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Kidney Transplantation Confers Survival Benefit for Candidates With Pulmonary Hypertension

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Background. Kidney transplantation (KT) is controversial in patients with pretransplant pulmonary hypertension (PtPH). We aimed to quantify post-KT graft and patient survival as well as survival benefit in recipients with PtPH. **Methods.** Using UR Renal Data System (2000–2018), we studied 90 819 adult KT recipients. Delayed graft function, death-censored graft failure, and mortality were compared between recipients with and without PtPH using inverse probability weighted logistic and Cox regression. Survival benefit of KT was determined using stochastic matching and stabilized inverse probability treatment Cox regression. **Results.** Among 90 819 KT recipients, 2641 (2.9%) had PtPH. PtPH was associated with higher risk of delayed graft function (odds ratio, 1.23; 95% CI, 1.10-1.36; $P<0.01$), death-censored graft failure (hazard ratio [HR], 1.23; 95% CI, 1.11-1.38; $P<0.01$), and mortality (HR, 1.56; 95% CI, 1.44-1.69; $P<0.01$). However, patients with PtPH who received a KT had a 46% reduction in mortality (HR, 0.54; 95% CI, 0.48-0.61; $P<0.01$) compared with those who remained on the waitlist. **Conclusions.** Although PtPH is associated with inferior post-KT outcomes, KT is associated with better survival compared with remaining on the waitlist. Therefore, KT is a viable treatment modality for appropriately selected patients with PtPH.

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INTRODUCTION

Pulmonary hypertension (PH), a common comorbidity in patients with chronic kidney disease (CKD), has important prognostic implications for postkidney transplantation (KT) outcomes. Several cross-sectional studies have reported PH in 13% to 50% of transplant candidates.[1-8] Driven by left heart failure, high cardiac output, hypoxic lung diseases, and metabolic derangements, the incidence and severity of PH is closely linked to CKD stage, volume status, and mode and duration of dialysis.[9,10] The hemodynamic changes and alterations in vasoactive substances that contribute to pulmonary arterial vasoconstriction can lead to right ventricular dysfunction and further activation of neurohormonal pathways, which can convey significant mortality risk in transplant candidates, particularly those who are on chronic hemodialysis.[11-15] The pathophysiology linking PH with CKD has been hypothesized to affect the vasculature of renal grafts after KT and can contribute to increased risk of delayed graft function (DGF) leading to increased morbidity and subsequent decreased long-term graft and patient survival.[16-25] As a result, PH remains an important clinical risk factor in patients undergoing assessment for KT.

Although recipients with pretransplant PH (PtPH) are at higher risk for adverse outcomes compared with those without PtPH, successful KT has been associated with reductions in volume overload and reversal of hemodynamic abnormalities, especially with well-functioning allografts in the immediate postoperative period.[4,26-30] Further, patients with CKD and PH often have additional comorbidity that influences the progression of renal dysfunction and can be associated with

an increased waitlist mortality.[11,31-34] Therefore, it is important to weigh the relative risks of graft dysfunction and mortality among KT recipients with PtPH in the context of high mortality faced by transplant candidates with PtPH who remain on the waitlist.

To further define PH as a pretransplant clinical risk factor, we used national longitudinal Medicare claims data to evaluate outcomes and survival benefit of KT in recipients with PtPH. These results may inform risk prediction and improve patient counseling for transplant candidates with PtPH.

MATERIALS AND METHODS

Posttransplant Population

We studied 123 983 first-time adult KT-only recipients between January 1, 2000 and December 31, 2016, as reported by the Organ Procurement and Transplantation Network and linked to Medicare claims data by the US Renal Data System (USRDS). We excluded those who did not have Medicare as their primary payer within 1 y before transplant (N = 33 164), resulting in a study cohort of 90 819 recipients. Recipient, donor, and transplant factors were extracted from Centers for Medicare and Medicaid Services-2728 Medical Evidence Report, waitlist, donor registration records, transplant records, and claims (for obstructive sleep apnea [OSA]) as listed in Table 1. For complete case analysis within the models, 1168 were excluded because of missing variables. Recipients were followed from date of transplant to date of death-censored graft failure (DCGF), death, or administrative censorship on July 31, 2018. Follow-up duration was 0–18 y posttransplant. The median (interquartile range [IQR]) of follow-up was 4.3 y (2.4–7.1) for PtPH recipients and 6.7 (3.6–10.6) for those without PtPH.

PtPH Ascertainment

PtPH was defined by a 2-component algorithm requiring (1) at least 1 inpatient or 2 outpatient diagnosis codes 30 d apart during listing (ICD-9: 4160, 4168; ICD-10: I270, I2789; I272×); and (2) right heart catheterization (RHC) procedure codes within 1 y of PH diagnosis and before transplant (ICD-9: 3721, 3723; ICD-10: 4A023N6, 4A023N8; CPT10: 93501, 93526, 93527, 93528, 93529; CPT11: 93451, 93453, 93454, 93455, 93456, 93457, 93460, 93461; HCPCS: C9741), as previously described.[35] Recipients who did not have eligible claims for either component were classified as unexposed. The median (IQR) duration between earliest date of Medicare-primary coverage and earliest KT was 3.4 (2.1–5.3), 4.8 (3.2–7.0), and 3.4 (2.1–5.2) y in recipients with and without PtPH, respectively. The median (IQR) duration between eligible RHC claim and transplant was 495 (225–938) d, with the median (IQR) duration between eligible diagnosis of PtPH and transplant of 746 (338–1313) d.

