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The association of pretransplant dialysis exposure with transplant failure is dependent on the state-specific rate of dialysis mortality

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Longer pretransplant dialysis exposure is associated with a higher risk of transplant failure. Whether patients who receive dialysis in a region with a higher rate of dialysis mortality are a higher risk for transplant failure is unknown. Adjusted state-specific hemodialysis mortality rates were determined in 3-year intervals among prevalent dialysis patients in the United States between 1995 and 2012. The effect of state- and period-specific dialysis mortality on the association of pretransplant dialysis exposure with transplant survival through December 2017 was determined using multivariable models. Dialysis mortality within states ranged from 128 deaths/1000 patient-years to 330 deaths/1000 patient-years. Each additional year of dialysis was associated with a 4% higher risk of transplant failure in states within the lowest quartile of dialysis mortality, compared with an 8% higher risk in states within the highest quartile of dialysis mortality. Patients who received pretransplant dialysis treatment in a state with a high rate of dialysis mortality are at a higher risk for transplant failure compared with patients with the same duration of pretransplant dialysis treatment in a state with a lower mortality rate. The findings may have implications for dialysis care in transplant candidates and the design of future outcome metrics.

KEYWORDS
dialysis, graft survival, health services and outcomes research, kidney transplantation/nephrology

1 | INTRODUCTION

There are far more end-stage kidney disease (ESKD) patients who could benefit from transplant compared with treatment with dialysis if there were more transplantable kidneys. This imbalance between supply and demand causes enormous societal harm including premature loss of life and higher health-care costs.[1]

Patient access to transplant in the United States is decreasing as assessed by waiting times: after 5 years, approximately 37% of wait-listed transplant candidates remain waiting for a transplant in the United States compared with 22% at the start of the millennium.[2] The consequences of the organ shortage are not limited to longer waiting times for transplant. Numerous studies have shown a strong association between the duration of dialysis before transplant and transplant survival.[3-5] In a mate kidney analysis comparing the outcomes of transplant recipients from the same deceased donor, 5-year transplant survival in patients who had received a transplant after 24 months of dialysis was 58% compared to 78% in patients who received a transplant within 6 months.[6] The basis for the association between dialysis exposure and transplant failure is multifactorial and incompletely understood, but the progression of comorbid diseases during dialysis treatment including cardiovascular disease is believed to be an important factor.[7,8] Minimizing dialysis exposure before transplant is well recognized as one of the most important strategies to improve transplant outcomes.[6,9,10]

The high level of regulatory oversight of transplant in the United States has contributed to concerning trends in waitlist practices.[11] Because transplant center performance assessment is based on 1-year posttransplant outcomes, centers have stopped listing or removed patients with a high burden of comorbid disease from their waitlists.[2] Current methods for calculating expected posttransplant outcomes used in the assessment of transplant center performance include consideration of the pretransplant duration of dialysis but do not account for variation in dialysis that may affect posttransplant outcomes.[12] For example, there are large regional differences in dialysis mortality even after accounting for differences in patient characteristics.[13]

The emergence of value-based care and recognition of the relatively poor outcomes of dialysis-treated patients in the United States have led to several initiatives and proposed legislation to improve the quality of dialysis care.[14,15] Ironically, transplant, which is associated with better health outcomes and lower costs than dialysis, is underemphasized in these efforts, which have narrowly focused on improving the integration of dialysis care and have raised concern in the transplant community.[16,17]

The current study was motivated by the need to inform the fairness of the current regulatory procedures for kidney transplant in the United States that do not consider the potential impact of regional differences in dialysis mortality on posttransplant outcomes and to inform the importance of broader consideration of transplant in future initiatives to improve the integration of care for ESKD patients. The objective of the study was to determine whether the association of pretransplant dialysis exposure with transplant failure was stronger among patients treated in regions with higher dialysis mortality.

2 | METHODS

This study was approved by our hospital research ethics board and adheres to the Principles of the Declaration of Istanbul.

2.1 | Data source

The data used for this analysis are available in the public domain. The standard analysis files of the United States Renal Data System (USRDS) were used for this analysis.[13]

2.2 | Analytical methods

We first determined state- and period-specific dialysis mortality rates, defined in 6 equal 3-year time periods during January 1, 1995, through December 31, 2012, to account for changes in dialysis survival during the study period. We then determined the association between pretransplant dialysis exposure and transplant outcomes ascertained through December 31, 2017, and how this association was modified by the dialysis mortality rate in the state and time period in which transplant recipients received dialysis before transplant.

2.3 | Calculation of dialysis mortality

Dialysis mortality rates were determined among prevalent adult dialysis patients aged 18 to 70 years, in whom at least 90% of their dialysis treatment modality was hemodialysis and who received all of their dialysis treatments in the same state of residence.

The adjusted dialysis mortality rates per 1000 patient-years for each state were estimated in 6 separate 3-year time periods using Poisson regression. The analysis included period-prevalent adult dialysis patients and was restricted to patients who had <15 years of dialysis treatment before the start date of each time period (1995-1997, n = 182 855; 1998-2000, n = 221 858; 2001-2003, n = 253 926; 2004-2006, n = 283 741; 2007-2009, n = 314 385; 2010-2012, n = 340 204). The 15-year time period was chosen to ensure a similar duration of pretransplant dialysis exposure among patients in each of the 3-year time periods analyzed.

