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RESEARCH ARTICLE

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Effect of pulmonary hypertension on 5-year outcome of kidney transplantation

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Abstract

Pulmonary hypertension affects about one in four patients with advanced chronic kidney disease and significantly increases the risk of death. Kidney transplantation is the recommended management option for patients with progressive or end-stage kidney disease. However, the resource-limited nature of kidney transplantation and its intensive peri-operative and post-transplantation management motivates careful consideration of potential candidates' medical conditions to optimally utilize available graft organs. Since pulmonary hypertension is known to increase peri-operative morbidity and mortality among patients living with chronic kidney disease, we performed a retrospective cohort study to assess the impact of pretransplantation pulmonary hypertension on posttransplantation outcome. All patients who underwent single-organ kidney transplantation at our center in calendar years 2010 and 2011 were identified and the presence of pulmonary hypertension was determined from pretransplantation echocardiography. Outcome was assessed at 5 years following kidney transplantation. Of 350 patients who were included, 117 (33%) had evidence of pulmonary hypertension. The risk of death, graft dysfunction, or graft failure at 5 years after kidney transplantation was higher among those with pulmonary hypertension, primarily owing to an increased risk of graft dysfunction. Importantly, in this institutional cohort of kidney transplant recipients, pretransplant pulmonary hypertension was not associated with a difference in posttransplant survival at 5 years. While institutional and regional differences in outcome can be expected, this report suggests that carefully selected patients with pulmonary hypertension receive similar long-term benefits from kidney transplantation.

KEYWORDS
epidemiology, kidney, pulmonary hypertension, survival, transplantation

INTRODUCTION

Kidney transplantation is the recommended management strategy for patients with advanced progressive chronic kidney disease (CKD) and end-stage renal disease (ESRD).[1,2] Successful kidney transplantation improves both quality of life and survival compared to maintenance dialysis, with the average transplant recipient gaining an additional 5 years of life than they otherwise would have had.[3] Some CKD/ESRD patients are not appropriate candidates for kidney transplantation due to conditions that significantly limit life expectancy or his/her ability to adhere to posttransplantation medical care.[1] While not absolute contraindications to transplantation, a candidate's age, presence of diabetes, and cardiovascular diseases are each associated with increased 1-year mortality after kidney transplantation.[4] However, even among high-risk patient groups, there is a demonstrable survival benefit of kidney transplantation.[5,6] These known benefits of kidney transplantation are juxtaposed against the increasing complexity of potential transplant recipients over time and a desire to use the limited available donor organs in a way that is both just and to maximal benefit. Consequently, transplant eligibility determination is a complex and sometimes subjective process. The Estimated Post Transplant survival score is an instrument to predict posttransplant outcome which includes age, diabetes, prior solid organ transplant, and duration of dialysis.[7] However, many patients evaluated for kidney transplantation have conditions that are cause for concern but not included in this tool.

Pulmonary hypertension (PH) is a state of elevated pressure in the pulmonary circulation, which occurs from various underlying pathophysiologic mechanisms.[8] PH, most often due to chronically elevated pulmonary venous pressures, is common in CKD and ESRD, with prevalence recently estimated at 23%.[9] PH more than doubles the risk of all-cause and cardiovascular-specific mortality in those on dialysis and it increases the risk of adverse perioperative outcomes including death in noncardiac surgeries irrespective of kidney function.[9,10] This risk profile may suggest that patients with PH are poor kidney transplantation candidates. However, limited reports suggest that restoring normal volume status (e.g., through kidney transplantation in ESRD or mechanical support in advanced left-sided heart failure) results in improvements in both PH and symptoms likely through correcting chronic volume overload.[11,12] Thus an important clinical question becomes whether the advantages of kidney transplantation extend to this high-risk subset of patients with PH and outweigh the known increased perioperative risk.

