



Original Investigation | Nephrology

Survival Outcomes Following Preemptive vs Nonpreemptive Kidney Transplantation

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Abstract

IMPORTANCE Preemptive kidney transplantation (before dialysis) is promoted as optimal therapy for kidney failure, yet evidence of a true survival advantage remains uncertain due to confounding, selection, and lead-time biases.

OBJECTIVE To estimate the associations of preemptive vs nonpreemptive kidney transplantation with mortality and graft outcomes using a target trial emulation among transplant recipients.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study used data from the Scientific Registry of Transplant Recipients, a nationwide registry of all US kidney transplant centers, from January 1, 2005, to November 30, 2023. Adult first kidney-alone transplant recipients with recorded wait-time start at an estimated glomerular filtration rate (eGFR) of 20 mL/min/1.73 m² or less were included. Groups were balanced using stabilized inverse probability of treatment weighting (IPTW) to emulate randomization across demographic, clinical, and socioeconomic factors identified by a directed acyclic graph. Analyses were conducted from July to October 2025.

EXPOSURES Preemptive vs nonpreemptive kidney transplantation, defined by dialysis before transplant.

MAIN OUTCOMES AND MEASURES The primary outcome was all-cause mortality; secondary outcomes were all-cause graft failure, death-censored graft failure, and delayed graft function. IPTW was incorporated for baseline confounding to address selection bias. Weighted Kaplan-Meier curves estimated survival differences; hazard ratios (HRs) and odds ratios (ORs) were derived from weighted left-truncated Cox proportional hazards (to address lead-time bias) and logistic regression models, respectively.

RESULTS Among 32 770 recipients (15 894 [48.5%] preemptive [mean (SD) age, 53.7 (13.1) years; 7007 (44.1%) female] and 16 876 [51.5%] nonpreemptive [mean (SD) age, 54.5 (13.0) years; 6978 (41.3%) female]) with more than 265 369 person-years of follow-up, 6827 deaths occurred. Preemptive transplantation showed no mortality benefit (HR, 1.02; 95% CI, 0.96-1.07). The weighted survival differences were approximately 1% to 2% annually. Preemptive transplantation was associated with lower odds of delayed graft function (OR, 0.68; 95% CI, 0.64-0.72) and reduced risk of death-censored graft failure (HR, 0.81; 95% CI, 0.74-0.88), an association largely attenuated after adjustment for delayed graft function. There was no association with all-cause graft failure (HR, 0.96; 95% CI, 0.91-1.00).

CONCLUSIONS AND RELEVANCE In this study, preemptive transplantation was not associated with improved patient survival but was associated with lower rates of delayed graft function and death-censored graft failure. Findings challenge presumed survival advantages and suggest preemptive

(continued)

Key Points

Question Among adult kidney transplant recipients, is preemptive transplantation (before dialysis) associated with improved posttransplant survival compared with nonpreemptive transplantation?

Findings In this cohort study emulating a target trial that included 32 770 US kidney transplant recipients, apparent survival advantages for preemptive transplantation in crude analyses were no longer present after bias adjustment; however, preemptive transplantation was associated with reduced delayed graft function and death-censored graft failure.

Meaning These findings challenge the presumed survival benefit of preemptive transplantation and do not support prioritizing preemptive status in deceased-donor allocation for this reason, although benefits for early graft function remain relevant.

+ Supplemental content

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Abstract (continued)

strategies should focus on preventing early graft dysfunction and optimizing use of high-risk kidneys rather than expected mortality benefit.

JAMA Network Open. 2026;9(10):e2637964. doi:10.1001/jamanetworkopen.2026.37964

Introduction

Preemptive kidney transplantation, before dialysis, is widely promoted as the optimal treatment for kidney failure. Proposed benefits include avoiding dialysis-related morbidity and costs, with mixed evidence for graft and patient survival.^{1,2} These expectations are reflected in international guidelines and preemptive transplantation as a performance indicator.^{1,3-5} The Kidney Disease: Improving Global Outcomes guideline recommends early referral for transplant assessment, aiming for preemptive transplantation in living donor candidates.³ The British Transplantation Society and European Renal Best Practices similarly endorse preemptive transplantation programs to avoid dialysis initiation.^{1,5} However, in resource-constrained settings, prioritizing preemptive workups may divert capacity from nonpreemptive candidates, raising equity concerns for transplant access and timing.

Despite widespread endorsement of preemptive transplantation, supporting evidence remains observational and methodologically constrained. A 2016 systematic review found improved survival in 9 of 19 adult studies and 1 of 1 pediatric study, with reported benefits for rejection and graft survival.¹ Importantly, all studies were high-risk for selection bias, and treatment effect heterogeneity was unexamined.¹ A 2023 meta-analysis with 46 studies reported lower graft loss with living and deceased donors, and lower mortality-risk with living donors (relative risk, 0.74; 95% CI, 0.60-0.91). However, associations disappeared in adjusted analyses, suggesting residual confounding and uncertain causality.²

Taken together, these findings highlight the need to disentangle true treatment effects from bias. Selection bias arises when healthier, better-resourced patients are more likely to receive preemptive transplants.^{6,7} Lead-time bias occurs when survival is measured from transplant rather than a shared baseline, artificially favoring preemptive recipients whose transplants occur earlier.^{6,8,9} Residual confounding may persist if key prognostic factors influencing both treatment and outcomes are unmeasured or imperfectly adjusted. An Australian registry study of 2147 living donor recipients addressed these limitations using propensity score matching, lead-time adjustment using assumed rates of estimated glomerular filtration rate (eGFR) decline, and left-truncated Cox models and found no survival benefit of preemptive living donor transplantation.⁶

Randomized clinical trials comparing preemptive vs nonpreemptive transplantation are not feasible.³ We therefore applied a target trial emulation framework using a large US registry cohort to estimate whether preemptive vs nonpreemptive kidney transplantation was associated with improved posttransplant mortality and graft outcomes. Bias was mitigated through inverse probability of treatment weighting (IPTW) for baseline confounding and left-truncated Cox models anchored at eGFR of 20 mL/min/1.73 m² or less to address selection and lead-time biases.