A Poisson model was used to determine dialysis mortality rates for each state during each 3-year time period based on the number of deaths and patient-years at risk. For each patient, the contribution of patient-years begins at the start of the 3-year period or start date of hemodialysis, whichever is later, and ends at time of transplant, death, or the end of the 3-year time period. The model adjusted for differences in patient age, sex, race, cause of ESKD, dialysis vintage (<2, 2-3, 3-5, or >5 years), and year of first dialysis treatment. To allow comparison between state- and period-specific mortality rates, the model was used to predict mortality rates for a typical patient (specifically a non–African American male, 55 years of age, who started dialysis between 2000 and 2004, with a dialysis vintage of <2 years). The adjusted state- and period-specific dialysis mortality rates are reported in Table S1.

2.4 | Association of pretransplant dialysis and dialysis mortality rates with transplant outcomes

This analysis included adult patients, aged 18-70 years, who initiated maintenance dialysis on or after May 1, 1995, and underwent a deceased donor kidney-only transplant on or before December 31, 2012. Living donor transplant recipients were excluded from the study because most living donor transplants are performed within 2 years of dialysis initiation in the United States.[18] The start date was chosen to ensure all patients had a Centers for Medicare and Medicaid Services Form 2728, also known as the Medevid form, which contains information about comorbid conditions known to impact posttransplant outcomes. The dates of transplant were chosen to ensure at least 5 years of posttransplant follow-up for all study patients. The analysis was limited to patients in whom at least 90% of the pretransplant dialysis modality was hemodialysis and all pretransplant dialysis treatment was in the same state of residence.

Each transplant recipient was then assigned the state- and period-specific dialysis mortality rate of the time and place in which they received pretransplant dialysis. For patients in whom dialysis treatment spanned more than one 3-year period, a weighted average of the dialysis mortality rates for each of the periods was attributed to the patient (weighted by the number of dialysis days spent in each period). Patients were then allocated into quartiles of dialysis mortality based on the state/period mortality rates attributed to them to facilitate presentation and interpretation.

A multivariable Cox regression model was used to determine the association between the duration of pretransplant dialysis exposure and transplant survival. This model followed patients from the date of deceased donor transplant until the time of transplant failure from any cause including death or end of follow-up (December 31, 2017). A multilevel mixed-effects model, clustered by state, was used to allow the relative effect of a given covariate pattern on the baseline hazard function to vary across states. The model adjusted for differences in patient age at transplant, sex, race, cause of ESKD, body mass index (BMI), comorbid conditions (congestive heart failure, peripheral vascular disease, cerebrovascular disease, atherosclerotic heart disease, chronic obstructive pulmonary disease), tobacco use, inability to ambulate, insurer Medicare/Medicaid, private, other, or none), year of transplant (1995-1999, 2000-2004, 2005-2008, 2009-2012), PRA (0, 1-80, or >80), the degree of HLA mismatch at the -*A*, -*B*, and -*DR* gene loci (0, 1-5, or 6), and the Kidney Donor Profile Index (KDPI) of the deceased donor kidney (0-20, 21-50, 51-84, ≥85).[19]

To account for other ecological factors at the state level that may affect the association between pretransplant dialysis exposure and transplant survival, we included state-level poverty and state-level life expectancy. Information regarding state-level poverty was obtained from the 2018 US census.[20] Information regarding sex-specific life expectancy in individual states was obtained from the Institute for Health Metrics and Evaluation.[21] States were ranked by sex-specific life expectancy from shortest to longest and by the percentage of inhabitants living in poverty.

Because of the low level of missing data for individual variables (BMI: 4.2%, PRA: 6.5%, KDPI: 10.3%, HLA mismatch: 9.3%) and the fact that data were not differentially missing between patients grouped by quartile of dialysis mortality, a category of missing was created to allow all patients to be included in the Cox model.

The association of dialysis exposure and dialysis mortality rate with transplant survival was reported using adjusted cumulative incidence curves generated from the Cox multivariable model. To create these curves, the Cox model is stratified first by length of pretransplant dialysis treatment and then by the dialysis mortality quartile. The resulting curves are representative of a cohort of patients with the mean values of the nonstratified model covariates; the curves depict the estimated cumulative incidence of an event separately for each category level of dialysis duration or quartile of dialysis mortality.

An interaction term was used to determine if the association of pretransplant dialysis duration was modified by dialysis mortality characterized by the quartile of state- and period-specific dialysis mortality rate. These interactions are visualized on surface plots that demonstrate the variation in hazard associated with each combination of these 2 factors. We compared the outer boundaries of the hazard surface plots, representing the quartiles with the lowest and highest dialysis mortality rates, to contrast the increase in risk of transplant failure associated with longer increments of pretransplant dialysis exposure. Least squares regression was used to estimate the change in the risk of transplant failure with each additional year of dialysis exposure in the highest versus the lowest quartile of dialysis mortality.

Subset analyses were performed to determine the consistency of associations in different patient subgroups (patients with and without ESKD resulting from diabetes, African American and non-African American patients, and patients above and below 40 years of age at time of transplant). A separate surface plot is shown for each subgroup, and the relationships between the pairs of surfaces are analyzed to distinguish subset patterns.