Based on these considerations the objective of the current study was to describe the outcome of patients transplanted in our center and assess the effect of pretransplant PH on both patient and graft outcomes. We hypothesized that among transplant recipients, PH would be associated with increased mortality in those with PH not due to left-sided cardiac dysfunction.

METHODS

This study is a retrospective cohort study to evaluate the influence of PH and related clinical factors on 5-year graft and patient outcome among patients who underwent kidney transplantation at Emory Transplant Center between January 1, 2010, and December 31, 2011, inclusive. All patients who undergo kidney transplantation at Emory Transplant Center are entered into an institutional clinical data registry. Patients from the registry who had kidney transplantation at our center during the study period were evaluated for inclusion. Echocardiogram reports and other clinical data were obtained from the electronic medical record and our institutional transplant program data sources. Patients without available echocardiography data, and those who received a dual organ transplant (e.g., kidney-pancreas or kidney-liver) were excluded. Baseline and outcome data were collected for those patients excluded and were compared to the analysis cohort.

The date of kidney transplantation was defined as baseline and outcomes were assessed at 5 years. The exposure of interest was the presence of PH on echocardiogram obtained in the pretransplant evaluation. Reports from these studies were reviewed and relevant data were abstracted. We defined PH as echocardiography reporting an estimated right ventricular systolic pressure (RVSP) $\geq$35 mmHg and/or a maximum tricuspid regurgitant jet velocity (TRJV) $\geq$2.9 m/s. This RVSP cutoff was selected because it is commonly reported in the CKD, ESRD, and kidney transplantation literature.[9,13,14] In population studies, higher echocardiogram-estimated RVSP is positively-associated with mortality beginning at 33 mmHg.[15] While specific thresholds for defining PH severity are arbitrary, we divided the PH group into those with lower and higher echocardiographic findings of PH for a sensitivity analysis. Moderate to severe PH was defined as either TRJV $\geq$3.2 m/s or RVSP $\geq$45 mmHg and patients with PH below this threshold were defined as having mild PH. Reported left ventricular (LV) diastolic and systolic function were also collected from echocardiograms. Demographics and clinical factors including the presence of diabetes, hypertension, connective tissue disease, and lung disease

were obtained from review of the electronic medical record. Transplant-related factors included the cause of pretransplant renal dysfunction and whether the transplant was categorized as a retransplant. Outcomes included all-cause mortality and graft dysfunction, defined as a stable creatinine of ≥1.4 mg/dl, each assessed at 5 years. Graft failure was defined as the return to dialysis or requiring retransplant. The dates of graft failure and patient death were obtained.

Baseline clinical factors and outcomes are reported as mean and standard deviation (SD), median, and the 25th and 75th percentiles or number and percent as noted. Baseline factors were compared among those patients with PH and those without PH using Kruskal–Wallis rank-sum test for continuous variables, χ^2 tests for categorical variables with expected cell counts ≥5, and Fisher exact test for categorical variables with any expected cell count <5. The Benjamini and Hockberg method was used to correct raw p values for multiple comparisons and the corrected p values are reported.[16] The effect of baseline factors on the outcome at 5 years was estimated by modeling.[17] Univariate and multivariable models were constructed using Poisson regression with robust standard errors using the classical sandwich method and effect estimates are reported here as risk ratios (RR) with 95% confidence intervals (95% CI). Because of the low rate of missing outcome data ($N = 3$ of the 350 patients), a complete case analysis was performed. Separate sensitivity analyses were conducted using the same model covariates and included best- and worst-case scenarios (all missing values were assumed to have and not have the outcome, respectively) as well as optimistic and pessimistic scenarios (where missing subjects with PH and without PH had divergent outcomes). Time from kidney transplant to death or graft failure was analyzed using the Kaplan–Meier method. All analyses were performed in R and modeling used the *sandwich* package.[18–20] The study was approved by the Emory University Institutional Review Board (IRB00101152) with waiver of informed consent.