Association Between PtPH and DGF

We defined DGF as recipient dialysis within 7 d following transplant. We used stabilized inverse probability of treatment weights (IPTW) to create balanced populations of recipients with versus without PtPH, weighting on recipient factors (age, sex, race, body mass index (BMI), glomerulonephritis, coronary artery disease, diabetes [DM], hypertension [HTN], years on dialysis), donor type (living donor [LDKT] versus deceased donor [DDKT]), and transplant calendar year. We then compared the risk of DGF between the weighted populations of recipients with versus without PtPH using logistic regression.

Association Between PtPH and DCGF and Mortality

We used weighted Cox proportional hazards regression to estimate the weighted hazard ratio (HR) of mortality and DCGF comparing recipients with and without PtPH, using the weights calculated as described above. We then performed subgroup analysis comparing LDKT and DDKT recipients with PtPH, recalculating IPTW for each subgroup using the same variables as described earlier, except for donor type for which we stratified. Additionally, we tested for interaction between donor type (LDKT and DDKT) and PtPH by examining the significance of interaction coefficient in unweighted multivariable regression models.

Survival Benefit of KT for Candidates With PtPH

To quantify the benefit of KT in the PtPH population, we analyzed the survival benefit of KT among waitlisted PtPH candidates, using a stochastic extension of the sequential stratification method of Schaubel.[36] We excluded PtPH candidates who had neither activation date, nor transplant, nor a record of active candidate status. Including ever-active PtPH candidates from 2000 to 2016 (n = 5618), we defined time origin as the latter of listing date and earliest PtPH diagnosis claim date. Each transplant recipient was matched with a single randomly chosen transplant candidate with PtPH who was still on the waitlist who had accrued the same amount of waiting time since the time origin. This candidate became the counterfactual waitlist counterpart of the respective recipient. Recipients were then followed from time of transplant to death or administrative censorship. Counterfactual waitlist counterparts were followed from time of matching to death, censorship for KT, or administrative censorship. We compared mortality in KT recipients versus counterfactual waitlist counterparts using Cox regression, applying IPTW based on age at listing, sex, cause of end-stage renal disease (ESRD), race and ethnicity, peak panel-reactive antibody (PRA), BMI, blood type, and dialysis vintage.

Sensitivity Analyses

With regard to the potential confounding nature of obstructive sleep apnea (OSA) and congestive heart failure (CHF) on PtPH and posttransplant outcomes, we performed 2 sensitivity analyses to understand how OSA and CHF could affect our inference. In the first analysis, we added OSA into the model used to calculate IPTW, whereas in the second, we added both OSA and CHF. Pretransplant OSA was identified by at least 1 inpatient or 2 outpatient diagnosis codes 30 d apart (ICD-9: 32723; ICD-10: G4733), as it was not reported in the Centers for Medicare and Medicaid Services-2728 form and therefore not available in the USRDS database.

Transplant candidate and recipient characteristics were compared using t-test for normally distributed continuous variables, Wilcoxon rank-sum test for skewed distributed continuous variables, and Fischer's exact test for binary or categorical variables. Weighted risk ratios and coefficients from multivariable adjustment models were obtained through complete case analysis. Weighted confidence intervals were reported as per the method of Louis and Zeger.[37] All analyses were performed using Stata 16.0/MP for Linux (College Station, TX).

TABLE 1.

