Incidence, Clinical Correlates, and Outcomes of Pulmonary Hypertension After Kidney Transplantation: Analysis of Linked US Registry and Medicare Billing Claims

Krista L. Lentine, MD, PhD,[1] Ngan N. Lam, MD,[2] Yasar Caliskan, MD,[1] Huiling Xiao, MD,[1] David A. Axelrod, MD,[3] Salvatore P. Costa, MD,[4] Deborah J. Levine, MD,[5] James R. Runo, MD,[6] Helen S. Te, MD,[7] Janani Rangaswami, MD,[8] Darshana M. Dadhania, MD,[9] Mark A. Schnitzler, PhD,[1] Bertram L. Kasiske, MD,[10] and Todd C. Villines, MD[11]

Background. The incidence, risks, and outcomes associated with pulmonary hypertension (P-HTN) in the kidney transplant (KTx) population are not well described. **Methods.** We linked US transplant registry data with Medicare claims (2006–2016) to investigate P-HTN diagnoses among Medicare-insured KTx recipients (N = 35 512) using billing claims. Cox regression was applied to identify independent correlates and outcomes of P-HTN (adjusted hazard ratio [aHR] $_{95\%LCL}$aHR$_{95\%UCL}$) and to examine P-HTN diagnoses as time-dependent mortality predictors. **Results.** Overall, 8.2% of recipients had a diagnostic code for P-HTN within 2 y preceding transplant. By 3 y posttransplant, P-HTN was diagnosed in $_{10.3}$10.6%$_{11.0}$ of the study cohort. After adjustment, posttransplant P-HTN was more likely in KTx recipients who were older (age ≥60 versus 18–30 y a HR, $_{1.91}$2.40$_{3.01}$) or female (aHR, $_{1.15}$1.24$_{1.34}$), who had pretransplant P-HTN (aHR, $_{4.38}$4.79$_{5.24}$), coronary artery disease (aHR, $_{1.05}$1.15$_{1.27}$), valvular heart disease (aHR, $_{1.22}$1.32$_{1.43}$), peripheral vascular disease (aHR, $_{1.05}$1.18$_{1.33}$), chronic pulmonary disease (aHR, $_{1.20}$1.31$_{1.43}$), obstructive sleep apnea (aHR, $_{1.15}$1.28$_{1.43}$), longer dialysis duration, pretransplant hemodialysis (aHR, $_{1.17}$1.37$_{1.59}$), or who underwent transplant in the more recent era (2012–2016 versus 2006–2011: aHR, $_{1.29}$1.39$_{1.51}$). Posttransplant P-HTN was associated with >2.5-fold increased risk of mortality (aHR, $_{2.57}$2.84$_{3.14}$) and all-cause graft failure (aHR, $_{2.42}$2.64$_{2.88}$) within 3 y posttransplant. Outcome associations of newly diagnosed posttransplant P-HTN were similar. **Conclusions.** Posttransplant P-HTN is diagnosed in 1 in 10 KTx recipients and is associated with an increased risk of death and graft failure. Future research is needed to refine diagnostic, classification, and management strategies to improve outcomes in KTx recipients who develop P-HTN.

(*Transplantation* 2022;106: 666–675).

INTRODUCTION

Kidney transplant (KTx) is the optimal therapy for patients with end-stage kidney disease (ESKD), as it is associated with longer patient survival, better quality of life, and lower costs to the healthcare system.[1,2] To realize these benefits, KTx recipients must avoid or overcome various

Received 8 September 2020. Revision received 23 March 2021.

Accepted 24 March 2021.

[1] *Center for Abdominal Transplantation, Saint Louis University, School of Medicine, St Louis, MO.*

[2] *University of Calgary, Calgary, AB, Canada.*

[3] *University of Iowa, Iowa City, IA.*

[4] *Dartmouth-Hitchcock Medical Center, Lebanon, NH.*

[5] *UT Health, San Antonio, TX.*

[6] *University of Wisconsin, Madison, WI.*

[7] *University of Chicago, Chicago, IL.*

[8] *Einstein Medical Center, Philadelphia, PA.*

[9] *Weill Cornell Medicine, New York, NY.*

[10] *Hennepin County Medical Center, Minneapolis, MN.*

[11] *University Virginia, Charlottesville, VA.*

K.L.L. and N.N.L. are cofirst authors.