Similar models were constructed for the outcomes of death-censored transplant failure (defined by the need to resume maintenance dialysis or preemptive repeat transplant) and death with a functioning transplant.

Cox model assumptions were tested with plots of the log of the negative log of the estimated survival density function versus the log of survival time, and no violations were identified. Analyses were conducted in R v3.4.4 (2018-03-15) with the "survival" package.

2.5 | Sensitivity analyses

To address the variability in dialysis mortality that exists between dialysis units within the same state, we repeated this analysis at the dialysis facility level. This analysis was restricted to dialysis units that had at least 10 prevalent dialysis patients during each of the 3-year time periods examined. The average number of patients per dialysis units was 48; therefore, only unadjusted dialysis mortality rates were determined. As in the primary state-level analysis, each patient was attributed a "dialysis center mortality rate" as a weighted average of the rates at their dialysis center during the time periods spanned by their dialysis treatment. The patients were then grouped into quartiles based on these weighted mortality rates. An adjusted Cox model was used to determine the relationship between pretransplant dialysis exposure and transplant outcomes as in the state-level analysis. The adjusted Cox model was run as a multilevel model to account for clustering at the dialysis center level.

To determine whether the association of dialysis with posttransplant outcomes remained consistent in later cohorts, we performed a sensitivity analysis restricted to patients who initiated dialysis between 2010 and 2012.

3 | RESULTS

3.1 | State- and period-specific dialysis mortality rates

The adjusted dialysis mortality per 1000 patient-years for each state in the United States in 3-year time periods ranged from a low of 128 deaths/1000 patient-years to 330 deaths/1000 patient-years with a median [IQR] of 229 [201-252] deaths/1000 patient-years. A listing of the 6 state-specific dialysis mortality rates in 3-year time increments during the study period 1995-2012 is shown in Table S1. The adjusted average dialysis mortality rate in individual states during the entire study period is shown in Figure 1. These mortality rates are provided to illustrate the variation in dialysis mortality between states during the study period and were calculated using a typical patient (ie, a non–African American man, aged 55 years, with diabetes, and treated with dialysis for <2 years) to facilitate comparison.

3.2 | Transplant cohort

Figure 2 summarizes the assembly of the transplant patient cohort used to determine the association of dialysis exposure and dialysis mortality with transplant survival. The characteristics of the transplant patients overall and grouped by quartile of their state- and period-specific dialysis mortality rate are shown in Table 1.

3.3 | Association of dialysis exposure and dialysis mortality with transplant outcomes

Figure 3 shows the association of pretransplant dialysis exposure and state- and period-specific dialysis mortality (in quartiles) with the risk of transplant failure from any cause including death. Longer pretransplant dialysis treatment was progressively associated with an increased risk of transplant failure (Figure 3A). Patients who received dialysis in states and time periods with higher dialysis mortality had a higher risk of transplant failure (Figure 3B). The full Cox model output is shown in Table S2.

3.4 | Interactive effect of dialysis exposure and dialysis mortality on transplant failure

Figure 4A shows how the association of pretransplant dialysis exposure with transplant failure from any cause including death varies depending on the dialysis mortality. Figure 4B,C shows the same information for the outcomes of death-censored transplant failure (defined by the need for maintenance dialysis or repeat transplant) and death with a functioning transplant. The hazard ratios shown in these figures are compared with the reference group of patients with <1 year of pretransplant dialysis exposure who received dialysis in a state and time period within the lowest quartile of dialysis mortality. For any given duration of dialysis exposure, the risk of transplant failure from any cause is greater among patients who received their pretransplant dialysis treatment in a state and time period with a higher dialysis mortality rate (Figure 4A). The greatest hazard of transplant failure from any cause is associated with a combination of ≥ 6 years of pretransplant dialysis exposure in the highest dialysis mortality quartile, Q4—hazard ratio (HR) = 1.61 (95% confidence

