29, 1.88)	1.18 (.89, 1.56)	1.68 (.99, 2.85)	1.29 (.73, 2.27)	4.54 (1.34, 15.37)	3.43 (.89, 13.21)
Donor Type						
Living Donor	–	–	Ref	Ref	Ref	Ref
Deceased Donor	–	–	2.00 (1.27, 3.15)	1.70 (.93, 3.09)	1.14 (.41, 3.16)	1.04 (.27, 4.05)

Adjusted models account for age group, sex, race, education level of high school or below, dialysis type (no dialysis, hemodialysis, or peritoneal dialysis), diabetes status, frailty, and donor type (deceased donor compared to living donor). Bolded scores represent statistically significant differences by global cognitive impairment.

Abbreviations: AOR, adjusted odds ratio; cOR, crude odds ratio; 95%CI, 95% confidence interval.

of community-dwelling older adults aged 65 years or older[42,43] and KT recipients in the first clinic visit post-KT,[21] the burden of cognitive impairment increases with age among KT candidates and recipients at time of evaluation and admission, respectively. For global cognitive impairment, this increase is linear for those ages 18 years and older among KT candidates, and for those ages 50 years and older among KT recipients. Despite being screened to be free of dementia, the burden of global cognitive impairment found among older KT candidates (22.0%) and recipients at admission for KT (15.7%) is roughly equivalent to those found among community-dwelling older adults of the same ages.[25,44] However, strikingly the burden of global cognitive impairment among younger KT candidates aged 35–49 years (14.0%) and 50–64 years (19.5%) is comparable to that found among community-dwelling older adults aged 65 years and older (range: 16%–20%).[25,44] This finding reinforces the link between kidney failure-specific factors and worse cognitive function across all age groups,[45–49] putting patients with kidney failure at greater risk of adverse outcomes on the waitlist[7] and post-KT,[14] regardless of age. Future studies incorporating longer prospective follow-up are needed to better characterize cognitive impairment outcomes and etiologies in younger cohorts across the kidney care continuum.

This study also expands upon prior findings on cognitive function and kidney failure[1,2,21,50] by examining the burden of impairment in executive function by age across the KT care continuum. The substantial burden found among all ages across the care continuum is important to consider in parallel with prior studies that have

demonstrated similar findings among hemodialysis patients; about 37% of older patients undergoing hemodialysis had impairment in executive function,[9,34] which amounts to over three times the prevalence found in the general population of older adults aged 65 years and older (5%–10%).[9,51] Our study supports and expands upon those findings by highlighting the burden among adult candidates of all ages, including among younger age groups 18–64 years of age. Interestingly, executive function impairment burden appears to increase post-KT for some age groups, particularly in those ages 35–49 years (evaluation: 2.2%, admission: 3.6%, 1-year post-KT: 4.4%); however, given the differences in sample sizes across all three cohorts, these differences across the care continuum are likely not significantly different. Nonetheless, the persistent burden in executive function impairment even at 1-year post-KT reinforces that, despite restoration of kidney function, KT recipients are still susceptible to cognitive health problems post-KT, putting them at risk of subsequent severe cognitive impairment, like dementia.[7,23] Though causes remain largely unknown, prior studies have found that history of stroke, subclinical cerebrovascular disease, arterial stiffness, central pressure, and lack of physical activity in patients with ESKD, as well as reliance on immunosuppressive medications post-KT may be important contributors to cognitive impairment risk post-KT.[1,9,52–55] Clinicians should consider monitoring KT recipients for persistent impairments in cognitive function even after undergoing KT during follow-up visits.

This study further illustrates that this burden of impaired executive function increases approximately linearly for candidates and recipients across the KT care continuum, particularly among those ages 50 years and older. Prior studies have demonstrated that patients living with kidney failure are most often impacted by declines in executive function,[50] which can impede ability to make informed decisions and comply with dialysis schedules, fluid/dietary restrictions, and complicated medication regimens, often leading to dependence[12,56–58] and even death.[9,59] Impairment in executive function is a particular concern for KT recipients, as it is likely to impact their ability to manage daily maintenance immunosuppression regimens, and contribute to higher rates of subsequent dementia, such as Alzheimer's Disease or vascular dementia progression, allograft loss, and mortality post-KT.[23] However, cognitive function, and particularly executive function, can be preserved with non-pharmacologic interventions, such as with foot peddlers and tablet-based brain games, based on evidence from a pilot study among hemodialysis patients.[60]