This work was conducted under the auspices of the Hennepin Healthcare Research Institute (HHRI), contractor for the Scientific Registry of Transplant Recipients (SRTR), as a deliverable under contract no. HHSH250201000018C (US Department of Health and Human Services, Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation). K.L.L. is supported by the Mid-America Transplant/Jane A. Beckman Endowed Chair in Transplantation and NIH National Institute of Diabetes and Digestive and Kidney Disease (NIDDK) grant R01DK120518.

Previous Presentation: An abstract describing preliminary findings of this work was presented at the American Transplant Congress (ATC) virtual program, June 2020.

The authors declare no conflicts of interest.

K.L.L. participated in study design, acquisition of data and regulatory approvals, interpretation, and writing of the article. N.N.L. and Y.C. participated in study design, interpretation, and writing of the article. H.X. participated in data analysis and article preparation. D.A.A., S.P.C., D.J.L., J.R.R., H.S.T., J.R., D.M.D., M.A.S., B.L.K., and T.C.V. participated in interpretation and manuscript review/critical editing.

Supplemental digital content (SDC) is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.transplantjournal.com).

Correspondence: Krista L. Lentine, MD, PhD, Saint Louis University Transplant Center, 1201 S Grand Blvd, St Louis, MO 63104. (krista.lentine@health.slu.edu).

ISSN: 0041-1337/20/1063-666

DOI: 10.1097/TP.0000000000003783

<zdoi;10.1097/TP.0000000000003783>

immunologic and nonimmunologic complications that threaten patient and allograft survival.[3,4] Cardiovascular disease is the leading cause of nonimmunologic morbidity and mortality for KTx recipients.[5,6] Previously, the focus for this patient population has been on ischemic heart disease and heart failure,[7-9] but in recent years, pulmonary hypertension (P-HTN) has gained recognition as a clinically important cardiovascular condition.[10] However, information is limited on the incidence, clinical correlates, and outcomes of P-HTN in the KTx population.

P-HTN, currently defined hemodynamically as mean pulmonary artery pressure ≥20 mm Hg at rest when measured by right heart cardiac catheterization,[11,12] may be related to multiple underlying diseases intrinsic to or affecting the pulmonary vasculature. The *6th World Symposium on Pulmonary Hypertension* classifies patients with P-HTN into 5 groups. Group 1, which in the past has been designated as "primary" P-HTN, is now referred to as pulmonary arterial hypertension (PAH). This group includes diseases that affect the small pulmonary muscular arterioles (precapillary pattern). Fifty percent of these patients have idiopathic PAH. Groups 2–5, which in the past have been designated as "secondary" P-HTN, include P-HTN secondary to cardiac disease, hypoxemic lung disease, thromboembolic disease, and other multisystem etiologies.[12,13]

One systematic review and meta-analysis reported that the estimated pooled prevalence of P-HTN in patients with kidney diseases was 33% (range, 16%–68%), 3 times higher than reported in the general population.[14,15] The prevalence of P-HTN appears higher in the dialysis population than in the nondialysis chronic kidney disease population (35% versus 30%).[14] Patients with ESKD are at higher risk of P-HTN caused by associated comorbidities, such as heart failure, and to dialysis-related risk factors causing increased cardiac output and pulmonary blood flow, such as volume overload, anemia, and presence of arteriovenous fistulas (AVF) for hemodialysis access.[16] The systematic review included only 1 study with KTx recipients (n = 215), by Issa et al, which reported a prevalence of pretransplant P-HTN of 32%, and strong associations of P-HTN with reduced posttransplant survival. The majority of the evidence in the systemic review of P-HTN in the population with kidney diseases was of low-to-moderate quality, derived mainly from single-center cohort studies, and the review included heterogenous diagnostic criteria for identifying P-HTN.[14] A subsequent study of 778 KTx recipients evaluated in the University of North Carolina Cardiorenal Registry using validated echocardiographic criteria identified P-HTN in 12% based on peak tricuspid regurgitant jet velocity ≥2.9 m/s, which represents a pulmonary artery systolic pressure of approximately 40 mm Hg.[17]