Methods

This study used a target trial framework in alignment with methods described by Hernán et al.^{10,11} The target trial protocol is provided in eTable 1 in [Supplement 1](#).¹⁰

The study was approved by the University Health Network Research Ethics Board (24-6023) with a waiver for individual participant informed consent because we used secondary deidentified registry data from a US national registry with mandatory reporting. It is reported consistent with Transparent Reporting of Observational Studies Emulating a Target Trial ([TARGET](#))¹² and

Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines for cohort studies.

Study Design and Population

We included all adult first kidney-alone transplant recipients in the United States with a recorded date of wait-time accrual (first eGFR ≤ 20 mL/min/1.73 m²) between January 1, 2005, and January 1, 2015, who were wait-listed for transplant while not receiving dialysis and subsequently received a transplant before administrative censoring (November 30, 2023). This eGFR date served as time-zero, the point at which wait time begins to accrue and both preemptive and nonpreemptive transplantation strategies remain possible.

This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donors, waitlisted candidates, and transplant recipients in the US, submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration (HRSA), US Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors. Data are mandatorily reported by transplant centers at the time of donation and transplantation and with posttransplant follow-up records at 6 months, 1 year, and then annually, until the recipient is retransplanted, dies, or is lost to follow-up.

Race and ethnicity were reported by the organ donation organization and captured in the SRTR registry. We included groups of Black, White, and other groups, including American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, and multiracial recipients, which were collapsed into a single category due to smaller numbers. This information was included in the study as race and ethnicity have historically been associated with access to transplantation.

Outcomes

The primary outcome was all-cause mortality as a time-to-event outcome, with patients censored at last follow-up or administrative censoring. Secondary outcomes were time to all-cause graft failure (ACGF), death-censored graft failure (DCGF), and delayed graft function (DGF). Binary DGF was defined as either dialysis within 7 days after transplant or less than 25% decline in serum creatinine within 24 hours after transplant. ACGF was defined as graft loss from any cause, including death, with follow-up until last known graft function, death, or administrative censoring. DCGF was defined as return to chronic dialysis or preemptive retransplant, censoring for death with graft function.

Exposures

Preemptive vs nonpreemptive transplantation status was classified binarily; recipients were classified as nonpreemptive if any dialysis history was recorded before transplant. Intention to pursue preemptive transplantation is not recorded in the registry, so preemptive wait-listing served as a surrogate for the population of interest who could reasonably receive a preemptive transplant. Exposure was therefore defined at transplant rather than at time-zero (eGFR ≤ 20 mL/min/1.73 m²), and the estimand is the association of preemptive vs nonpreemptive transplantation among preemptively listed recipients who were transplanted.

Statistical Analysis

Baseline characteristics were summarized as means with SDs for continuous variables and frequencies with percentages for categorical variables. Between-group differences by preemptive transplantation status were assessed using standardized mean differences (SMDs), with absolute SMD greater than 0.10 indicating notable imbalance.¹³ Missing baseline covariable data were handled using multiple imputation by chained equations under the assumption of missing at random, with 10 imputed datasets pooled using Rubin rules^{14,15} (eTable 2 and eMethods in Supplement 1).

To address baseline confounding, IPTW was applied using logistic regression model for probability of preemptive transplantation based on covariables from a directed acyclic graph (eFigure 1 in Supplement 1). Stabilized weights were truncated at the 1st and 99th percentiles, with

model discrimination (area under the receiver operating characteristic curve, 0.76) and postweighting balance (SMD <0.10; Love plot) confirming adequate performance (eMethods in Supplement 1).

We first performed crude survival analyses using Kaplan-Meier curves and unadjusted Cox proportional hazards models for mortality. To mitigate selection and lead-time biases, we evaluated models incorporating IPTW and left truncation (delayed entry) individually; primary analysis included both approaches. Patients entered the risk set at transplant and were followed up to death or censoring, with time-zero at first recorded eGFR of 20 mL/min/1.73 m² or less. This time-zero accounted for longer intervals from eGFR decline to transplant for nonpreemptive recipients. Weighted Kaplan-Meier survival probabilities estimated annually (1 to 10 years after transplant) quantified absolute survival differences, complemented by IPTW-weighted left-truncated Cox models estimating hazard ratios (HRs) with 95% CIs.¹⁶ Group comparisons used Wald tests.

Because IPTW assigns unequal influence to individuals, we used robust (sandwich) variance estimators for all models to account for nonconstant variability.^{17,18} Two-sided $P < .05$ denoted statistical significance. Analyses were conducted in R Studio version 4.3.2 (R Project for Statistical Computing) from July to October 2025.

Sensitivity Analyses

We assessed robustness of primary analyses using alternative model specifications. To assess potential residual confounding, we adjusted for donor characteristics from the Kidney Donor Risk Index (KDRI).^{19,20} To account for center- and era-level clustering, we used models with robust sandwich variance estimators and, separately, shared frailty models including random effects for transplant center and year.