To our knowledge, this is the first study to report the joint burden of functional dependence and cognitive impairment among patients with kidney failure across the care continuum. Given that more severe forms of cognitive impairment, like dementia, involve the interference of daily life and function, it is alarming that even a small proportion of candidates at evaluation (18–34 years: 1.1%, 35–49 years: 2.9%, 50–64 years: 6.0%, ≥65 years: 7.4%), recipients at admission (18–34 years: 1.3%, 35–49 years: 1.4%, 50–64 years: 2.1%, ≥65 years: 4.2%), and recipients at 1-year post-KT (18-34 years: .0%, 35–49 years: 1.7%, 50–64 years: 2.2%, ≥65 years: 3.3%) had global cognitive impairment and functional dependence, even among younger ages. Whether this observed joint prevalence of cognitive impairment and functional dependence truly captures a vulnerable subset of patients with unrecognized severe cognitive impairment remains an open question; however, given the substantial underdiagnosis of dementia,[29] and the high incidence of dementia among patients with kidney failure,[22,23] further investigation into cognitive impairment severity across the care continuum is warranted.

This study also highlights important risk factors of cognitive impairment in patients with kidney failure. Lower education was a consistent risk factor associated with greater global cognitive impairment burden for KT candidates at evaluation and recipients at admission, exhibiting similar patterns found among community-dwelling older adults.[61,62] For KT candidates at evaluation and recipients at admission, older age and non-White race were additionally associated with greater cognitive impairment burden, which is also consistent with prior studies.[43,63,64] Notably, hemodialysis was associated with greater cognitive impairment burden among KT candidates only, though differences by dialysis type among KT candidates have been attributed to the fact that more cognitively impaired patients with kidney disease less likely to initiate peritoneal dialysis as a form of renal replacement therapy.[65,66] Interestingly, diabetes status was only associated with impairment in executive function among KT candidates at evaluation and recipients at 1-year post-KT, which is key to consider in parallel with studies demonstrating the link between diabetes, decline in executive function, and vascular cognitive impairment among community-dwelling older adults.[67–70] Frailty was markedly not associated with global cognitive impairment among all three cohorts, but was associated with executive function impairment among KT candidates at evaluation (aOR = 2.06, 95% CI: 1.17, 3.64). This finding fits similar patterns presented in prior studies among community-dwelling older adults, whereby frailty was more strongly associated with deterioration in executive function (a critical domain in the development of vascular dementia) over other domains, such as memory (a critical domain in the development of Alzheimer's Disease).[44,71–73]

There were several limitations in this study to consider. Firstly, this study is limited by the transplant centers included; it is likely that cognitive impairment burden varies by geographic location across the United States, as was found in prior studies of dementia.[74] Additionally, this study uses a single instrument to define cognitive impairment. The 3MS is one of many validated screening tools widely used to assess global cognitive functioning in older adults generally,[32,33] and is particularly appealing given its high inter-rater and retest reliability, as well as having high specificity and sensitivity.[75–77] We would also be remiss not to mention that this study follows precedence of prior studies on cognition and kidney failure by imposing a global cutoff, such as 3MS < 80 in this study, or the Montreal Cognitive Assessment (MoCA) < 26 in other studies.[21] While prior studies have thoroughly determined age- and education-adjusted cutoffs for community-dwelling older adults generally,[78,79] such cutoffs specific for adult kidney failure patients are lacking but need to account for premorbid abilities that can inaccurately trigger impairment criteria.[80] Lastly, this study does not include a comparison group of healthy controls in order to distinguish the impact of age-related cognitive deteriorations from ESKD- and/or KT-specific deteriorations. Despite these

limitations, this study has notable strengths, including its large sample size among two different populations of KT candidates and KT recipients, and use of multiple valid measures cognitive function.[32–34,38]

In conclusion, global cognitive impairment and impairment in executive function burden increases with age among patients with kidney failure undergoing evaluation and KT; however, younger patients 18–64 years of age have a high burden, especially among KT candidates at time of evaluation for KT. Transplant centers should recognize that younger KT candidates may experience cognitive impairment, and encourage patient screening among all age groups 18 years and older at time of evaluation for KT; by the time of KT admission, screening can then be targeted to those aged 50 years and older. Candidates who are observed to have cognitive impairment can be targeted for interventions to preserve cognitive function prior to KT.[81] Higher burden of cognitive impairment in younger patients with kidney failure underscores the need for screening among all age groups at time of evaluation for KT, even among candidates who might not otherwise be deemed as "at risk" due to age alone.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Collaborations are welcome upon request to the senior author.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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