To better elucidate the frequency and clinical implications of P-HTN after KTx, an American Society of Transplantation (AST) Kidney Pancreas Community of Practice (KPCOP) workgroup was formed to evaluate the current state of evidence based on a systematic literature review.[18] This review identified limited information on the incidence and outcomes of P-HTN after KTx. To further the existing knowledge, we performed a retrospective cohort study of Medicare-insured KTx recipients using linked national databases to examine the incidence, risk factors, and outcomes of P-HTN in this population. The goal was to provide a description grounded in large-sample epidemiology to help inform future clinical studies. This article is a work product of the AST KPCOP.

MATERIALS AND METHODS

Data Sources and Study Sample

Data from the Scientific Registry of Transplant Recipients (SRTR) were analyzed for this study. The SRTR system includes data on all donors, waitlisted candidates, and transplant recipients in the United States, submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration, US Department of Health and Human Services, provides oversight of the activities of the OPTN and SRTR contractors.

Medicare billing claims data include diagnostic and procedure codes for patients with Medicare fee-for-service primary or secondary insurance. After regulatory approvals, beneficiary identifier numbers from Medicare's databases were linked using Social Security number, sex, and birth date to unique, anonymous registry identification numbers. Because of the large sample size, the anonymity of the patients studied, and the nonintrusive nature of the research, a waiver of informed consent was granted per the Department of Health and Human Services Code of Federal Regulations (Title 45, Part 46, Paragraph 46.116). Analyses were performed using Health Information Portability and Accountability Act-compliant, limited datasets from which all direct identifiers were removed. This study was approved by the Institutional Review Board of Saint Louis University.

The study included patients with Medicare parts A and B eligibility at transplant (2006–2016) who also had 2 y of pretransplant Medicare eligibility, to enable assessment of pretransplant P-HTN and other baseline conditions using claims data.

Exposure and Outcome Definitions

Identification of P-HTN was based on submission of billing claims with International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10, after October 2015) diagnostic codes for P-HTN (primary P-HTN, now designated as group 1 or PAH: ICD-9-CM 416.0 and ICD-10 I27.0; secondary P-HTN, now designated as groups 2–5: ICD-9-CM 416.8 and ICD-10 I27.2), as previously described.[19,20] We assessed time to first diagnosis of P-HTN posttransplant as our primary analysis, including primary and secondary diagnostic codes. In an ancillary analysis, we examined time to first diagnosis of secondary causes of P-HTN posttransplant. We also examined "newly diagnosed" P-HTN after transplant, defined by absence of a diagnostic code for P-HTN in the 2 y before KTx. Patterns of testing by echocardiography (Common Procedural Terminology codes: 93306, 93308, 93312–93314, C8921–C8930) and right heart catheterization (Common Procedural Terminology codes: 93451, 93453) procedures in patients with P-HTN diagnoses were also examined.

Death dates were identified by OPTN reporting and supplemented with the Social Security Death Master File, including cause of death based on center reports. All-cause graft failure was defined as return to dialysis, retransplant, or death with a functioning graft.

Covariates

Recipient, donor, and transplant-related clinical and demographic factors were defined by the OPTN Transplant Candidate Registration and Transplant Recipient Registration forms (Table 1). Additional clinical conditions not available in the registry were ascertained from Medicare claims, including history of acute myocardial infarction (AMI), congestive heart failure, valvular disease, chronic obstructive pulmonary disease (COPD), obstructive sleep apnea, venous thromboembolism, connective tissue disease, and smoking (**Table S1, SDC**, http://links.lww.com/TP/C229).