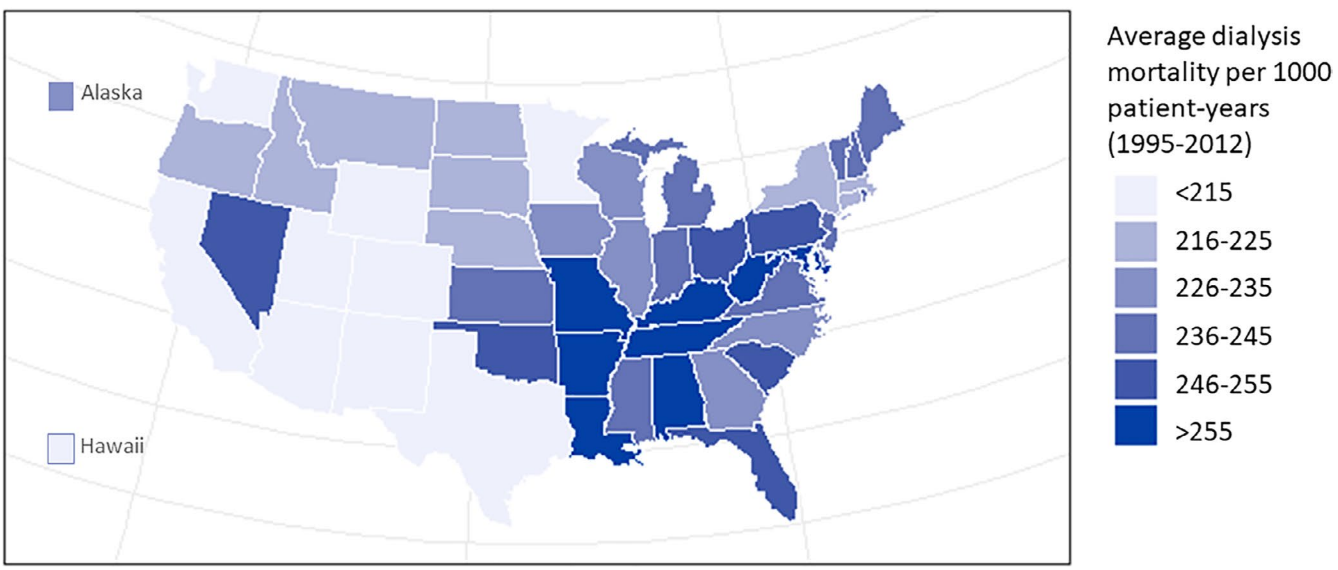

FIGURE 1 Average dialysis mortality per 1000 patient-years by state during the study period January 1, 1995, through December 31, 2012. Rates were estimated using a Poisson regression model adjusted for age, sex, race, cause of ESKD. The map shows estimated rates for a typical patient (ie, a non–African American male, aged 55 years, with diabetes and treated with dialysis for <2 years)

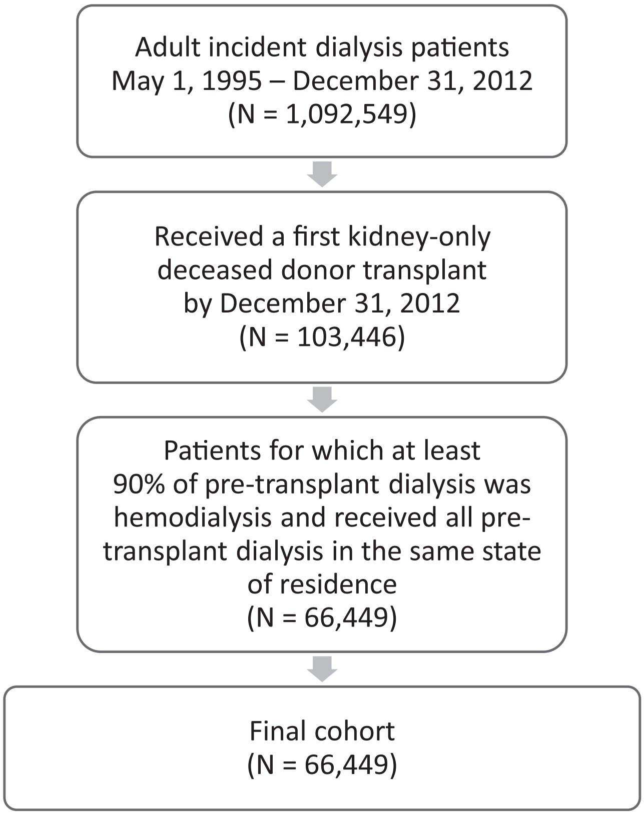

FIGURE 2 Assembly of the transplant patient cohort

interval [CI]: 1.40-1.84)—compared with a reference population having < 1 year of dialysis in the lowest quartile of dialysis mortality (Q1). In comparison, the HR for patients with ≥ 6 years of dialysis exposure in the lowest dialysis mortality quartile was 1.24 (95% CI: 1.12-1.36). The number of patients, HRs, and 95% CIs for each level of dialysis exposure and dialysis mortality quartile are provided in Tables S3 and S4. The interaction of dialysis exposure and dialysis mortality was not significant for the outcome of death-censored transplant failure (P = .23) as shown by the relatively flat surface hazard plot in Figure 4B but was significant for the outcome of death with a functioning transplant (P = .01) as shown by the sharp incline in the surface hazard plot with higher combinations of dialysis exposure and dialysis mortality (Figure 4C).

Figure 5A shows the average increase in risk of transplant failure from any cause associated with each additional year of dialysis exposure among patients who received pretransplant dialysis in a state and time period within the lowest dialysis mortality quartile compared with patients in the highest dialysis mortality quartile. With each additional year of dialysis exposure, the risk of transplant failure was estimated to increase by approximately 0.08 for patients in the highest quartile of dialysis mortality compared with 0.04 for patients in the lowest quartile; This would correspond to a 48% and 24% increase in the risk of transplant failure over 6 years of pretransplant dialysis exposure for patients in the highest and lowest quartile of dialysis mortality, respectively. Figure 4B,C shows the same information for the outcomes of death-censored transplant failure and death with a functioning transplant.