Subgroup Analyses

Effect modification was assessed using interaction terms with donor type (living vs deceased) or donor and recipient age (continuous). We also fit models stratified by donor type allowing separate baseline hazards and examined time to death within deceased- and living-donor subcohorts.

Secondary Outcomes Analyses

For ACGF and DCGF, we fit IPTW-weighted left-truncated Cox proportional hazards models consistent with primary analyses; DCGF models censor at death with a functioning graft and therefore estimate cause-specific hazards, with cumulative incidence displayed using the Aalen-Johansen estimator. Post hoc sensitivity analyses adjusted for DGF to explore its role as a potential pathway; DGF occurs early after transplant, minimizing immortal time bias. Interaction terms were tested for donor type, donor age, and recipient age.

For binary DGF, IPTW-weighted logistic regression models estimated odds ratios (ORs) with 95% CIs. Sensitivity analyses included unweighted, KDRI-adjusted, and age-adjusted (donor and recipient) models. We tested interactions with donor type, donor age, and recipient age; donor type and recipient age were statistically significant, prompting stratified analyses by living vs deceased donors and modeling the outcomes associated with preemptive transplantation across continuous recipient age. Sensitivity analyses evaluated whether associations varied by DGF definition: (1) receipt of dialysis within 7 days after transplant or (2) less than 25% decline in serum creatinine level within 24 hours after transplant. The latter analysis was restricted to recipients transplanted from 2005 to 2015, when this outcome was reported.

Results

Study Population

The analyzed population included 32 770 kidney transplant recipients with 265 369 person-years follow-up. Among these, 15 894 (48.5%) received preemptive (mean [SD] age, 53.7 [13.1] years; 7007

[44.1%] female; 1716 [10.8%] Black, 13 263 [83.4%] White, and 915 [5.8%] belonging to additional groups [American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, or multiracial]) and 16 876 (51.5%) nonpreemptive (mean [SD] age, 54.5 [13.0] years; 6978 [41.3%] female; 3479 [20.6%] Black, 11 762 [69.7%] White, and 1635 [9.7%] belonging to additional groups) transplants (**Table 1**). Overall, 16 991 transplants (51.9%) were from deceased donors and 15 779 (48.1%) from living donors (**Figure 1**).

Before weighting, preemptive recipients compared with nonpreemptive recipients were younger, were more often White, and had fewer comorbidities, including diabetes and vascular

Table 1. Baseline Demographic Characteristics of Study Population at Time of Transplant by Preemptive vs Nonpreemptive Status, With SMDs, Before Inverse Probability of Treatment Weighting

Characteristic	Participants, No. (%) ^a		SMD
	Preemptive transplantation (n = 15 894)	Nonpreemptive transplantation (n = 16 876)	
Age, mean (SD), y	53.7 (13.1)	54.5 (13.0)	0.059
Sex assigned at birth			
Female	7006 (44.1)	6978 (41.3)	0.055
Male	8888 (55.9)	9898 (58.7)	
Race ^b			
Black	1716 (10.8)	3479 (20.6)	0.330
White	13 263 (83.4)	11 762 (69.7)	
Additional group ^c	915 (5.8)	1635 (9.7)	
Blood group ^b			
A	6713 (42.2)	6039 (35.8)	0.162
B	1933 (12.2)	2287 (13.6)	
AB	888 (5.6)	704 (4.2)	
O	6360 (40.0)	7846 (46.5)	
Primary kidney disease ^b			
Diabetes	2744 (17.3)	3917 (23.2)	0.184
Hypertension	2572 (16.2)	2913 (17.3)	
Glomerulonephritis	4147 (26.1)	4453 (26.4)	
Cystic	3362 (21.2)	3054 (18.1)	
Other	3069 (19.3)	2539 (15.0)	
Body mass index, mean (SD) ^d	27.9 (5.4)	28.3 (5.4)	0.071
Weight, mean (SD), kg	81.8 (18.4)	82.5 (18.9)	0.037
Height, mean (SD), cm	170.9 (10.8)	170.4 (11.0)	0.045
Comorbidities ^e			
Diabetes ^b	3626 (22.9)	5070 (30.1)	0.165
Malignant neoplasm ^b	138 (0.9)	361 (2.2)	0.104
Coronary artery disease	676 (4.8)	674 (4.8)	0.002
Peripheral vascular disease	671 (4.3)	960 (5.7)	0.068
Cerebrovascular disease	320 (2.2)	365 (2.5)	0.020
Post-high school education ^b	9977 (65.8)	9714 (59.8)	0.123
Employed ^b	8456 (56.4)	6706 (42.1)	0.290
Private insurance ^b	10 856 (68.4)	7475 (44.3)	0.501
No. of HLA mismatches (ABDR), mean (SD) ^b	3.56 (1.74)	3.96 (1.55)	0.244
Time from eGFR ≤20 mL/min/1.83 m ² to listing, mean (SD), d	111.5 (221.5)	115.5 (198.7)	0.019
Time from eGFR ≤20 mL/min/1.83 m ² to transplantation, mean (SD), d ^b	600.3 (642.2)	1279.4 (884.1)	0.879
Time from listing to transplantation, mean (SD), d ^b	488.8 (617.6)	1164.0 (866.9)	0.897
Transplant year ^{b,f}	NA	NA	0.595
Transplant center ^{b,f}	NA	NA	0.364
US state of residence ^{b,f}	NA	NA	0.199

Abbreviations: eGFR, estimated glomerular filtration rate; NA, not applicable; SMD, standardized mean difference.