Statistical Analyses

Data management and analyses were performed with SAS for Windows software, version 9.4 (SAS Institute Inc, Cary, NC). We estimated the cumulative incidence of P-HTN by 3 y posttransplant (with 95% lower and upper confidence limits, $_{95\%LCL}$incidence$_{95\%UCL}$) using the product-limit method of Kaplan and Meier. Observations were censored at the earliest of the following: loss of Medicare, 3 y after transplant (when Medicare coverage ends unless the recipient is aged ≥65 y or disabled), death not concomitant with P-HTN, or end of observation (December 31, 2016). Bivariate comparisons of the cumulative incidence of P-HTN according to baseline factors were performed with the log-rank test. To form clinical strata, continuous variables were categorized into clinically relevant groupings. Missing categorical covariate data were grouped with the absence of a characteristic when such a category was relevant, or into a category distinct from the reference group, allowing estimation of the effect of the known and indicated presence of specified conditions.

We used multivariate Cox hazard analysis to estimate associations (adjusted hazard ratio [aHR] $_{95\%LCL}$aHR$_{95\%UCL}$) of baseline recipient, donor, and transplant factors with P-HTN after transplant. The proportionality of hazards over time was assessed by testing interactions between predictors and a continuous linear function of years after transplant. We also quantified the association of P-HTN with subsequent mortality and graft failure by Cox hazard analysis, including the P-HTN diagnosis date as a time-varying covariate.

Finally, we explored the impact of KTx as a time-dependent exposure on subsequent P-HTN among listed candidates, compared with continued waiting without transplant, using multivariable Cox regression stratified by candidate age and including adjustment for baseline clinical and demographic factors, per previous methods.[7,21] Analogous to the KTx recipient sample, the candidate sample was also limited by 2 y of prelisting Medicare eligibility to distinguish newly diagnosed P-HTN. P-HTN risk associated with KTx versus waiting was partitioned by exposure time into within <6 mo and ≥6 mo of the transplant event and stratified by candidate age at listing, per previous methods.[7,21]

RESULTS

Baseline Characteristics

Of 178 092 KTx recipients in the study period, 35 512 met inclusion criteria. In the study sample, 91.4% of recipients were aged >30 y, and 61.0% were men. Compared with excluded recipients, the study sample included higher proportions of recipients who were aged ≥60 y (35.0% versus 28.3%), non-White (63.7% versus 45.3%), who had longer pretransplant dialysis duration (>5 y: 47.0% versus 17.0%), while fewer received living donor transplants (15.0% versus 40.8%) (**Table S2, SDC**, http://links.lww.com/TP/C229). Most patients were White (36.3%) or African American (35.6%). The leading causes of ESKD were hypertension (30.7%), diabetes mellitus (26.2%), and glomerulonephritis (21.2%). The majority of recipients were receiving hemodialysis (62.4%) before KTx, and 9.4% were receiving peritoneal dialysis.

Incidence of Posttransplant P-HTN

Overall, 8.2% of recipients had a diagnostic code for P-HTN in the 2 y before KTx. Of those, 11.8% had codes for primary P-HTN only, 97.4% for secondary P-HTN only, and 9.2% for both. By 3 y posttransplant, P-HTN was diagnosed in $_{10.3}$10.6%$_{11.0}$ of the cohort, including $_{36.7}$38.7%$_{40.7}$ of recipients with and $_{7.8}$8.1%$_{8.5}$ of recipients without pretransplant P-HTN (Table 1). Overall, 96.4% of patients with P-HTN diagnoses had undergone echocardiography, and 61.2% had undergone right heart catheterization. By comparison, 76.5% patients without P-HTN diagnoses had undergone echocardiography during the study period.