3.5 | Subgroup analyses

Figure 6A shows the interaction of dialysis exposure and dialysis mortality for patients with and without diabetes-related ESKD. The surface hazard plots for patients with diabetes increased more rapidly with higher combinations of dialysis exposure and dialysis mortality. Figure 6B shows the interaction of dialysis exposure and dialysis mortality for African American patients and non–African American patients. The HR plots for these groups separate with increasing dialysis exposure and dialysis mortality rates. In regions with higher dialysis mortality, non–African American patients had a greater increase in the HR for transplant failure with longer pretransplant dialysis exposure compared with African Americans. Figure 6C shows the interaction of dialysis exposure and dialysis mortality for patients > 40 years and ≤ 40 years of age. The hazard planes are interwoven at the lowest quartile of dialysis mortality (Q1) indicating that old and young patients experience similar increases in the risk of a posttransplant event with increasing time on dialysis in regions with low dialysis mortality. For the other quartiles of dialysis mortality, longer exposure to dialysis was associated with a greater increase in the risk of transplant failure among patients > 40 years.

3.6 | Sensitivity analyses

Dialysis unit level analysis: the results of a Cox multivariable model showing the association of unadjusted dialysis mortality rate (by quartile) and dialysis exposure with the outcome of transplant failure from any cause is shown in Table S8. Consistent with the state-level analysis, longer dialysis exposure before transplant was associated with an increased risk of transplant failure, and this association was stronger in dialysis units with higher dialysis mortality rates.

In analyses restricted to patients who initiated dialysis between 2010 and 2012 (Figure S1), each additional year of dialysis exposure was associated with a 0.04 risk of transplant failure for any cause among patients in the highest quartile of dialysis mortality compared with 0.0067 for patients in the lowest quartile. This would correspond to a 24% and 4% increase in the risk of transplant failure from any cause over 6 years of pretransplant dialysis exposure for patients in the highest and lowest quartiles of dialysis mortality.

4 | DISCUSSION

This study found that the risk of transplant failure associated with pretransplant dialysis exposure was higher when the rate of dialysis mortality in the environment (ie, the combination of state and time period) where transplant recipients received their pretransplant dialysis treatment was higher. Consistent with known secular improvements in dialysis care, the highest state dialysis mortality rates were observed earlier in the study period.[13] The fact that improvements in dialysis survival over the study period were associated with a lower risk of transplant failure suggests that initiatives to

TABLE 1 Characteristics of the transplant patients

		Hemodialysis mortality rate quartiles (per 1000 patient-years)			
	All patients N = 66,449	Low Q1 128-196 n = 16,613	Med-low Q2 197-221 n = 16,627[b]	Med-high Q3 222-247 n = 16,597	High Q4 248-330 n = 16,612
Duration of pretransplant dialysis (y) (median [IQR])	3.0 [1.7, 4.7]	3.4 [1.9, 5.3]	3.0 [1.7, 4.6]	3.1 [1.8, 4.9]	2.6 [1.4, 4.2]
State-level dialysis mortality rates	222	180	209	235	261
Deaths/1000 patient-years:	[197,247]	[166,190]	[203,215]	[229,241]	[254,267]
Median [IQR]					
Range	128-330	128-196	197-221	222-247	248-330
Age at transplant	53.8	55.0	54.0	53.8	52.5
Median [IQR]	[44.2,61.9]	[45.4,62.9]	[44.1,62.1]	[44.2,61.8]	[43.0,60.7]
Sex					
Male	63%	63%	63%	64%	64%
Race					
White	59%	65%	61%	54%	57%
African American	33%	20%	31%	41%	39%
Other	8%	15%	8%	5%	4%
Cause of ESKD					
Diabetes	39%	42%	40%	38%	37%
Cystic kidney disease	8%	7%	8%	8%	8%
Glomerulonephritis	19%	18%	20%	20%	20%
Hypertension	23%	22%	21%	23%	25%
Other	11%	11%	11%	11%	10%
Comorbid conditions					
Peripheral vascular disease	5%	5%	5%	5%	5%
Congestive heart failure	13%	13%	13%	14%	14%
Cerebrovascular disease	4%	3%	4%	4%	4%
Atherosclerotic heart disease	3%	5%	4%	2%	0%
Chronic obstructive pulmonary disease	2%	1%	2%	2%	2%
Inability to ambulate	1%	1%	1%	1%	1%
Current smoker	5%	3%	4%	5%	6%
Body mass index (kg/m^2)[a]					
<18.5	4%	3%	4%	3%	5%
18.5-24.99	33%	34%	32%	31%	36%
5-29.99	31%	33%	30%	31%	30%
≥30	32%	30%	34%	35%	29%
Medical insurance					
Medicare/Medicaid	30%	33%	29%	29%	29%
Private	43%	40%	44%	45%	45%
Other	14%	14%	15%	13%	14%
None	13%	13%	12%	13%	12%
PRA[a]					
0	54%	59%	56%	48%	50%
1-80	36%	32%	34%	41%	39%

(Continues)

TABLE 1 (Continued)