RESULTS

Subjects were included in this data set if they received a kidney transplant (not combined with another organ transplant) at Emory Transplant Center in calendar years 2010 or 2011 (Figure 1). In total, $n = 389$ patients were transplanted during this study period. Echocardiogram data were available in $n = 350$ (90%) which formed the analysis cohort. Patients with missing echocardiogram data had similar baseline characteristics as the cohort available for analysis (Table S1).

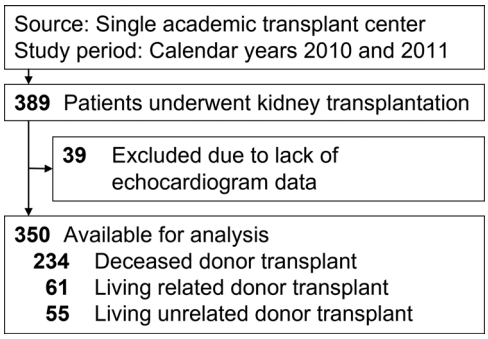

FIGURE 1 Cohort flow diagram. A total of 389 patients were identified who underwent kidney transplantation at our institution during the study period. Of these, 350 were eligible for inclusion in this study

The median age at the time of kidney transplantation was 51 years and 60% were male (Table 1). Nearly all patients had a history of hypertension (96%) and diabetes mellitus was present in 34%. Before kidney transplant, 85% of subjects were on dialysis, predominantly hemodialysis (65%), for a median of 2 years 10 months. The graft organ was from deceased donors in 67% of recipients. There was no significant difference in age, comorbidities, or pretransplant renal replacement therapy in those with compared to without PH. Follow-up data were available in 99% of the cohort. Ten percent of the cohort had died at 5 years and an additional 10% had experienced graft failure.

Echocardiography data were used to determine the presence of PH and LV dysfunction (Table 2). Echocardiographic evidence of PH was present in 117 of the 350 kidney transplant recipients (33%). LV dysfunction, predominantly abnormal diastolic function, was present in most patients who underwent kidney transplantation. While the presence of impaired LV systolic and diastolic function was similar among those with and without echocardiographic evidence of PH, diastolic dysfunction parameters tended to be more severe (Grade II and higher) in those with PH compared to those without.

Patient survival, graft survival, and graft function were assessed at 5 years posttransplantation (Table 1). Graft dysfunction, but not graft failure or death, was more common among patients with PH (57% compared to 33% in those without PH, unadjusted Chi-sq $p < 0.001$). The time from kidney transplant to death and time to death or graft failure was the same for patients with and without PH (Figure 2a,b). Estimates of the effect of baseline factors including PH on the composite outcome of death or graft dysfunction are given in Table 3. Male sex, longer pretransplant dialysis duration, the absence of systemic hypertension, and the presence of PH were associated with increased risk of the adverse

TABLE 1 Clinical characteristics by PH status in subjects who had kidney transplantation