Characteristics of kidney transplant recipients with and without PtPH

	Without PtPH (n = 88 178)	With PtPH (n = 2641)	*P*
Recipient			
Age at transplant, mean (SD), y	52.5 (13.5)	55.7 (12.1)	<0.001
Female, n (%)	33 861 (38.4)	1004 (38.0)	0.69
Race, n (%)			<0.001
White	49 015 (55.6)	1325 (50.2)	
Black	31 756 (36.0)	1110 (42.0)	
Asian	4351 (4.9)	122 (4.6)	
Others	2928 (3.3)	80 (3.0)	
Not reported	128 (0.1)	4 (0.2)	
Hispanic ethnicity, n (%)	16 497 (18.8)	460 (17.5)	0.081
BMI, median (IQR)	27.7 (24.0–31.8) (n = 81 954)	27.1 (23.7–31.3) (n = 2514)	<0.001
Pretransplant dialysis, n (%)	88 177 (100.0)	2641 (100.0)	1.0
Dialysis vintage, median (IQR), y	4.3 (2.8–6.1) (n = 88 177)	5.9 (4.0–8.1) (n = 2641)	<0.001
Comorbidities, n (%)			<0.001
HTN	76 415 (86.8)	2352 (89.2)	
DM	32 950 (37.4)	1252 (47.5)	<0.001
COPD	1458 (1.8)	66 (2.6)	0.001
CAD	7289 (8.4)	308 (11.7)	<0.001
CHF	10 576 (12.8)	493 (19.7)	<0.001
OSA	7303 (8.3)	574 (21.7)	<0.001
Primary ESRD diagnosis, n (%)			<0.001
Glomerular diseases	18 568 (21.1)	469 (17.8)	
DM	25 639 (29.1)	969 (36.7)	
HTN	25 820 (29.3)	819 (31.0)	
PCKD	5773 (6.5)	120 (4.5)	
Neoplasm/tumor	362 (0.4)	13 (0.5)	
Other	3736 (4.2)	79 (3.0)	
Not reported	8280 (9.4)	172 (6.5)	
Donor			
Age, mean (SD), y			
Female, n (%)	39.8 (15.3) (n = 88 177)	41.2 (14.6) (n = 2641)	<0.001
Race, n (%)	38 502 (43.7)	1164 (44.1)	0.68
White	71 483 (81.1)	2104 (79.7)	0.21
Black	13 494 (15.3)	442 (16.7)	
Asian	2232 (2.5)	69 (2.6)	
Others	955 (1.1)	25 (0.9)	
Not reported	14 (<1)	1 (<1)	
Ethnicity, n (%)	13 741 (15.6)	367 (13.9)	0.018
BMI, median (IQR), kg/m^2	26.5 (23.2–30.4) (n = 84 534)	26.8 (23.4–30.9) (n = 2546)	0.030
Comorbidities, n (%)			0.001
HTN	20 640 (24.7)	704 (27.5)	
DM	5054 (6.0)	164 (6.4)	0.46
Donor type, n (%)			0.011
Living donor	15 194 (17.2)	405 (15.3)	
DCD	9357 (12.8)	357 (16.0)	<0.001
Transplant			
HLA mismatches, median (IQR)	5.0 (4.0–6.0) (n = 87 066)	5.0 (5.0–6.0) (n = 2611)	<0.001
CIT, median (IQR), h	15.0 (9.0–22.0) (n = 80 743)	15.0 (9.0–22.0) (n = 2489)	0.93
CIT over 24 h, n (%)	15 691 (19.4)	464 (18.6)	0.43

BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; CIT, cold ischemia time; COPD, chronic obstructive pulmonary disorder; DCD, donation after circulatory death; DM, diabetes mellitus; ESRD, end-stage renal disease; HTN, hypertension; IQR, interquartile range; OSA, obstructive sleep apnea; PCKD, polycystic kidney disease; PtPH, pretransplant pulmonary hypertension.

RESULTS

Posttransplant Study Population

Among 90 819 KT recipients, 2641 (2.9%) had PtPH. Recipients with PtPH were older (55.7 versus 52.5 y, $P < 0.001$), more often Black (42% versus 36%, $P < 0.001$), had lower BMI (27.1 versus 27.7, $P < 0.001$), longer dialysis vintage (5.9 versus 4.3 y, $P < 0.001$), and higher rates of comorbidities, such as HTN (89.2% versus 86.8%, $P < 0.001$), DM (47.5% versus 37.4%, $P < 0.001$), chronic obstructive pulmonary disorder (COPD) (2.6% versus 1.8%, $P = 0.001$), coronary artery disease (11.7% versus 8.4%, $P < 0.001$), CHF (19.7% versus

12.8%, $P<0.001$), and OSA (21.7% versus 8.3%, $P<0.001$) compared with those without PtPH. The primary ESRD diagnoses of DM (36.7% versus 29.1%) and HTN (31% versus 29.3%) were more common in recipients with PtPH. With regard to donor characteristics, recipients with PtPH received organs from older donors (41.2 versus 39.8 y, $P<0.001$), and donors with higher rates of HTN (27.5% versus 24.7% y, $P=0.001$), and circulatory death (donation after circulatory death [DCD]) (16% versus 12.8%, $P<0.001$). There were no differences in HLA mismatch or cold ischemia time between recipients with or without PtPH (Table 1).

PtPH and Post-KT Outcomes

DGF

Overall, 23 484 (25.9%) recipients experienced DGF. DGF occurred in 857 (32.5%) of recipients with PtPH and 22 627 (25.7%) without PtPH. Weighted for recipient and donor factors, recipients with PtPH were more likely to experience DGF compared with those without PtPH (odds ratio [OR], 1.23; 95% CI, 1.10-1.36; $P<0.001$) (Table 2).