	All patients N = 66,449	Hemodialysis mortality rate quartiles (per 1000 patient-years) Low Q1 128-196 n = 16,613	Med-low Q2 197-221 n = 16,627[b]	Med-high Q3 222-247 n = 16,597	High Q4 248-330 n = 16,612
>80	10%	9%	10%	11%	11%
HLA mismatch[a]					
0	11%	12%	10%	11%	12%
1-5	75%	72%	75%	75%	77%
6	14%	16%	15%	14%	11%
KDPI[a]					
0%-20%	22%	20%	21%	22%	24%
21%-50%	30%	30%	29%	30%	29%
51%-84%	36%	38%	37%	36%	35%
85%+	12%	12%	13%	12%	12%
Year of transplant					
1995-1999	15%	1%	15%	13%	32%
2000-2004	30%	14%	24%	32%	51%
2005-2008	31%	36%	27%	43%	15%
2009-2012	24%	49%	34%	12%	2%
State-level percentage poverty** median [IQR]	13% [11,14]	13% [12,14]	13% [11, 14]	12% [11, 14]	13% [11, 14]
State-level life expectancy rank** (from 1 to 51, shortest-longest)	26 [15, 42]	43 [24, 50]	26 [18, 42]	20 [12, 36]	20 [7, 27]

[a]BMI has 4% missing data; PRA has 7% missing data; HLA mismatch has 9% missing data; KDPI has 10% missing data.
[b]Populations in each quartile are not equal due to a tie at the median value.

improve the quality of dialysis care might have indirectly benefitted transplant recipients. The associations were consistent in subgroup analyses but were stronger in patients known to have higher dialysis mortality including older patients, non–African American patients, and patients with diabetes-related ESKD. The association of dialysis exposure and dialysis mortality with transplant failure from any cause was primarily due to the higher risk of death with a functioning transplant rather than death-censored transplant failure consistent with the hypothesis that dialysis exposure increases the progression of comorbid conditions such as cardiovascular disease, which manifests as premature death after transplant. The rate of dialysis mortality in this study was determined at the state level. Because dialysis mortality likely varies between dialysis facilities within a state, our findings based on the average state-level dialysis mortality rate may underestimate the association of dialysis mortality with posttransplant outcomes. The study findings may help refocus attention on the importance of pretransplant factors in determining transplant outcomes. The findings also indicate that regional differences in dialysis mortality may warrant consideration in the evaluation of transplant center performance by regulatory bodies. For example, it may be relevant to consider both the duration and location where a patient received their pretransplant dialysis treatment in future models of expected posttransplant survival.

The higher risk of transplant failure associated with longer pretransplant dialysis exposure in states with higher dialysis mortality reported in this study may or not be related to the quality of the dialysis procedure. The dialysis mortality rate in a state may be in part be related to social, environmental, and health system factors that affect health outcomes both on dialysis and after transplant. A recent study by Schold and colleagues reported that residential area life expectancy (a proxy for socioeconomic, environmental, genetic, and behavioral factors) was independently associated with mortality in patients with ESKD and the risk of graft loss.[22] In general, mortality rates are more reliable indicators of the quality of care in acute illnesses that pose a low risk of death, but mortality rates are less indicative of the quality of care when patients have multiple chronic diseases and are at higher risk of death.[23] Our analysis did not directly assess parameters of dialysis care. The standard analysis files of the USRDS contain only limited information about the quality of dialysis care in dialysis facilities. Previous studies have shown an association between dialysis facility ownership and access to transplant, but to our knowledge no studies have examined the association of clinical measures of the quality of dialysis such as vascular access, dialysis adequacy, adequacy of bone and mineral metabolism, or transfusion utilization with posttransplant

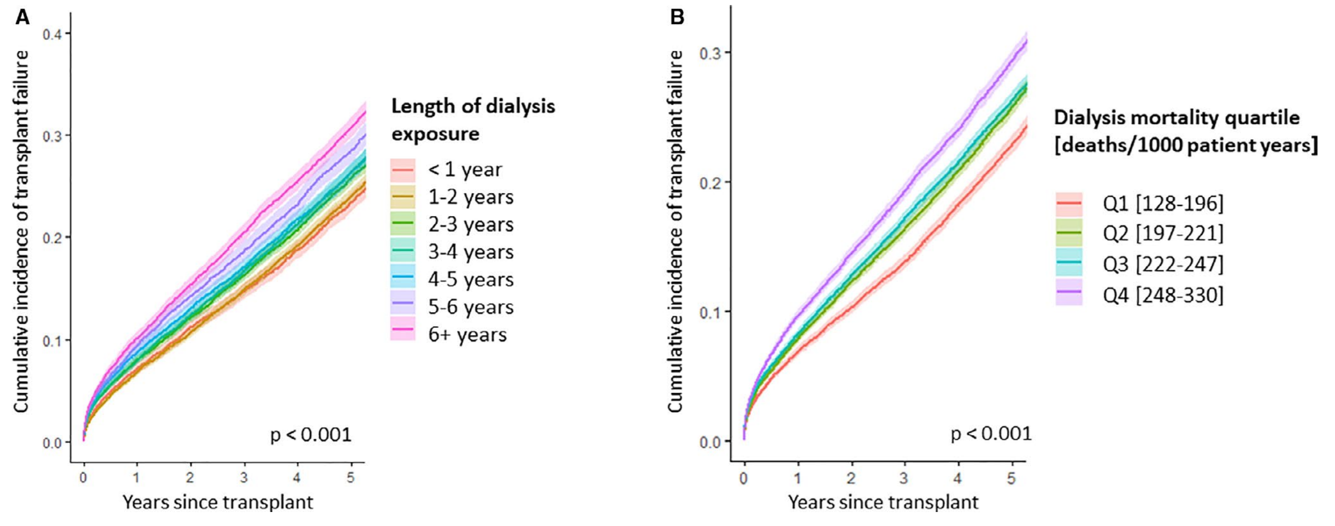

FIGURE 3 Adjusted cumulative incidence of transplant failure from any cause with 95% confidence intervals stratified by pretransplant dialysis duration (A) and quartile of dialysis mortality (B). Cox multivariable model adjusted for patient age at transplant, sex, race, cause of ESKD, BMI, comorbid conditions, transplant year, insurance provider, panel reactive antibody, HLA mismatch, kidney donor profile index, state-level poverty, and state-level life expectancy