^a Percentages reflect nonmissing values. Missing proportion for each variable is shown in eTable 2 in Supplement 1.

^b SMD was greater than 0.10, suggesting meaningful imbalance between groups.

^c Additional groups include American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, and multiracial recipients.

^d Body mass index was calculated as weight in kilograms divided by height in meters squared.

^e Comorbidities reported at time of wait-listing for kidney transplantation.

^f Note that individual levels for transplant year, transplant center, and US state were not shown here due to a large number of levels.

disease. They were also more likely to be employed, have private insurance, and have a postsecondary education. Differences were also observed in HLA mismatch, blood group, transplant timing, center, state, and transplant year (Table 1). IPTW produced excellent covariable balance (SMD <0.10) (eFigures 2-4 in Supplement 1).

Time-to-Event Outcomes

Overall, 6827 deaths occurred: 3222 (20.3%) among preemptive recipients and 3605 (21.4%) among nonpreemptive recipients. Apparent survival benefit of preemptive transplantation in crude models (HR, 0.75; 95% CI, 0.71-0.79) (eFigure 5 in Supplement 1) diminished with bias adjustment: the HR was 0.88 (95% CI, 0.84-0.92) with left-truncation and 0.95 (95% CI, 0.90-1.00) with IPTW. There was no benefit in the primary analysis when both IPTW and left-truncation were applied (HR, 1.02; 95% CI, 0.96-1.07) (Table 2). Weighted survival probability differences were approximately 1% to 2% annually (Figure 2A; eTable 3 in Supplement 1).

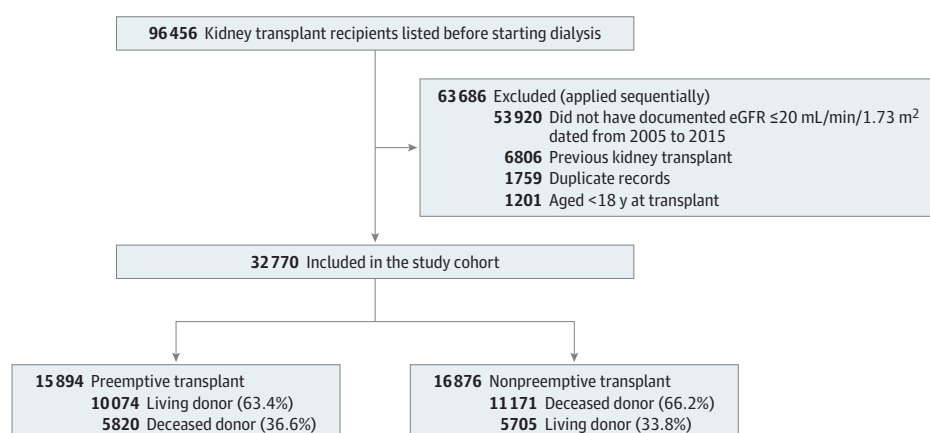
Findings were consistent across sensitivity analyses. No interactions were detected for donor type, recipient age, or donor age. Results were similar in a donor-stratified model (HR, 1.00; 95% CI, 0.95-1.06) and in subcohorts of deceased- (HR, 0.99; 95% CI, 0.92-1.06) or living- (HR, 1.03; 95% CI, 0.94-1.12) donor transplants (Table 2; eFigure 6 in Supplement 1).

ACGF and DCGF occurred in 9081 (27.7%) and 2776 (8.5%) recipients, respectively. Weighted survival curves showed slightly higher graft survival among preemptive recipients for ACGF, and a more pronounced advantage for DCGF (Figure 2B and C). In IPTW-weighted left-truncated Cox proportional hazards models, preemptive transplantation was not associated with ACGF risk (HR, 0.96; 95% CI, 0.91-1.00), but it was associated with lower DCGF risk (HR, 0.81; 95% CI, 0.74-0.88), similar across sensitivity analyses. Adjustment for DGF mitigated the ACGF association and attenuated DCGF when analysis was restricted to deceased-donor transplants or used dialysis-defined DGF (eTable 4 in Supplement 1). Any DGF was strongly associated with both ACGF (HR, 1.55; 95% CI, 1.48-1.63) and DCGF (HR, 1.84; 95% CI, 1.68-2.00), and dialysis-defined DGF conferred even higher DCGF risk (HR, 2.50; 95% CI, 2.22-2.82). No interactions were detected for donor type, recipient age, or donor age for DCGF (Table 3; eFigures 7 and 8 in Supplement 1).

DGF

When DGF was defined as either dialysis within 1 week or a less than 25% creatinine level decline within 24 hours, incidence was 26.9% (8820 of 32 739 recipients), and preemptive transplantation was associated with lower odds of DGF (OR, 0.68; 95% CI, 0.64-0.72) in an IPTW-weighted logistic regression model, consistent across sensitivity analyses (eTable 5 in Supplement 1). Significant 2-way interactions were observed with donor type and recipient age. The association was stronger in

Figure 1. Patient Flow Diagram



The field for estimated glomerular filtration rate (eGFR) of 20 mL/min/1.73 m² or less was not recorded before 1999 and was progressively adopted thereafter (8.9% of transplants in 2001, 36.7% in 2005, and 72.7% in 2008, reaching 87%-91% in 2012-2015). The 50% overall missingness across all preemptively listed transplant recipients since 1987 therefore largely reflects transplants performed before the variable existed, rather than selective reporting.

deceased-donor recipients (OR, 0.56; 95% CI, 0.52-0.60) and was not present for living-donor recipients (OR, 0.92; 95% CI, 0.84-1.01). The association also varied across recipient age, strengthening progressively with increasing age (eFigure 9 in Supplement 1). Effect measure modification by donor age did not reach conventional statistical significance (eFigure 9 in Supplement 1). No significant 3-way interaction between preemptive status, recipient age, and donor age was detected.