DCGF

Overall, 23 520 (25.9%) experienced DCGF including 581 (22%) of recipients with PtPH and 22 939 (26%) without PtPH. KT recipients with PtPH had a higher DCGF rate at 1 y (8.3% versus 6.2%), 3 y (14.6% versus 11.8%), and 5 y (21.6% versus 17.8%) compared with those without PtPH. After adjusting for recipient and donor factors, recipients with PtPH were more likely to experience DCGF compared with those without PtPH (HR, 1.23; 95% CI, 1.11-1.38; $P<0.001$) (Figure 1, Table 2).

Mortality

Overall, 32 989 (36.3%) of all KT recipients died at the end of follow-up, including 1029 (39%) of recipients with PtPH and 31 960 (36.2%) without PtPH. KT recipients with PtPH had a higher mortality rate at 1 y (8.3% versus 4.7%), 3 y (18.7% versus 10.5%), and 5 y (29.4% versus 17.9%) compared with those without PtPH. In an adjusted analysis, KT recipients with PtPH had higher risk of mortality (HR, 1.56; 95% CI, 1.44-1.69; $P<0.001$) compared with those without PtPH (Figure 2, Table 2).

Interaction Between PtPH and Donor Type (LDKT and DDKT)

Recipients with PtPH who received LDKT compared with those who received DDKT were less likely to experience DGF (PtPH with DDKT: 822, PtPH with LDKT: 35, non-PtPH with DDKT: 21 637, non-PtPH with LDKT: 990; OR, 0.14; 95% CI, 0.09-0.22; $P<0.001$), and DCGF (HR, 0.67; 95% CI, 0.50-0.89; $P=0.007$). There was no significant difference in mortality among recipients with PtPH who received LDKT compared with DDKT (HR, 0.87; 95% CI, 0.71-1.07; $P=0.2$). In an interaction analysis, the coefficients were not significant between PtPH and donor type in association with DGF ($P=0.84$), DCGF ($P=0.83$), or mortality ($P=0.086$) (Table 2).

Survival Benefit of KT in Recipients With PtPH

Among candidates with PH, those who received KT were more often male (61.4% versus 54.9%, $P<0.001$) and White (50.7% versus 45.2%, $P=0.002$), had lower BMI (28.2 versus 28.6, $P<0.001$), and higher dialysis vintage (1.68 versus 1.50 y, $P=0.002$) compared with their counterfactual waitlist counterparts before weighting (Table 3). These differences were not clinically significant. After applying for the weights, the waitlist and transplant populations were comparable with regard to age, sex, race, blood type, primary diagnosis of ESRD, PRA, and dialysis vintage (Table S1, SDC, http://links.lww.com/TXD/A350). Patients with PtPH who received a KT had higher survival rates compared with those who remained on the waitlist at 1 y (92.3% versus 88.3%), 3 y (81.9% versus 68.0%), and 5 y (70.9% versus 53.0%). Overall, patients with PtPH who received a KT had a 46% reduction in mortality compared with candidates eligible for KT who remained on the waitlist (HR, 0.54; 95% CI, 0.48-0.61; $P<0.001$) (Figure 3).

Sensitivity Analysis

After adding OSA to the list of variables used to calculate IPTW, the weighted DGF (OR, 1.26; 95% CI, 1.13-1.41; $P<0.001$), mortality (HR, 1.58; 95% CI, 1.46-1.72; $P<0.001$), and DCGF (HR, 1.26; 95% CI, 1.13-1.40; $P<0.001$) were consistent with the main findings. The main findings held true with the addition of both OSA and CHF, weighted DGF (OR, 1.25; 95% CI, 1.12-1.41; $P<0.001$), mortality (HR, 1.59; 95% CI, 1.46-1.73; $P<0.001$), and DCGF (HR, 1.25; 95% CI, 1.11-1.40; $P<0.001$).

DISCUSSION

In this national study of kidney transplant recipients using longitudinal Medicare claims data, recipients with PtPH had a 1.2-fold increase in the odds of DGF, 1.2-fold increase in risk of DCGF, and 1.5-fold increase in the risk of posttransplant mortality. Importantly, even though recipients with PtPH had inferior posttransplant outcomes compared with those

TABLE 2.

Association between PtPH and postkidney transplant outcomes including DGF, DCGF, and mortality

Outcome	With vs without PtPH	Without PtPH LDKT vs DDKT	With PtPH LDKT vs DDKT	Interaction between PtPH and donor type (LDKT vs DDKT)
DGF, mean (OR)	1.23 (1.10–1.36); $P<0.001$	0.20 (0.19–0.22); $P<0.001$	0.14 (0.09–0.22); $P<0.001$	0.96 (0.67–1.39); $P=0.84$
DCGF, mean (HR)	1.23 (1.11–1.38); $P<0.001$	0.72 (0.69–0.75); $P<0.001$	0.67 (0.50–0.89); $P=0.007$	1.03 (0.81–1.30); $P=0.83$
Mortality, mean (HR)	1.56 (1.44–1.69); $P<0.001$	0.84 (0.81–0.87); $P<0.001$	0.87 (0.71–1.07); $P=0.196$	1.16 (0.98–1.37); $P=0.086$

In a subgroup analysis, recipients with PtPH who received LDKT had lower odds of DGF and lower risk of DCGF. In an interaction analysis, the benefit in receiving LDKT was not significantly different in recipients with PtPH compared with those without PtPH.