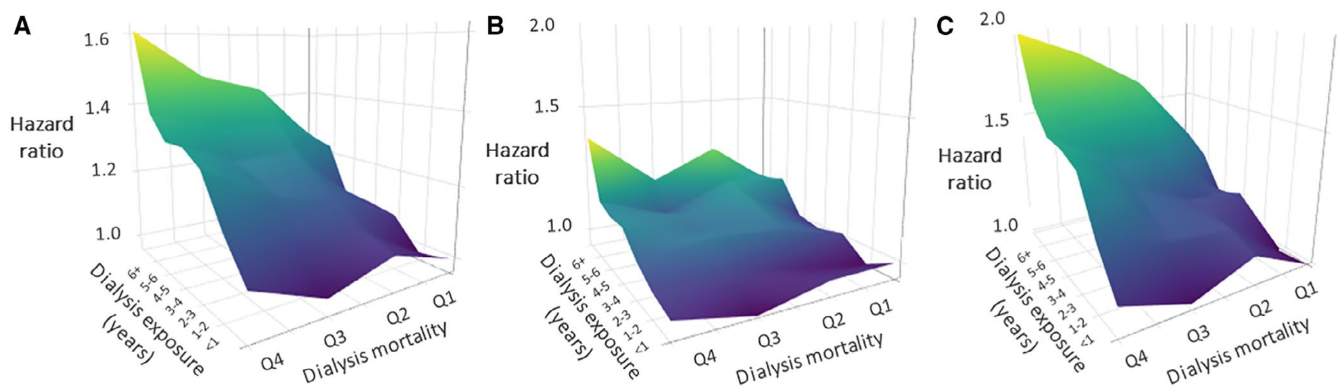

FIGURE 4 Interaction of dialysis duration and dialysis mortality on transplant outcomes. A, Transplant failure from any cause, *P* value for interaction = .02. B, Death-censored transplant failure, *P* value for interaction = .23. C, Death with a functioning transplant, *P* value for interaction = .01. Cox multivariable regression models adjusted for age at transplant, sex, race, cause of ESKD, BMI, comorbid conditions, year of transplant, insurance provider, PRA, HLA mismatch, KDPI, state-level poverty, and state-level life expectancy

outcomes.[24,25] Therefore, further studies are needed to determine if differences in the quality of dialysis care underlie differences in dialysis mortality and if improvements in dialysis care can modify the impact of longer durations of dialysis exposure on posttransplant outcomes.

This study builds on previous work that demonstrated the association of pretransplant dialysis duration with posttransplant outcomes.[3-5] These studies played a pivotal role in advancing strategies to minimize the duration of pretransplant exposure including expanded use of preemptive and living donor transplant and counseling patients to accept higher-risk deceased donor kidneys in exchange for shorter waiting times.[9,10,26,27] Our findings suggest that in addition to limiting pretransplant dialysis exposure, efforts to optimize the dialysis care of transplant candidates might also be important to mitigate the effects of increased dialysis waiting times on posttransplant survival and should be further studied.

Regardless of the factors contributing to the higher dialysis-associated risk of transplant failure in states with higher dialysis mortality, the finding that dialysis exposure is not a homogeneous risk should be considered in future transplant metrics. The calculation of expected posttransplant outcomes includes the duration of pretransplant dialysis exposure but does not include the assessment of regional differences in dialysis mortality.[12] More broadly, the study findings illustrate that the narrow focus on posttransplant outcomes without more thorough consideration of pretransplant factors that affect posttransplant outcomes is suboptimal and may be even more problematic in the future as waiting times for transplant continue to increase. More comprehensive approaches to assess the quality of care for CKD patients who encompass the entire spectrum of care from first diagnosis until death have been proposed to improve the value of care for CKD patients, and the need for better integration of care between dialysis and transplant care providers has been emphasized in the recent transplant literature.[17,28]