For DGF defined by dialysis receipt (32 739 recipients; 3325 events), preemptive transplantation was strongly associated with lower DGF (OR, 0.21; 95% CI, 0.18-0.23), irrespective of donor type (eTable 6 in Supplement 1). When defined by serum creatinine decline (17 943 recipients; 6458 events), the association was weaker (OR, 0.82; 95% CI, 0.77-0.88). In stratified analyses, the association persisted for deceased- (OR, 0.75; 95% CI, 0.68-0.82) but not living- (OR, 0.96; 95% CI, 0.86-1.06) donor recipients (eTable 7 in Supplement 1).

Discussion

Using a large US registry and a target trial emulation approach, we found that preemptive transplantation was not associated with a survival advantage over nonpreemptive transplantation, with no modification by donor type or recipient age. It was, however, associated with substantially lower DGF rates—particularly under the dialysis-based definition— that were largest among older recipients, deceased-donor recipients, and possibly older donor kidneys. This corresponded to reduced DCGF, an association largely attenuated by adjustment for DGF, consistent with early graft dysfunction as a potential pathway.

No mortality difference was observed after addressing lead-time bias through a common time-zero at eGFR of 20mL/min/1.73 m² or less, selection bias through left-truncation, and baseline confounding through IPTW. This null association persisted across donor types and recipient ages. Crude and partially adjusted models produced apparent survival advantages that did not persist after bias adjustment, raising the possibility that uncorrected biases contributed to earlier reports. Our

Table 2. Cox Proportional Hazards Models Estimating the Association Between Preemptive vs Nonpreemptive Transplantation Status and Mortality: Primary and Sensitivity Analyses Among 32 770 Recipients With 6827 Deaths

Model	Hazard ratio (95% CI)	P value
Primary analysis		
Main model with IPTW and left truncation	1.02 (0.96-1.07)	.60
Model building		
Crude model; no IPTW, no left truncation	0.75 (0.71-0.79)	<.001
Left truncation; no IPTW	0.88 (0.84-0.92)	<.001
IPTW; no left truncation	0.95 (0.90-1.00)	.06
Sensitivity analyses		
IPTW; left truncation; adjusted donor KDRI variables (n = 32 068) ^a	1.04 (0.98-1.10)	.16
IPTW; left truncation; clustering by center	1.02 (0.95-1.08)	.63
IPTW; left truncation; clustering by year	1.02 (0.97-1.07)	.54
IPTW; left truncation; frailty model with random effects for transplant center and year ^b	1.02 (0.97-1.07)	.44
IPTW; left truncation; extended follow-up ^c	0.98 (0.93-1.03)	.42
Subgroup analyses ^d		
Living donors	1.03 (0.94-1.12)	.50
Deceased donors	0.99 (0.92-1.06)	.76

Abbreviations: IPTW, inverse probability of treatment weight; KDRI, Kidney Donor Risk Index.

^a The model adjusted for donor KDRI variables included complete cases of the donor variables that were not imputed alongside the recipient variables. This model included 32 068 recipients and 6705 death events occurred.

^b When transplant center or year were included as random effects in frailty models, variance estimates were low (mean [SD], 0.07 [0.27] and 0.02 [0.16], respectively), indicating little additional explanatory value.

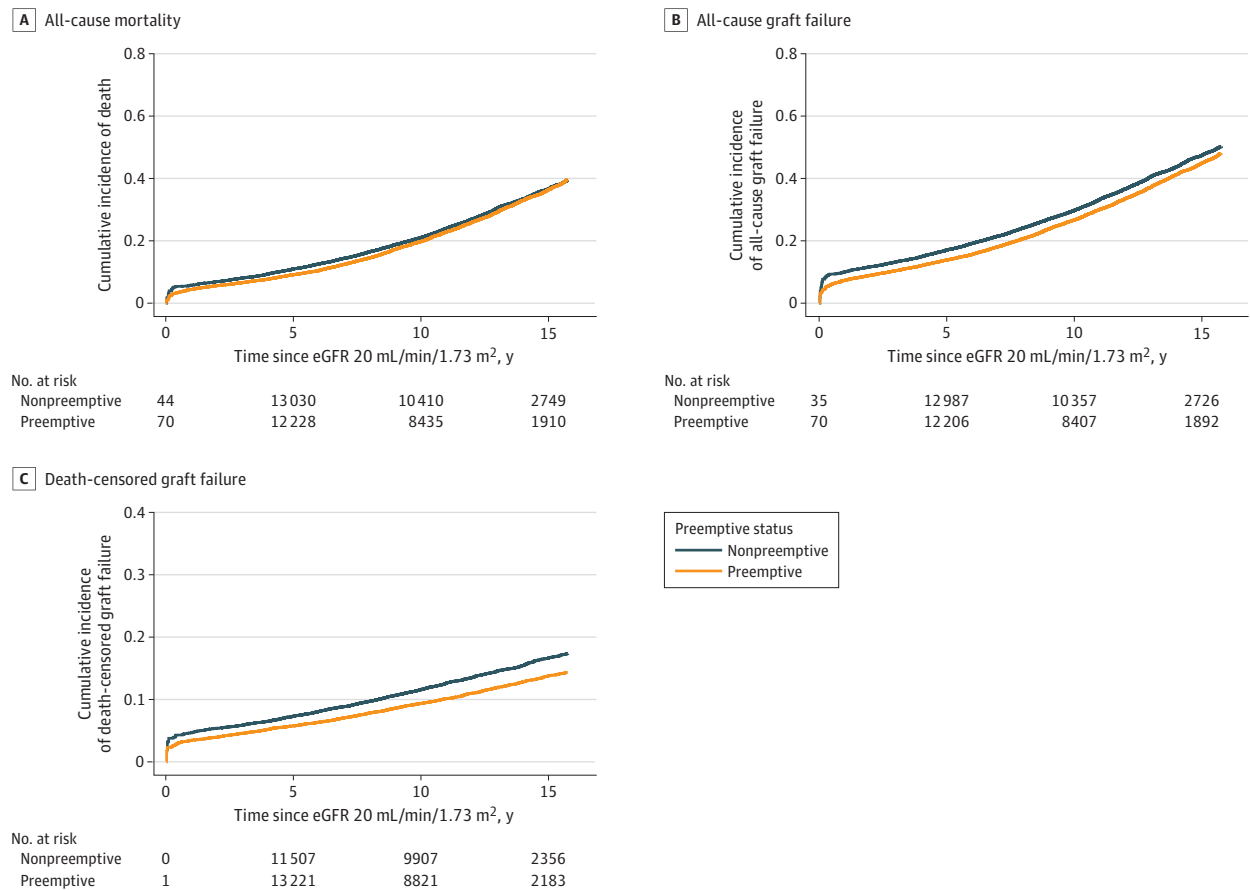
^c When follow-up was extended to administrative censoring date beyond last recorded follow-up in Scientific Registry of Transplant Recipients, there were 8494 deaths, including 4062 (25.6%) among preemptive vs 4432 (26.3%) among nonpreemptive transplantation recipients.