DCGF, death-censored graft failure; DDKT, deceased donor kidney transplant; DGF, delayed graft function; HR, hazard ratio; LDKT, living donor kidney transplant; OR, odds ratio; PtPH, pretransplant pulmonary hypertension.

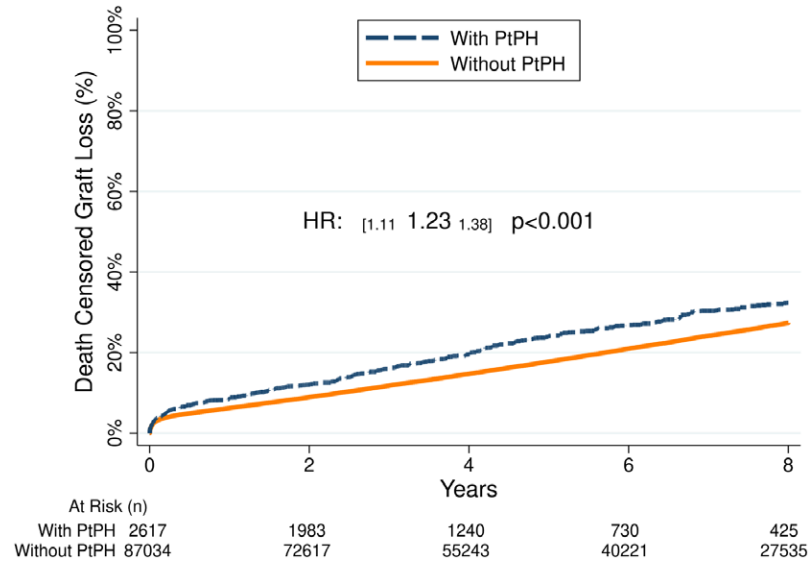

FIGURE 1. Death-censored graft failure after kidney transplant in recipients with and without PtPH. Recipients with PtPH had a 1.2-fold increased risk of death-censored graft failure. HR, hazard ratio; PtPH, pretransplant pulmonary hypertension.

without PtPH, they had a 46% reduction in mortality compared with PtPH candidates who remained on the waitlist. These findings suggest that KT is a viable treatment modality for appropriately selected ESRD patients with PtPH.

Our findings regarding PtPH and inferior post-KT outcomes are consistent with other studies on the topic. In a single-center study of 55 KT recipients, PtPH was identified in 38% of the cohort. Although DGF did not occur among LDKT recipients with PtPH, DGF was more common among DDKT recipients with PtPH (56% versus 11.7%, $P=0.01$) compared with those without PtPH. After adjusting for recipient, donor and other transplant factors, PtPH was associated with 15-times higher odds of DGF.[3] In another study of 215 KT recipients, pretransplant PtPH was present in 32% of transplant recipients. An RSVP ≥50 on echocardiography was found to be independently associated with an increased risk of posttransplant mortality (HR, 3.75; 95% CI, 1.17-11.97; $P=0.016$).[1] These findings, along with ours, support the notion that PtPH is a strong and independent predictor of DGF and mortality after KT.

Our study extends these findings and further analyzes the interaction between PtPH and donor type. Consistent with other studies, we found that PtPH is associated with DGF, which may lead to difficulties in optimization of volume status after transplantation and exacerbate hypertension, increased central pressure, and pulmonary artery pressure.[38] Therefore, successful KT may afford the opportunity for better volume control, especially with well-functioning allografts such as those from living donors. Although our subgroup analysis demonstrated that recipients with PtPH who received LDKT had lower odds of DGF and lower risk of DCGF, the interaction between donor type and PtPH in association with post-KT outcomes was not significant. In other words, although LDKT still offers better outcomes compared with DDKT

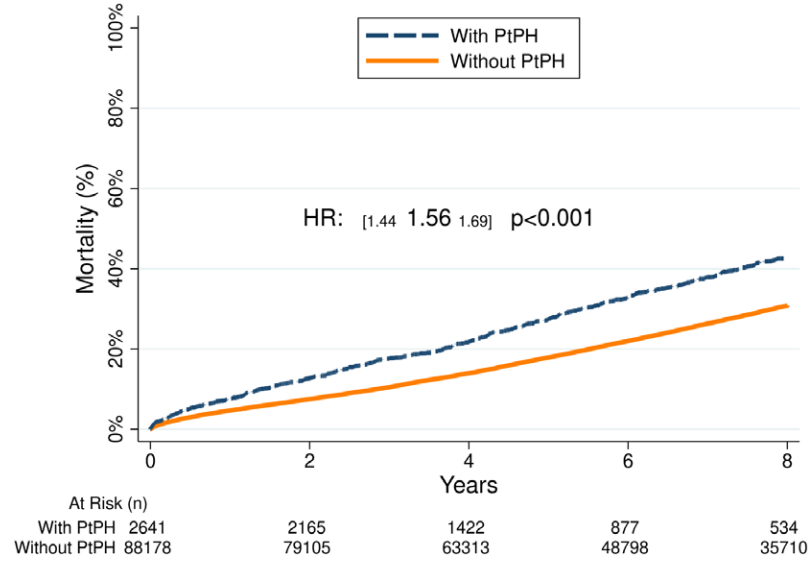

FIGURE 2. Mortality after kidney transplant in recipients with and without PtPH. Recipients with PtPH had a 1.5-fold increased risk of mortality. HR, hazard ratio; PtPH, pretransplant pulmonary hypertension.