The 3-y cumulative incidence of P-HTN was significantly higher in women than in men ($_{11.0}$11.6%$_{12.2}$ versus $_{9.6}$10.0%$_{10.5}$) and rose with increasing age (18–30 y versus 45–59 versus ≥60: $_{3.6}$4.4%$_{5.5}$ versus $_{9.9}$10.5%$_{11.1}$ versus $_{13.6}$14.4%$_{15.1}$) (Table 1). Compared with incidence among White recipients ($_{10.8}$11.5%$_{12.1}$), incidence was significantly lower in Hispanic recipients ($_{7.2}$7.9%$_{8.7}$) and in those of other races ($_{7.2}$8.3%$_{9.6}$). Posttransplant P-HTN was more common in recipients who were obese, who had limited physical capacity, and whose cause of ESKD was hypertension compared with glomerulonephritis. Longer pretransplant dialysis duration was associated with higher incidence of posttransplant P-HTN (>5 y: versus preemptive $_{11.4}$11.9%$_{12.5}$ versus $_{5.0}$6.4%$_{8.3}$). Patients who received maintenance hemodialysis pretransplant more commonly developed P-HTN posttransplant ($_{10.8}$11.3%$_{11.8}$) compared with those who received peritoneal dialysis ($_{5.7}$6.5%$_{7.7}$). Incidence of posttransplant P-HTN was higher for recipients with certain baseline comorbid conditions, including hypertension, diabetes mellitus, coronary artery disease/AMI, peripheral vascular disease, cerebral vascular disease, venous thromboembolism, and smoking than for recipients without these conditions. The 3-y incidence was particularly high in those with histories of COPD ($_{20.0}$21.2%$_{22.5}$), obstructive sleep apnea ($_{16.8}$18.5%$_{20.3}$), or valvular heart disease ($_{16.0}$17.0%$_{18.0}$). Transplant-related factors associated with increased 3-y incidence of P-HTN included deceased donor kidney with higher Kidney Donor Profile Index (>85% versus 20%–85%) and more recently performed transplants (2012–2016 versus 2006–2011) and delayed graft function. Patterns were similar for recipients

TABLE 1.

Three-y cumulative incidence of P-HTN after kidney transplant by baseline clinical factors, and independent correlates of posttransplant P-HTN