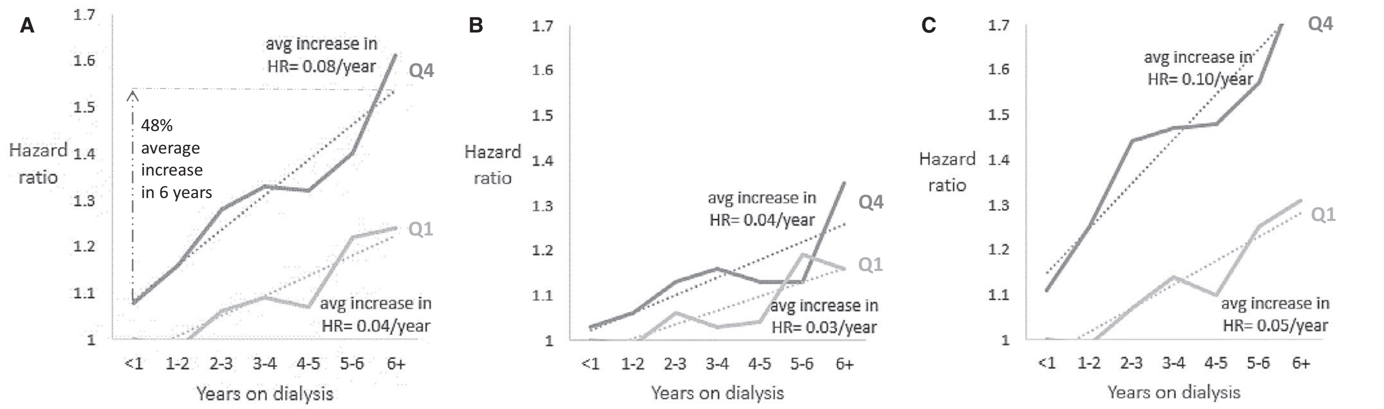

FIGURE 5 Comparison of increase in hazard of a posttransplant outcome with additional time on dialysis, among patients with the lowest (Q1) and highest (Q4) state- and period-specific dialysis mortality. The posttransplant outcomes include transplant failure from any cause including death (A), death-censored transplant failure (B), and death with functioning transplant (C)

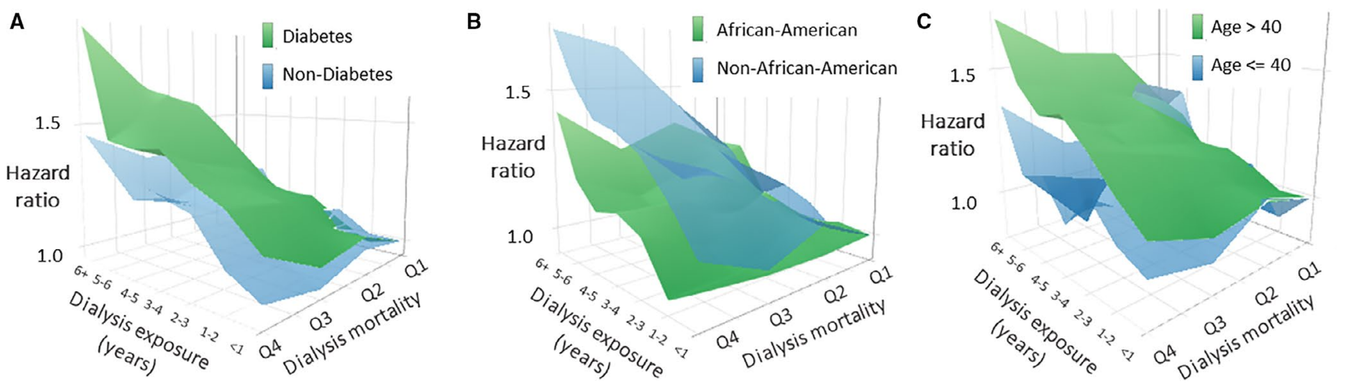

FIGURE 6 Subgroup analyses: The hazard ratio for transplant failure from any cause including death for patients with and without diabetes-related end-stage kidney disease, African American and non–African American patients, and patients ≤ 40 y and > 40 years old

A strength of the study is careful calculation of dialysis mortality rates and use of multivariable models to determine the association and interaction of pretransplant dialysis exposure and dialysis mortality on the risk of posttransplant outcomes. Dialysis mortality rates were determined by the state of residence in 3-year time intervals to account for secular improvements in dialysis care. Period-prevalent patients were included in these calculations only when >90% of their dialysis modality was hemodialysis and the patient received all of their dialysis treatment within the same state. Mortality rate calculations were adjusted for patient demographic characteristics, cause of ESKD, year of first dialysis treatment, and total duration of dialysis treatment. Individual transplant recipients were then assigned a dialysis mortality rate specific to the state and time period in which they received dialysis before transplant with weighted averages determined for patients whose pretransplant dialysis treatment spanned more than one 3-year time interval. How the association of pretransplant dialysis duration with posttransplant outcomes was modified by dialysis mortality rate was then determined in a multivariable time-to-event model that included adjustment for multiple relevant confounders associated with transplant survival. Despite these efforts, readers of this study should consider the inherent limitations of observational studies based on administrative data, including residual confounding by unmeasured factors including transplant center-related factors, when interpreting the study findings. Readers should also note that the study excluded patients treated with peritoneal dialysis.

In conclusion, this study found that the association of dialysis with transplant failure is stronger among patients who received dialysis in an environment with high dialysis mortality. Further studies are needed to determine whether higher rates of dialysis mortality are due to differences in the quality of dialysis care. The findings may have implications for the delivery of dialysis to transplant candidates and for the evaluation of transplant center performance by regulatory bodies.

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DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

AUTHOR CONTRIBUTIONS

Dr John Gill devised the study, oversaw all aspects of the study, and drafted the manuscript. Dr Stephanie Clark conducted all statistical analyses. Drs Matthew Kadatz and Jagbir Gill provided input to study design and reviewed the manuscript. All the authors approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

The data used for this analysis are available in the public domain. The standard analysis files of the United States Renal Data System (USRDS) were used for this analysis.[13]

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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