^d No interactions were detected for donor type (hazard ratio, 1.01; 95% CI, 0.91-1.13; P = .81), recipient age (hazard ratio, 1.00; 95% CI, 0.99-1.01; P = .89), or donor age (hazard ratio, 1.00; 95% CI, 0.99-1.00; P = .57).

findings replicate Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) findings and extend them to a larger North American cohort of both donor types, permitting subgroup comparison.⁶ A richly specified propensity model balanced covariables without sacrificing sample size, and left-truncation was anchored at a defined time-zero rather than assumed uniform GFR trajectories. The target trial framework shaped several choices. We restricted the sample to candidates wait-listed before dialysis, since preemptive listing signals possible intention to pursue transplant before dialysis and provides a closer approximation to randomizing that strategy than comparing all-comers. We also defined a single binary exposure at transplant, with prespecified outcomes for mortality and graft failure alongside multiple DGF definitions.

The dialysis-based DGF definition showed the largest association, but it may overestimate injury in patients undergoing nonpreemptive transplantation and lacking residual renal reserve. The creatinine-based measure, capturing injury, attenuated the association, but it was recorded for only a small subcohort and is measured relative to a pretransplant creatinine level that is higher in recipients receiving dialysis. Benefit was strongest among deceased-donor and older recipients. Older recipients have greater vascular disease burden and typically receive kidneys less tolerant of ischemia-reperfusion injury, so residual native function in preemptive recipients may matter most where baseline DGF risk is higher. The DCGF association was not observed after adjusting for dialysis-based DGF in deceased-donor transplants, suggesting early graft function may lie on the causal

Figure 2. Cumulative Incidence Curves of Death and Graft Failure by Preemptive Transplantation Status



Curves are inverse probability of treatment-weighted and left-truncated at the date when estimated glomerular filtration rate was first recorded as 20 mL/min/1.73 m² or less, with recipients entering the risk set at transplant. A, There were 6827 events; numbers are weighted. B, There were 9081 events; numbers are weighted. C, There

were 2776 events; numbers are unweighted. A and B, Weighted Kaplan-Meier estimates were plotted as 1 - S(t). C, The Aalen-Johansen cumulative incidence function was used, treating death with a functioning graft as a competing event. All panels include 32 770 recipients.

pathway between preemptive status and graft survival. Adjustment for creatinine-defined DGF did not attenuate the association, but this measure captures more subtle injury less strongly linked to graft loss and was reported only through 2015, restricting that analysis to an earlier subcohort. Given the strong link between DGF and graft loss, the graft survival association may operate through improved early graft function.

By reducing DGF risk, preemptive transplantation may lower subsequent DCGF risk, particularly for high-KDRI or marginal kidneys that might otherwise not be used. Prior SRTR analyses reported superior graft survival when these kidneys were preemptively transplanted, hypothesized to be mediated by decreased DGF.²¹ Because dialysis exposure amplifies ischemic and inflammatory stress, high-risk kidneys may fare better when transplanted preemptively, although we did not directly assess effect measure modification by KDRI. Recognizing DGF risk is relevant to recipient selection (favoring those likely to tolerate DGF), perioperative strategies for DGF prevention (minimizing ischemia and hypotension), resource planning (dialysis access removal timing, hospital length of stay, posttransplant dialysis readiness), and prognostication. When DGF risk is high, preemptive transplantation could facilitate kidney utilization and improve long-term graft survival. Crucially, graft survival associations were not modified by donor type, recipient age, or donor age and did not emerge after KDRI variable adjustment.