Variable	Overall ($N = 350$)	No PH present ($N = 233$; 67%)	PH present ($N = 117$; 33%)	p value[a]
Age at transplant, years	51 (41, 60)	51 (41, 59)	52 (40, 60)	0.8
Sex				0.8
Female	140 (40%)	96 (41%)	44 (38%)	
Male	210 (60%)	137 (59%)	73 (62%)	
Comorbid conditions				
Hypertension	336 (96%)	223 (96%)	113 (97%)	0.8
Diabetes mellitus	118 (34%)	75 (32%)	43 (37%)	0.7
Lung disease	12 (3.4%)	9 (3.9%)	3 (2.6%)	0.8
Autoimmune disease or vasculitis	37 (11%)	28 (12%)	9 (7.7%)	0.7
Specific condition predisposing to PH	41 (12%)	25 (11%)	16 (14%)	0.7
Etiology of pretransplant kidney disease				
Hypertension	266 (76%)	171 (73%)	95 (81%)	0.7
Diabetes mellitus	98 (28%)	62 (27%)	36 (31%)	0.7
Focal segmental glomerulosclerosis	27 (7.7%)	20 (8.6%)	7 (6.0%)	0.7
Systemic lupus erythematosus	16 (4.6%)	10 (4.3%)	6 (5.1%)	0.8
Glomerulonephritis	46 (13%)	33 (14%)	13 (11%)	0.7
Polycystic kidney disease	36 (10%)	29 (12%)	7 (6.0%)	0.6
Congenital renal disease	6 (1.7%)	5 (2.1%)	1 (0.9%)	0.8
Other	28 (8.0%)	16 (6.9%)	12 (10%)	0.7
Pretransplant dialysis duration, months[b]	34 (11, 62)	33 (9, 62)	36 (12, 61)	0.7
Mode of HD before transplant				0.7
None	52 (15%)	38 (16%)	14 (12%)	
HD only	229 (65%)	145 (62%)	84 (72%)	
PD only	56 (16%)	42 (18%)	14 (12%)	
HD and PD	13 (3.7%)	8 (3.4%)	5 (4.3%)	
AVF present	228 (65%)	142 (61%)	86 (74%)	0.4
Prior kidney transplant	33 (9.4%)	21 (9.0%)	12 (10%)	0.8
Outcome (at 5 years)				
Died	35 (10%)	20 (8.7%)	15 (13%)	0.2[c]
Unknown vital status	2 (0.6%)	2 (0.9%)	0 (0%)	
Graft failure[d]	44 (13%)	28 (12%)	16 (14%)	0.7[c]
Unknown graft failure status	11	8	3	
Alive with graft dysfunction	124 (36%)	67 (29%)	57 (49%)	<0.001[c]
Unknown graft function status	3	2	1	
Death, graft dysfunction, or failure	180 (52%)	104 (45%)	76 (66%)	0.001[c]
Unknown	3	2	1	

Note: N (%) and median (25th, 75th percentile) are given.

Abbreviations: AVF, arteriovenous fistula; HD, hemodialysis; PD, peritoneal dialysis; PH, pulmonary hypertension.

[a]For baseline clinical characteristics, p values are corrected for multiple comparisons.

[b]One patient without PH had an unknown duration of dialysis before transplant.

[c]These p values are uncorrected.

[d]Seven of these patients died after graft failure including three without PH and four with PH.

TABLE 2 Echocardiographic features by PH status in subjects who had kidney transplantation

Variable	Overall ($N = 350$)	No PH present ($N = 233$; 67%)	PH present ($N = 117$; 33%)	p value*
Echocardiographic criteria indicating PH				
Maximal TR jet velocity ≥2.9 m/s	39 (11%)	0 (0%)	39 (33%)	<0.001
RVSP reported ≥35 mmHg	116 (33%)	0 (0%)	116 (99%)	<0.001
Maximal TR jet velocity, m/s	2.40 (2.20, 2.70)	2.22 (2.09, 2.40)	2.78 (2.61, 3.00)	<0.001
Unknown	53	48	5	
RVSP, mm/Hg	33 (29, 39)	30 (27, 33)	40 (38, 46)	<0.001
Unknown	44	38	1	
Systolic dysfunction present	22 (6.3%)	10 (4.3%)	12 (10%)	0.04
LV ejection fraction	60 (55, 60)	60 (55, 60)	60 (55, 60)	0.4
Diastolic dysfunction present	178 (51%)	118 (51%)	60 (51%)	>0.9
Degree of diastolic dysfunction (if present)				0.008
I (impaired relaxation)	135 (78%)	98 (85%)	37 (65%)	
II (pseudonormal)	32 (19%)	14 (12%)	18 (32%)	
III (restrictive/reversible)	5 (2.9%)	3 (2.6%)	2 (3.5%)	
IV (restrictive/irreversible)	0 (0%)	0 (0%)	0 (0%)	
Unknown/not reported	178	118	60	

Note: N (%) and median [25th, 75th percentile] are given.