TABLE 3.

Characteristics of candidates with pulmonary hypertension who received a KT or remained on the waitlist

	KT (n = 2331)	Waitlist (n = 2331)	*P*
Age at listing, mean (SD), y	52.8 (12.3)	52.6 (11.5)	0.67
Female gender, n (%)	900 (38.6)	1051 (45.1)	<0.001
Race, n (%)			0.002
White	1181 (50.7)	1054 (45.2)	
Black	985 (42.3)	1099 (47.1)	
Asian	102 (4.4)	102 (4.4)	
Others	63 (2.7)	76 (3.3)	
Ethnicity, n (%)			0.97
Non-Hispanic	1908 (81.9)	1901 (81.6)	
Probable Hispanic origin	423 (18.1)	423 (18.1)	
Missing	0 (0.0)	7 (0.3)	
BMI, mean (SD), kg/m^2	28.2 (5.56) (n = 2325)	28.6 (5.90) (n = 2286)	<0.001
ABO blood group, n (%)			<0.001
O	1101 (47.2)	1258 (54.0)	
A	795 (34.1)	565 (24.2)	
B	327 (14.0)	436 (18.7)	
AB	108 (4.6)	72 (3.1)	
Primary ESRD diagnosis, n (%)			0.050
DM	925 (39.7)	983 (42.2)	
HTN	675 (29.0)	647 (27.8)	
GN	478 (20.5)	419 (18.0)	
PCKD	84 (3.6)	75 (3.2)	
Others	169 (7.3)	201 (8.6)	
Missing	0 (0.0)	6 (0.3)	
Dialysis vintage, median (IQR), y	1.68 (0.72–3.73)	1.50 (0.71–3.05)	0.002
Maximum PRA, median (IQR), %	0 (0–26.7)	0.3 (0–45)	<0.001

BMI, body mass index; DM, diabetes mellitus; ESRD, end-stage renal disease; GN, glomerulonephritis; HTN, hypertension; IQR, interquartile range; KT, kidney transplant; PCKD, polycystic kidney disease; PRA, panel-reactive antibody.

among recipients with PtPH, LDKT did not mitigate the risk associated with PtPH.

This study has a few notable limitations. Our study population is limited to Medicare-primary patients, which may not be generalizable to non-Medicare patients. However, given that all ESRD patients requiring dialysis therapy are eligible for Medicare, this is a common inclusion criterion in studies of ESRD patients.[39-41] Another important limitation of this study is the use of administrative claims data to identify candidates with PtPH. Currently, the gold standard in diagnosing PtPH is by RHC measuring mean pulmonary artery pressure of 25 mm Hg or greater at rest.[42] These granular data are not available in large registries to directly measure the severity of PtPH. Furthermore, it is plausible that patients with PtPH who are on the waitlist may be less likely to have severe disease. However, our study population only consists of candidates with PtPH who were deemed clinically appropriate for transplantation, excluding those who were listed but never active on the waitlist potentially because of disease severity. Therefore, the estimates of the association between PtPH and post-KT outcomes are likely conservative. As such, although we cannot be certain, we do not believe selection bias is likely to play a large role in our findings. The 2-component algorithm method including diagnosis codes and RHC procedure codes used in this study has been shown to improve the true-positive cases of PtPH.[35] This method likely reduced our sample size as indicated by the lower percentage of PtPH recipients compared with other single-center studies. Finally, this study was based on observational data and therefore remains unclear whether improved treatment and management of PH before transplant would result in improved renal allograft outcomes and patient survival.

In conclusion, PtPH is a strong and independent risk factor for inferior post-KT outcomes; however, compared with remaining on the waitlist, getting transplanted is associated with better survival. Therefore, KT is a viable treatment modality for appropriately selected ESRD patients with