	Cumulative incidence of posttransplant P-HTN	Adjusted correlates of posttransplant P-HTN	Cumulative incidence of newly diagnosed posttransplant P-HTN[a]	Adjusted correlates of newly diagnosed posttransplant P-HTN[a]
Baseline characteristics	**% (95% CI)**	**aHR (95% CI)**	**% (95% CI)**	**aHR (95% CI)**
Pretransplant P-HTN				
No	8.1 (7.8-8.5)	Reference	8.1 (7.8-8.5)	N/A
Yes	38.7 (36.7-40.7)[b]	4.79 (4.38-5.24)[b]	N/A	N/A
Age, y				
<18	2.6 (1.5-4.5)[c]	0.83 (0.47-1.48)	1.7 (0.8-3.5)	0.69 (0.32-1.47)
18–30	4.4 (3.6-5.5)	Reference	3.0 (2.3-4.0)	Reference
31–44	7.4 (6.8-8.2)[b]	1.48 (1.17-1.87)[d]	5.3 (4.7-6.0)[b]	1.55 (1.15-2.10)[c]
45–59	10.5 (9.9-11.1)[b]	1.84 (1.47-2.30)[b]	8.0 (7.5-8.6)[b]	2.18 (1.63-2.91)[b]
≥60	14.4 (13.6-15.1)[b]	2.40 (1.91-3.01)[b]	11.4 (10.7-12.1)[b]	2.88 (2.15-3.86)[b]
Sex				
Male	10.0 (9.6-10.5)	Reference	7.7 (7.2-8.1)	Reference
Female	11.6 (11.0-12.2)[b]	1.24 (1.15-1.34)[b]	8.9 (8.3-9.5)[c]	1.29 (1.17-1.41)[b]
Race				
White	11.5 (10.8-12.1)	Reference	8.9 (8.3-9.5)	Reference
African American	11.9 (11.2-12.5)	0.98 (0.90-1.07)	9.1 (8.5-9.7)	0.96 (0.86-1.08)
Hispanic	7.9 (7.2-8.7)[b]	0.70 (0.63-0.79)[b]	5.9 (5.2-6.6)[b]	0.67 (0.58-0.77)[b]
Other[e]	8.3 (7.2-9.6)[b]	0.73 (0.62-0.85)[b]	6.1 (5.1-7.3)[b]	0.63 (0.52-0.76)[b]
Body mass index, kg/m^2				
<18.5	8.7 (6.9-10.9)	1.11 (0.87-1.41)	5.3 (3.8-7.3)	1.07 (0.77-1.50)
18.5 to <25	9.2 (8.6-9.9)	Reference	6.4 (5.9-7.1)	Reference
25 to <30	10.6 (9.9-11.3)[c]	1.02 (0.92-1.12)	8.1 (7.5-8.8)[d]	1.08 (0.96-1.22)
≥30.0	12.3 (11.6-13.0)[b]	1.09 (0.99-1.20)	10.0 (9.3-10.7)[b]	1.18 (1.05-1.33)[c]
Physical capacity status				
Not limited	9.7 (9.2-10.2)	Reference	7.5 (7.1-8.0)	Reference
Limited	14.0 (12.5-15.6)[b]	1.21 (1.07-1.38)[c]	10.5 (9.2-12.1)[b]	1.17 (1.00-1.37)[c]
Comorbid conditions				
Hypertension	10.9 (10.5-11.3)[c]	1.03 (0.93-1.15)	8.3 (7.9-8.7)[c]	1.02 (0.90-1.17)
Diabetes mellitus	13.7 (13.0-14.4)[b]	1.14 (1.01-1.29)[c]	10.9 (10.2-11.6)[b]	1.23 (1.07-1.42)[c]
CAD/AMI	15.7 (14.5-16.9)[b]	1.15 (1.05-1.27)[c]	11.3 (10.2-12.5)[b]	1.15 (1.02-1.30)[c]
Congestive heart failure	13.3 (12.4-14.2)[b]	1.08 (1.00-1.18)	9.8 (9.0-10.7)[b]	1.10 (0.99-1.22)
Valvular disease	17.0 (16.0-18.0)[b]	1.32 (1.22-1.43)[b]	12.3 (11.4-13.3)[b]	1.51 (1.37-1.67)[b]
Cerebral vascular disease	14.6 (12.2-17.5)[c]	1.09 (0.90-1.32)	12.0 (9.6-14.9)[d]	1.12 (0.89-1.41)
Peripheral vascular disease	16.1 (14.5-17.9)[b]	1.18 (1.05-1.33)[c]	12.2 (10.7-14.0)[b]	1.14 (0.99-1.32)
COPD	21.2 (20.0-22.5)[b]	1.31 (1.20-1.43)[b]	13.1 (11.9-14.4)[b]	1.44 (1.28-1.61)[b]
Obstructive sleep apnea	18.5 (16.8-20.3)[b]	1.28 (1.15-1.43)[b]	12.6 (11.1-14.4)[b]	1.28 (1.11-1.49)[d]
Venous thromboembolism	13.0 (11.9-14.2)[b]	1.09 (0.98-1.21)	9.4 (8.4-10.5)[c]	1.09 (0.96-1.24)
Connective tissue disease	11.3 (9.8-13.0)	1.17 (0.99-1.38)	7.4 (6.1-9.0)	1.15 (0.93-1.44)
Smoking history	14.1 (11.7-17.0)[c]	1.13 (0.92-1.39)	11.0 (8.7-13.9)[c]	1.32 (1.03-1.70)[c]
Cause of ESKD				
Hypertension	13.7 (12.9-14.6)[b]	1.20 (1.06-1.35)[c]	10.8 (10.0-11.6)[b]	1.18 (1.02-1.37)[c]
Diabetes mellitus	8.3 (7.6-9.0)[b]	1.12 (0.96-1.31)	6.1 (5.5-6.9)[b]	1.10 (0.91-1.33)
Glomerulonephritis	11.5 (10.8-12.3)	Reference	9.0 (8.3-9.7)	Reference
Polycystic kidney disease	6.7 (5.6-8.0)[c]	0.74 (0.60-0.91)[c]	4.6 (3.7-5.8)	0.65 (0.50-0.85)[c]
Other	8.6 (7.7-9.4)	1.08 (0.94-1.24)	6.4 (5.6-7.2)	1.06 (0.89-1.25)
Duration of dialysis, y				
None (pre-emptive)	6.4 (5.0-8.3)[d]	1.04 (0.76-1.43)	5.3 (4.0-7.0)[c]	1.10 (0.76-1.58)
>0–2	10.4 (9.4-11.6)	Reference	8.2 (7.2-9.4)	Reference
>2–5	9.6 (9.0-10.2)	1.06 (0.93-1.21)	7.4 (6.8-7.9)	1.02 (0.87-1.19)
>5	11.9 (11.4-12.5)[c]	1.34 (1.17-1.52)[b]	9.1 (8.5-9.6)	1.26 (1.07-1.47)[c]
Pretransplant dialysis modality				
Hemodialysis	11.3 (10.8-11.8)[b]	1.37 (1.17-1.59)[b]	8.8 (8.3-9.3)[b]	1.58 (1.30-1.91)[b]
Peritoneal dialysis	6.6 (5.7-7.7)	Reference	4.6 (3.8-5.6)	Reference