Abbreviations: LV, left ventricular; PH, pulmonary hypertension; RVSP, right ventricular systolic pressure; TR, tricuspid regurgitation.

*p values corrected for multiple comparisons.

outcome. Adjusted for the other factors in Table 3, pretransplant PH was associated with a 43% increased risk of the outcome (RR: 1.432, 95% CI: 1.189–1.724, $p < 0.001$). Notably, this finding was adjusted for the presence of LV dysfunction and no interaction between PH and LV dysfunction was observed (data not shown). The adverse association of pretransplant PH did not significantly vary in the sensitivity analyses, which included the three additional cases with missing outcome data.

To evaluate whether the severity of PH affected outcome, the group of patients with PH was divided into mild versus moderate to severe PH based on echocardiogram-reported pulmonary artery pressure estimates (moderate to severe defined as either a TRJV ≥ 3.2 m/s or RVSP ≥ 45 mmHg and otherwise defined as mild). Compared to those without echocardiogram evidence of PH, each PH group had higher risk of the composite outcome, but the risk was highest in the group with moderate to severe PH (Tables S2 and S3).

In the subset of patients with PH, we assessed whether other baseline or comorbid factors are associated with the composite outcome using Poisson modeling (Table 4). Among those with PH, the only factor associated with posttransplant mortality and graft dysfunction was the duration of time spent on dialysis before kidney transplantation.

DISCUSSION

This study demonstrates that PH is common in kidney transplant recipients and is associated with worsened 5-year transplant outcomes mainly driven by the increased incidence of graft dysfunction but without an impact on patient or graft survival. These findings extend prior reports on the impact of PH in patients with CKD by focusing on those patients who undergo kidney transplantation. PH is known to independently increase morbidity and risk of mortality in many conditions as well as peri-operative risk.[10,21] Kidney transplantation is a desirable, although scarce, management option for patients with ESRD and has been shown to reduce long-term mortality by 68% compared with patients who remain on the transplant waiting list.[22] Yet, operative risk must be considered in evaluating patients for kidney transplantation, and PH increases this risk. Among those patients at our center selected for kidney transplantation, the presence of PH was not associated with a higher risk

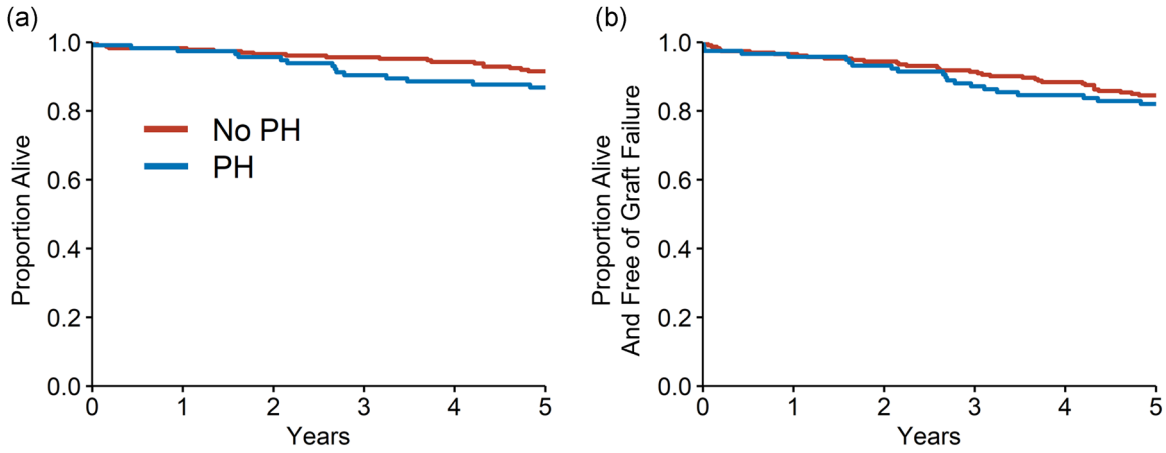

FIGURE 2 Graft and patient survival after kidney transplantation. The presence of pretransplant echocardiographic evidence of PH was not associated with time to (a) all-cause mortality, nor (b) the development of either graft failure or death (p = NS by log-rank test for each outcome). Overall survival after kidney transplantation was 90% at 5 years