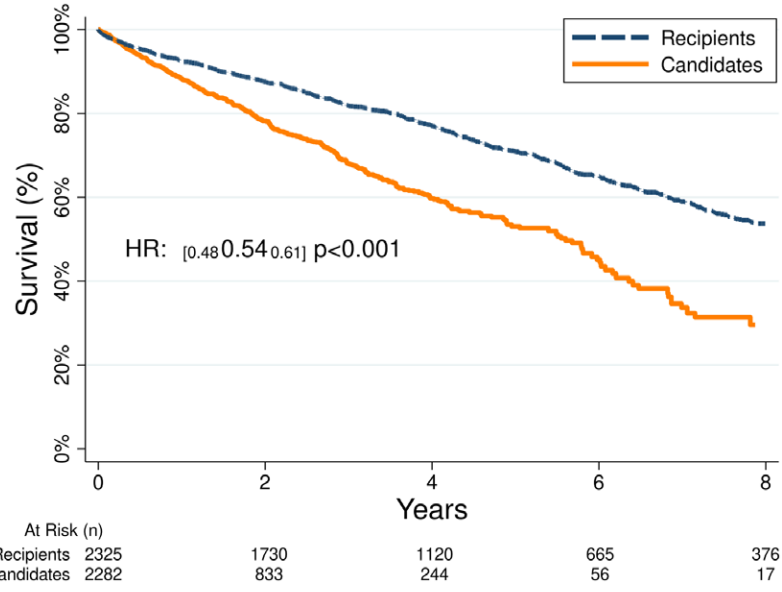

FIGURE 3. Overall survival in kidney transplant recipients with pretransplant pulmonary hypertension compared with candidates with pretransplant pulmonary hypertension who remained on the waitlist. Recipients with pretransplant pulmonary hypertension who received a kidney transplant had a 46% reduction in mortality compared with candidates eligible for kidney transplant who remained on the waitlist. HR, hazard ratio.

PtPH. These results inform risk stratification and improve pretransplant planning and counseling for transplant candidates with PtPH.