Continued next page

TABLE 1. (Continued)

Baseline characteristics	Cumulative incidence of posttransplant P-HTN % (95% CI)	Adjusted correlates of posttransplant P-HTN aHR (95% CI)	Cumulative incidence of newly diagnosed posttransplant P-HTN[a] % (95% CI)	Adjusted correlates of newly diagnosed posttransplant P-HTN[a] aHR (95% CI)
Previous organ transplant	10.4 (9.6-11.2)	1.14 (1.03-1.25)[c]	7.4 (6.6-8.2)	1.15 (1.01-1.30)[c]
Donor type				
Living donor	9.6 (8.8-10.6)[c]	1.13 (1.01-1.27)[c]	7.0 (6.2-7.9)[c]	1.14 (0.99-1.32)
Deceased, KDPI <20	8.5 (7.6-9.4)[b]	0.95 (0.85-1.07)	6.4 (5.6-7.3)[d]	0.97 (0.84-1.12)
Deceased, KDPI 20–85	10.9 (10.4-11.4)	Reference	8.1 (7.7-8.6)	Reference
Deceased, KDPI >85	14.1 (12.7-15.5)[b]	1.17 (1.05-1.31)[c]	12.3 (11.0-13.8)[b]	1.30 (1.14-1.48)[b]
Induction at transplant				
No	10.2 (9.3-11.2)	Reference	8.1 (7.2-9.0)	Reference
Yes	10.7 (10.3-11.1)	1.03 (0.93-1.15)	8.1 (7.8-8.5)	0.99 (0.88-1.12)
Maintenance ISx at discharge				
Triple therapy	10.8 (10.3-11.3)	Reference	8.2 (7.7-8.6)	Reference
Tac+MPA/AZA	10.1 (9.3-10.9)	0.98 (0.90-1.08)	7.7 (7.0-8.5)	0.97 (0.87-1.09)
Tac or Tac+Pred	10.4 (8.3-13.0)	1.11 (0.88-1.40)	6.9 (5.1-9.3)	0.88 (0.65-1.20)
mTORi-based	12.7 (10.2-15.7)	1.05 (0.84-1.31)	11.3 (8.8-14.5)	1.23 (0.95-1.59)
CsA-based	9.1 (7.5-11.0)[c]	0.88 (0.72-1.07)	6.7 (5.3-8.6)	0.83 (0.64-1.06)
Other	12.1 (10.1-14.5)	1.09 (0.90-1.31)	9.9 (8.0-12.3)[c]	1.18 (0.95-1.46)
Delayed graft function	14.4 (13.6-15.1)[b]	1.43 (1.32-1.54)[b]	11.5 (10.8-12.3)[b]	1.53 (1.40-1.68)[b]
Transplant era				
2006–2011 (reference)	9.1 (8.7-9.6)	Reference	7.3 (6.9-7.8)	Reference
2012–2016	12.0 (11.4-12.6)[b]	1.39 (1.29-1.51)[b]	8.8 (8.3-9.4)[b]	1.29 (1.17-1.42)[b]