TABLE 3 Association of baseline factors on the occurrence of death, graft failure, or graft dysfunction in the 5 years following kidney transplantation

Predictor	Univariate RR (95% CI, *p* value)	Multivariable RR (95% CI, *p* value)
Age at transplant, years	0.995 (0.987–1.003, $p = 0.228$)	0.994 (0.985–1.002, $p = 0.135$)
Male sex	1.406 (1.120–1.764, $p = 0.003$)	1.432 (1.148–1.785, $p = 0.001$)
History of hypertension	0.715 (0.505–1.012, $p = 0.058$)	0.605 (0.414–0.885, $p = 0.010$)
History of diabetes mellitus	1.166 (0.950–1.430, $p = 0.142$)	1.179 (0.961–1.446, $p = 0.115$)
History of autoimmune disease or vasculitis	0.785 (0.526–1.172, $p = 0.237$)	0.812 (0.554–1.189, $p = 0.284$)
History of lung disease	0.634 (0.283–1.421, $p = 0.269$)	0.729 (0.319–1.665, $p = 0.454$)
Presence of PH by echocardiogram	1.455 (1.198–1.767, $p < 0.001$)	1.432 (1.189–1.724, $p < 0.001$)
Systolic LV dysfunction by echocardiogram	1.010 (0.663–1.539, $p = 0.961$)	Not in model
Diastolic LV dysfunction by echocardiogram	1.086 (0.886–1.331, $p = 0.427$)	Not in model
Systolic or diastolic LV dysfunction by echocardiogram	1.070 (0.872–1.313, $p = 0.515$)	1.031 (0.844–1.258, $p = 0.767$)
Pretransplant dialysis duration, years	1.063 (1.038–1.089, $p < 0.001$)	1.058 (1.032–1.084, $p < 0.001$)
Prior kidney transplant	0.703 (0.444–1.113, $p = 0.133$)	0.680 (0.440–1.048, $p = 0.081$)

Note: Multivariable RRs were calculated from a model including all variables in this table except systolic LV dysfunction and diastolic LV dysfunction which were combined into a single variable "systolic or diastolic LV dysfunction."

Abbreviations: CI, confidence interval; LV, left ventricular; PH, pulmonary hypertension; RR, risk ratio.

of short-term or 5-year mortality. However, in addition to the factors included in the Estimated Post Transplant Survival score,[7] this report supports that PH is associated with inferior graft outcome at 5 years, which may inform the risk/benefit assessment in pretransplant ESRD patients or modify the intensity of posttransplantation monitoring.

The CKD population is known to have a high risk of cardiovascular comorbidities including PH. A recent meta-analysis included 18 studies that assessed the effect of PH in CKD including ESRD.[14] In that study, the prevalence of PH in the pooled ESRD population was 32%, the same as our cohort. PH was associated with remarkably increased risk of overall mortality (RR: 1.90) and cardiovascular-specific mortality (RR: 3.77) in ESRD patients. However, a limitation of that meta-analysis—and the existing literature more broadly—is that the effect of PH on kidney transplant outcomes is poorly defined. Patients with kidney transplantation were a defined population in only one of the 18 studies in that analysis.[13] In addition to that single study, two recent reports have evaluated the influence of PH in kidney transplantation outcomes.[23,24] Similar to our current report, all are single-center retrospective studies.