These findings have implications for clinical practice and organ-allocation policy. Despite guidelines recommending preemptive transplantation, we found no survival advantage justifying prioritization of preemptive status in deceased-donor allocation, which weighs wait time, urgency,

Table 3. Cox Proportional Hazards Models Estimating the Association Between Preemptive vs Nonpreemptive Transplantation Status and ACGF and DCGF Among 32 770 Recipients With 9081 ACGF Events and 2776 DCGF Events

Model	ACGF		DCGF	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Primary analysis				
Main model with IPTW and left truncation	0.96 (0.91-1.00)	.06	0.81 (0.74-0.88)	<.001
Model building				
Crude model; no IPTW, no left truncation	0.70 (0.67-0.73)	<.001	0.59 (0.55-0.64)	<.001
Left truncation; no IPTW	0.81 (0.77-0.84)	<.001	0.65 (0.60-0.70)	<.001
IPTW; no left truncation	0.90 (0.86-0.94)	<.001	0.78 (0.72-0.85)	<.001
Sensitivity analyses				
IPTW; left truncation; adjusted for donor KDRI variables (n = 32 068) ^a	0.98 (0.93-1.03)	.37	0.82 (0.76-0.90)	<.001
IPTW; left truncation; clustering by center	0.96 (0.91-1.01)	.11	0.81 (0.74-0.88)	<.001
IPTW; left truncation; clustering by year	0.96 (0.92-0.99)	.02	0.81 (0.76-0.86)	<.001
IPTW; left truncation; frailty model with random effects for transplant center and year	0.96 (0.92-1.00)	.04	0.81 (0.75-0.87)	<.001
IPTW; left truncation; adjusted for any DGF as an early mediator (n = 32 739) ^b	0.98 (0.94-1.03)	.51	0.84 (0.77-0.92)	<.001
IPTW; left truncation; adjusted for dialysis-defined DGF as an early mediator (n = 32 739)	1.03 (0.98-1.08)	.21	0.92 (0.84-1.01)	.07
IPTW; left truncation; adjusted for creatinine decline-defined DGF as an early mediator (n = 17 943)	0.87 (0.82-0.92)	<.001	0.73 (0.66-0.81)	<.001
Subgroup analyses ^c				
Living donors	0.96 (0.89-1.03)	.25	0.82 (0.72-0.93)	.002
Deceased donors	0.94 (0.88-1.00)	.03	0.79 (0.70-0.88)	<.001

Abbreviations: ACGF, all-cause graft failure; DCGF, death-censored graft failure; DGF, delayed graft function; IPTW, inverse probability of treatment weighting; KDRI, Kidney Donor Risk Index.

^a In the model adjusted for KDRI, there were 8913 ACGF events and 2721 DCGF events.

^b Any DGF was associated with ACGF (hazard ratio, 1.55; 95% CI, 1.48-1.63) and DCGF (hazard ratio, 1.84; 95% CI, 1.68-2.00). Dialysis-defined DGF was associated with DCGF (hazard ratio, 2.50; 95% CI, 2.22-2.82). DGF was defined as either dialysis within 1 week after transplantation or a less than 25% decline in serum creatinine level within 24 hours after transplantation. The creatinine-based measure was reported only through 2015, so the model adjusting for it is restricted to recipients who received a transplant between 2005 and 2015 and is not directly comparable with models using the full cohort. Recipients who did not receive dialysis within the first week for whom the creatinine measure was unavailable were classified as not having DGF. Mediator-adjusted estimates are exploratory, as adjustment for a posttransplant variable does not estimate a direct effect given noncollapsibility of the hazard ratio.

^c No interactions were detected for donor type in ACGF (hazard ratio, 0.99; 95% CI, 0.90-1.08; $P = .79$) or DCGF (hazard ratio, 0.98; 95% CI, 0.82-1.16; $P = .80$) models or recipient age (hazard ratio, 1.00; 95% CI, 0.99-1.01; $P = .84$) or donor age (hazard ratio, 1.00; 95% CI, 0.99-1.01; $P = .65$) in DCGF models.

compatibility, and expected graft longevity.³ Our findings support current practice, ensuring patients already receiving dialysis are not disadvantaged. Preemptive timing may nonetheless offer selective advantages for kidneys with high DGF risk, improving kidney utilization and reducing early graft dysfunction, thereby facilitating shorter hospitalizations, lower posttransplant resource use, and modestly longer graft survival in appropriate candidates.

While preemptive transplantation was associated with lower DGF and DCGF, these benefits did not extend to patient survival. This raises tension with guidelines encouraging broad preemptive referral, since prioritizing preemptive workup may divert capacity from candidates already receiving dialysis. Our cohort speaks to transplant timing rather than listing practices; studies capturing the full referred population are needed to evaluate preemptive listing and its equity implications. We could not assess quality of life or cost-effectiveness, relevant considerations that may favor preemptive living-donor kidney transplantation, which is donor directed rather than allocated and expands the organ pool without diverting kidneys from others. Finally, absence of apparent survival benefit may provide meaningful reassurance for patients unable to receive a preemptive transplantation due to no available donors or rapid kidney function decline. Decisions about preemptive transplantation should balance equity, feasibility, and benefits beyond mortality.

Our study benefits from a prespecified, target trial emulation framework with preemptive wait-listing inclusion criterion reflecting possible preemptive transplantation treatment intent, IPTW for confounding control, setting a common time-zero to mitigate lead-time bias, and left-truncated Cox proportional hazards models to address selection bias. Leveraging nationwide data enabled analysis of a large, diverse North American cohort of both living and deceased donor kidney transplants, extending prior ANZDATA findings.