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REFERENCES

1. Issa N, Krowka MJ, Griffin MD, et al. Pulmonary hypertension is associated with reduced patient survival after kidney transplantation. *Transplantation.* 2008;86:1384–1388.
2. Stallworthy EJ, Pilmore HL, Webster MW, et al. Do echocardiographic parameters predict mortality in patients with end-stage renal disease? *Transplantation.* 2013;95:1225–1232.
3. Zlotnick DM, Axelrod DA, Chobanian MC, et al. Non-invasive detection of pulmonary hypertension prior to renal transplantation is a predictor of increased risk for early graft dysfunction. *Nephrol Dial Transplant.* 2010;25:3090–3096.
4. Casas-Aparicio G, Castillo-Martínez L, Orea-Tejeda A, et al. The effect of successful kidney transplantation on ventricular dysfunction and pulmonary hypertension. *Transplant Proc.* 2010;42:3524–3528.
5. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis.* 2002;39(2 Suppl 1):S1–266.
6. Alhamad EH, Al-Ghonaim M, Alfaleh HF, et al. Pulmonary hypertension in end-stage renal disease and post renal transplantation patients. *J Thorac Dis.* 2014;6:606–616.
7. Yigla M, Fruchter O, Aharonson D, et al. Pulmonary hypertension is an independent predictor of mortality in hemodialysis patients. *Kidney Int.* 2009;75:969–975.
8. Yigla M, Nakhoul F, Sabag A, et al. Pulmonary hypertension in patients with end-stage renal disease. *Chest.* 2003;123:1577–1582.
9. Kosmadakis G, Aguilera D, Carceles O, et al. Pulmonary hypertension in dialysis patients. *Ren Fail.* 2013;35:514–520.
10. Li Z, Liang X, Liu S, et al. Pulmonary hypertension: epidemiology in different CKD stages and its association with cardiovascular morbidity. *PLoS One.* 2014;9:e114392.
11. Navaneethan SD, Wehbe E, Heresi GA, et al. Presence and outcomes of kidney disease in patients with pulmonary hypertension. *Clin J Am Soc Nephrol.* 2014;9:855–863.
12. Bolignano D, Lennartz S, Leonardis D, et al. High estimated pulmonary artery systolic pressure predicts adverse cardiovascular outcomes in stage 2-4 chronic kidney disease. *Kidney Int.* 2015;88:130–136.
13. Mehra S, Efird J, Christiano C, et al. Pulmonary hypertension in patients undergoing kidney transplant—A single center experience. *Int J Cariovasc Res.* 2013;2. doi: 10.4172/2324-8602.1000153
14. Nakhoul F, Yigla M, Gilman R, et al. The pathogenesis of pulmonary hypertension in haemodialysis patients via arterio-venous access. *Nephrol Dial Transplant.* 2005;20:1686–1692.
15. Abassi Z, Nakhoul F, Khankin E, et al. Pulmonary hypertension in chronic dialysis patients with arteriovenous fistula: pathogenesis and therapeutic prospective. *Curr Opin Nephrol Hypertens.* 2006;15:353–360.
16. Angelescu M, Kraus T, Wiesel M, et al. Assessment of renal graft function by perioperative monitoring of cortical microcirculation in kidney transplantation. *Transplantation.* 2003;75:1190–1196.
17. Perico N, Cattaneo D, Sayegh MH, et al. Delayed graft function in kidney transplantation. *Lancet.* 2004;364:1814–1827.
18. Schilling M, Holzinger F, Friess H, et al. Pathogenesis of delayed kidney graft function: role of endothelin-1, thromboxane B2, and leukotriene B4. *Transplant Proc.* 1996;28:304–305.
19. Inman SR, Plott WK, Pomilee RA, et al. Endothelin-receptor blockade mitigates the adverse effect of preretrieval warm ischemia on posttransplantation renal function in rats. *Transplantation.* 2003;75:1655–1659.
20. Huang C, Huang C, Hestin D, et al. The effect of endothelin antagonists on renal ischaemia-reperfusion injury and the development of acute renal failure in the rat. *Nephrol Dial Transplant.* 2002;17:1578–1585.
21. Sanfilippo F, Vaughn WK, Spees EK, et al. The detrimental effects of delayed graft function in cadaver donor renal transplantation. *Transplantation.* 1984;38:643–648.
22. Siedlecki A, Irish W, Brennan DC. Delayed graft function in the kidney transplant. *Am J Transplant.* 2011;11:2279–2296.
23. Irish WD, Ilsley JN, Schnitzler MA, et al. A risk prediction model for delayed graft function in the current era of deceased donor renal transplantation. *Am J Transplant.* 2010;10:2279–2286.
24. Halloran PF, Hunsicker LG. Delayed graft function: state of the art, November 10-11, 2000. Summit meeting, Scottsdale, Arizona, USA. *Am J Transplant.* 2001;1:115–120.
25. Ojo AO, Hanson JA, Wolfe RA, et al. Long-term survival in renal transplant recipients with graft function. *Kidney Int.* 2000;57:307–313.
26. Ferreira SR, Moisés VA, Tavares A, et al. Cardiovascular effects of successful renal transplantation: A 1-year sequential study of left ventricular morphology and function, and 24-hour blood pressure profile. *Transplantation.* 2002;74:1580–1587.
27. Rigatto C, Foley RN, Kent GM, et al. Long-term changes in left ventricular hypertrophy after renal transplantation. *Transplantation.* 2000;70:570–575.
28. Stokkel M, Duchateau CS, Jukema W, et al. Noninvasive assessment of left ventricular function prior to and 6 months after renal transplantation. *Transplant Proc.* 2007;39:3159–3162.
29. Iqbal MM, Rashid HU, Banerjee SK, et al. Changes in cardiac parameters of renal allograft recipients: A compilation of clinical, laboratory, and echocardiographic observations. *Transplant Proc.* 2008;40:2327–2329.
30. Wali RK, Wang GS, Gottlieb SS, et al. Effect of kidney transplantation on left ventricular systolic dysfunction and congestive heart failure in patients with end-stage renal disease. *J Am Coll Cardiol.* 2005;45:1051–1060.
31. Keane WF, Collins AJ. Influence of co-morbidity on mortality and morbidity in patients treated with hemodialysis. *Am J Kidney Dis.* 1994;24:1010–1018.
32. Khan IH, Catto GR, Edward N, et al. Influence of coexisting disease on survival on renal-replacement therapy. *Lancet.* 1993;341:415–418.
33. Wu C, Evans I, Joseph R, et al. Comorbid conditions in kidney transplantation: Association with graft and patient survival. *J Am Soc Nephrol.* 2005;16:3437–3444.
34. Pérez Fernández M, Martínez Miguel P, Ying H, et al. Comorbidity, frailty, and waitlist mortality among kidney transplant candidates of all ages. *Am J Nephrol.* 2019;49:103–110.
35. Mathai SC, Hemnes AR, Manaker S, et al. Identifying patients with pulmonary arterial hypertension using administrative claims algorithms. *Ann Am Thorac Soc.* 2019;16:797–806.
36. Schaubel DE, Wolfe RA, Port FK. A sequential stratification method for estimating the effect of a time-dependent experimental treatment in observational studies. *Biometrics.* 2006;62:910–917.
37. Louis TA, Zeger SL. Effective communication of standard errors and confidence intervals. *Biostatistics.* 2009;10:1–2.
38. Elias RM, Bradley TD, Kasai T, et al. Rostral overnight fluid shift in end-stage renal disease: Relationship with obstructive sleep apnea. *Nephrol Dial Transplant.* 2012;27:1569–1573.
39. McAdams-Demarco MA, Grams ME, Hall EC, et al. Early hospital readmission after kidney transplantation: Patient and center-level associations. *Am J Transplant.* 2012;12:3283–3288.
40. Dobbels F, Skeans MA, Snyder JJ, et al. Depressive disorder in renal transplantation: An analysis of Medicare claims. *Am J Kidney Dis.* 2008;51:819–828.
41. Weinhandl ED, Snyder JJ, Israni AK, et al. Effect of comorbidity adjustment on CMS criteria for kidney transplant center performance. *Am J Transplant.* 2009;9:506–516.
42. Lentine KL, Villines TC, Axelrod D, et al. Evaluation and management of pulmonary hypertension in kidney transplant candidates and recipients: concepts and controversies. *Transplantation.* 2017;101:166–181.