TABLE 4 Association of baseline factors on the occurrence of death, graft failure, or graft dysfunction in the 5 years following kidney transplant among patients with PH at the time of transplant

Predictor	Univariate RR (95% CI, *p* value)	Multivariable RR (95% CI, *p* value)
Age at transplant, years	1.000 (0.990–1.011, $p = 0.938$)	0.999 (0.989–1.010, $p = 0.890$)
Male sex	1.175 (0.880–1.570, $p = 0.275$)	1.266 (0.950–1.686, $p = 0.108$)
History of hypertension	0.869 (0.486–1.555, $p = 0.636$)	0.682 (0.415–1.122, $p = 0.132$)
History of diabetes mellitus	1.281 (0.995–1.650, $p = 0.055$)	1.243 (0.970–1.594, $p = 0.085$)
History of autoimmune disease or vasculitis	0.660 (0.314–1.388, $p = 0.273$)	0.706 (0.356–1.400, $p = 0.318$)
History of lung disease	0.502 (0.101–2.502, $p = 0.401$)	0.491 (0.090–2.688, $p = 0.413$)
Systolic LV dysfunction by echocardiogram	0.672 (0.347–1.302, $p = 0.239$)	--
Diastolic LV dysfunction by echocardiogram	1.073 (0.824–1.399, $p = 0.600$)	--
Systolic or diastolic LV dysfunction by echocardiogram	0.969 (0.744–1.263, $p = 0.817$)	1.000 (0.771–1.298, $p = 0.998$)
Pre-transplant dialysis duration, years	1.063 (1.038–1.089, $p < 0.001$)	1.045 (1.002–1.090, $p = 0.042$)
Prior kidney transplant	0.610 (0.309–1.207, $p = 0.156$)	0.665 (0.348–1.272, $p = 0.218$)

Abbreviations: CI, confidence interval; LV, left ventricular; PH, pulmonary hypertension; RR, risk ratio.

Issa et al.[13] and Wang et al.[23] have published studies similar to ours which reported the association between pretransplant echocardiographic evidence of PH and posttransplant graft and patient outcome. In the Issa cohort including 215 patients, echocardiographic evidence of PH (prevalence 32%) was associated with higher risk of death during an average of 23 months of follow-up. In a similarly sized cohort (192 patients), Wang reported that although echocardiographic evidence of PH (prevalence 27%) showed no association with survival over a mean of 48 months, it was associated with impaired graft function during the first 2 years of follow-up.

In a recent study, Caughey et al. also evaluated the effect of PH in patients evaluated for kidney transplantation.[24] Unlike the current and earlier reports discussed above, the Caughey study included all patients who were evaluated for transplant candidacy. Only 23% of patients underwent kidney transplantation and the proportion transplanted was lower among those with PH (15/97, 15.5%) compared to those without PH (164/681, 24.1%). Among kidney transplant recipients, the prevalence of PH was 8.4% (15/179) and mortality in those with PH was high (3/15). In contrast, our posttransplant population had a higher prevalence of pretransplant PH—similar to the ESRD population[9] and to the Issa and Wang cohorts.[13,23] In our cohort, death at 5 years occurred in 10% of kidney transplant recipients and did not vary on the basis of PH. The length of follow-up reported in these earlier cohorts varied from 1.2 years to 4 years. Our report followed patients longer and had overall mortality that was intermediate compared to the earlier reports: better than the Caughey cohort with 9.5% mortality at 1.2 years, and the Issa cohort with 6.5% mortality at 1.9 years, but inferior to the Wang cohort with 6.5% mortality at 4 years. Our report is reassuring that appropriately selected and monitored patients with PH can have an excellent posttransplant outcome.