Limitations

This study has limitations. Our design departs from an ideal target trial emulation, in which strategies are assigned at time-zero and all candidates are followed up thereafter given that intent to pursue preemptive transplantation is unrecorded; preemptive wait-listing served as a proxy that captures listing but not referral or evaluation timing. We included only patients who received transplants, so we could not observe eligible candidates never transplanted; whether a candidate is transplanted preemptively depends substantially on donor availability and the rate of eGFR decline. Planned analyses using granular Canadian data capturing transplant referral will permit exposure assignment at time-zero. IPTW balanced measured baseline risk factors at transplant, but residual confounding cannot be excluded. We could not evaluate patient-centered outcomes (eg, quality of life), cost, eGFR thresholds at transplant, or differences by dialysis modality. Pediatric and retransplant recipients were excluded due to distinct allocation strategies.

Conclusions

In this cohort study of 32 770 kidney transplant recipients, preemptive transplantation was not associated with improved patient survival, challenging results of prior comparative effectiveness studies. It was associated with reduced DGF and DCGF. Future work should incorporate patient-centered outcomes, cost-effectiveness, and strategies for high-risk donor kidneys, alongside evaluation of referral and listing practices, to optimize the role of preemptive transplantation in contemporary kidney care.

ARTICLE INFORMATION

Accepted for Publication: August 13, 2026.

Published: October 8, 2026. doi:[10.1001/jamanetworkopen.2026.37964](https://doi.org/10.1001/jamanetworkopen.2026.37964)

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Author Contributions: Dr Rampersad had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Statistical analysis: Rampersad, Liu, Kim.

Obtained funding: Rampersad, Kim.

Administrative, technical, or material support: Rampersad, Liew, Knoll, Kim.

Supervision: Liu, Irish, Kim.

Conflict of Interest Disclosures: Dr Rampersad reported receiving grants from the Kidney Research Scientist Core Education and National Training Program during the conduct of the study as well as grants from the Ajmera Transplant Centre and conference travel awards for from the Transplantation Society to attend the 30th International Congress of the Transplantation Society, the International Pancreas and Islet Transplant Association to attend the 20th International Pancreas & Islet Transplant World Congress, and the Canadian Society of Transplantation (CST) to attend 2025 CST Annual Scientific Meeting outside the submitted work. Dr Kim reported receiving personal fees from Eledon Pharmaceuticals as a member of the data monitoring committee for a phase 2 clinical trial outside the submitted work. No other disclosures were reported.

Funding/Support: Dr Rampersad is supported by a KRESCENT salary award, cofunded by the Kidney Foundation of Canada, the Canadian Society of Nephrology, and the Canadian Institutes of Health Research (CIHR). Dr Liu is supported by the Canada Research Chairs Program.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: The data reported here have been supplied by the Hennepin Healthcare Research Institute (HHRI) as the contractor for the Scientific Registry of Transplant Recipients (SRTR). The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy of or interpretation by the SRTR or the US government.

Data Sharing Statement: See [Supplement 2](#).

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SUPPLEMENT 1.

eMethods.

eTable 1. Target Trial Emulation Protocol: Comparing Preemptive vs Nonpreemptive Kidney Transplantation and Long-Term Mortality and Graft Outcomes

eTable 2. Missingness of Baseline Demographics of Study Population at Time of Transplant

eTable 3. Weighted Kaplan-Meier Survival Probabilities by Preemptive Transplantation Status From 1 to 10 Years After Transplant

eTable 4. Association Between Preemptive Transplantation Status and Death-Censored Graft Failure Stratified by Donor Type, Before and After Adjustment for Dialysis-Defined Delayed Graft Function

eTable 5. Models Estimating the Association Between Preemptive vs Nonpreemptive Transplantation Status and Delayed Graft Function Defined as Either Dialysis Received Within 1 Week After Transplant or Less Than 25% Decline in Serum Creatinine Within 24 Hours After Transplant (32 739 Recipients; 8820 Events)

eTable 6. Models Estimating the Association Between Preemptive vs Nonpreemptive Transplantation Status and Delayed Graft Function Defined as Dialysis Received Within 1 Week After Transplant (32 739 recipients; 3325 Events)

eTable 7. Models Estimating the Association Between Preemptive vs Nonpreemptive Transplantation Status and Delayed Graft Function Defined as Less Than 25% Decline in Serum Creatinine Level Within 24 Hours After Transplant (17 943 recipients; 6458 events)

eFigure 1. Directed Acyclic Graph Depicting Causal Relationships Between Exposure, Outcomes, and Covariables

eFigure 2. Distribution of Stabilized Inverse Probability of Treatment Weights, Trimmed at the 1st and 99th Percentiles, by Preemptive Transplantation Status

eFigure 3. Boxplot of Stabilized Inverse Probability of Treatment Weights, Trimmed at the 1st and 99th Percentiles, by Preemptive Transplantation Status

eFigure 4. Love Plot of Variables Between Preemptive and Nonpreemptive Transplantation Groups After IPTW Applied

eFigure 5. Cumulative Incidence of Death by Preemptive Transplantation Status, Crude Analysis

eFigure 6. Cumulative Incidence of Death by Preemptive Transplantation Status and Donor Type

eFigure 7. Cumulative Incidence of All-Cause Graft Failure by Preemptive Transplantation Status and Donor Type

eFigure 8. Cumulative Incidence of Death-Censored Graft Failure by Preemptive Transplantation Status and Donor Type

eFigure 9. Odds Ratio for Delayed Graft Function With Preemptive vs Nonpreemptive Transplantation Across the Range of Recipient Age and Donor Age

eReferences.

SUPPLEMENT 2.

Data Sharing Statement