The lack of a negative impact of PH on 5-year survival in our cohort compared to earlier reports may attest to differences in kidney transplant center practices, especially pretransplant screening and candidacy selection. In the Caughey study, patients with PH and the absence of elevated left atrial pressure (suggesting precapillary PH) experienced the highest mortality risk. In our study population, we assessed for comorbid conditions that predispose to precapillary PH as well as evidence of left heart dysfunction on echo. Reassuringly, our study suggests that these differences in potential causes of PH have no independent effect on posttransplant outcome. Indeed, it is PH itself that was associated with our composite outcome, driven by higher rates of graft dysfunction at 5 years. In our center, after kidney transplantation, patients have an ongoing life-long follow-up with our transplant nephrologists at specified intervals. For patients felt to be at high risk of graft dysfunction or failure (such as those with pretransplant PH), or those with more complex immunosuppression considerations, follow-up occurs at 6-month intervals.

PH may be expected to improve after kidney transplantation, especially when driven by left-sided heart dysfunction, and restored kidney function allows resolution of chronic volume overload and elevated pulmonary venous pressures. Even long-standing pulmonary venous hypertension, known to be associated with pulmonary vascular remodeling[25] has been shown to improve when left-heart filling pressures are

controlled long-term. For instance, patients with advanced left heart failure have improvements in pulmonary vascular resistance after the institution of destination or bridge LV mechanical support.[11,26] Further, specifically in kidney transplant recipients, pretransplant abnormal LV structure and systolic or diastolic function parameters have been reported to improve in several studies with longitudinal echocardiographic assessment.[12,27,28] Unfortunately, we cannot evaluate whether PH or left heart dysfunction improves after transplant with the available data from our cohort.

Our study has several limitations which must be acknowledged. The data are observational from a single center which adds to risk of bias, especially selection bias. As selection for kidney transplantation is a multidisciplinary assessment, patients selected for kidney transplantation at our center may differ from those at other centers which may limit the generalizability of the results we report here. We included only patients who underwent kidney transplantation and, thus, the risk of PH among those not selected for kidney transplantation cannot be evaluated nor inferred from our data. The presence of PH was determined from echocardiographic data, similar to prior reports,[13,23,24] rather than right heart catheterization which is the gold standard method for hemodynamic confirmation and assessment of PH.[29] While invasive hemodynamic assessment may provide additional insight, determinations of PH by echocardiography and invasive hemodynamics have been shown to have good agreement in screening programs for transplantation of other solid organs.[30] Among other factors, multivariable models adjusted for left heart disease and lung disease, but there remains the potential for confounding by other unmeasured variables.

In conclusion, our study shows that among patients selected for kidney transplantation, the presence of pretransplant PH is associated with graft dysfunction at 5 years, but importantly, survival in our cohort at 5 years was excellent (90% overall) and did not differ among those with and without PH. While further study of the role and management of PH in ESRD patients managed without kidney transplantation is desperately needed, our analyses provide reassurance that careful selection of candidates with PH for kidney transplantation permits effective donor organ utilization. Patients with PH should not be disregarded from consideration of kidney transplantation as an available treatment option for advanced CKD and ESRD. The known benefits of improved quality and quantity of life afforded by kidney transplantation likely outweigh the marginal increased risk of graft dysfunction at 5 years demonstrated in our study population.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

ETHICS STATEMENT

The study was approved by the Emory University Institutional Review Board (IRB00101152) with waiver of informed consent.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the work, drafted or critically evaluated the submitted manuscript, gave final approval for submission of this manuscript for publication and attest to the accuracy of the work. Fadi Rabih contributed to the analysis of data and interpretation of results, writing the original draft, and editing final submitted manuscript. Rhiannon L. Holden and Payaswini Vasanth contributed to the concept, methodology, collection of data, interpretation of results, critical editing, and review of the manuscript. Micah R. Fisher and Stephen O. Pastan contributed to the concept, methodology, critical editing, and review of the manuscript. Aaron W. Trammell contributed to the concept, methodology, collection of data, analysis of data and interpretation of results, writing the original manuscript draft, editing the final submitted manuscript, and funding acquisition.

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Additional supporting information may be found in the online version of the article at the publisher's website.

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