Full sample includes 35 512 kidney transplant recipients. Please see **Table S2** (**SDC**, http://links.lww.com/TP/C229) for distribution of baseline characteristic in the study sample.
[a]Estimated among those without evidence of P-HTN in the 2 y before transplant (n = 32 597).
[b]$P < 0.0001$.
[c]$P < 0.05$–0.002.
[d]$P = 0.001$–0.0002.
[e]Other race includes Asian, Native American, Pacific Islander, and multiracial.
aHR, adjusted hazard ratio; AMI, acute myocardial infarction; AZA, azathioprine; CAD, coronary artery disease; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CsA, cyclosporine; ESKD, end-stage kidney disease; ISx, immunosuppression; KDPI, Kidney Donor Profile Index; MPA, mycophenolic acid; mTORi, mammalian target of rapamycin inhibitors; N/A, not applicable; P-HTN, pulmonary hypertension; Pred, prednisone; Tac, tacrolimus.

who developed newly diagnosed P-HTN, although the 3-y cumulative incidence was lower across clinical strata.

Adjusted Correlates of Posttransplant P-HTN

Among the full cohort, after adjustment for other baseline factors, patient characteristics associated with increased likelihood of a P-HTN diagnosis by 3 y posttransplant ($P < 0.05$) included: pretransplant P-HTN (aHR, $_{4.38}4.79_{5.24}$), older age (31–44 y: aHR, $_{1.17}1.48_{1.87}$; 45–59 y: aHR, $_{1.47}1.84_{2.30}$; ≥60 y: aHR, $_{1.91}2.40_{3.01}$, versus 18–30 y), female sex (aHR, $_{1.15}1.24_{1.34}$), history of diabetes mellitus (aHR, $_{1.01}1.14_{1.29}$), coronary artery disease/AMI (aHR, $_{1.05}1.15_{1.27}$), valvular heart disease (aHR, $_{1.22}1.32_{1.43}$), peripheral vascular disease (aHR, $_{1.05}1.18_{1.33}$), COPD (aHR, $_{1.20}1.31_{1.43}$), and obstructive sleep apnea (aHR, $_{1.15}1.28_{1.43}$). Adjusted P-HTN risk was also higher in those with longer dialysis duration (>5 versus >0–2 y: aHR, $_{1.17}1.34_{1.52}$), pretransplant hemodialysis modality (hemodialysis versus peritoneal dialysis aHR, $_{1.17}1.37_{1.59}$), delayed graft function (aHR, $_{1.32}1.43_{1.54}$), and more recent transplant era (2012–2016 versus 2006–2011 aHR, $_{1.29}1.39_{1.51}$) (Table 1).

Compared with White recipients, Hispanic (aHR, $_{0.63}0.70_{0.79}$) and other race (aHR, $_{0.62}0.73_{0.85}$) recipients had significantly lower adjusted risk of P-HTN after KTx, as did recipients with polycystic kidney disease (aHR, $_{0.60}0.74_{0.91}$) compared to those with glomerulonephritis. Induction and maintenance immunosuppression were not independently associated with the likelihood of P-HTN diagnosis, after adjustment for other factors. Risk relationships were similar for newly diagnosed P-HTN, except that obesity (aHR, $_{1.05}1.18_{1.33}$) and smoking (aHR, $_{1.03}1.32_{1.70}$) were significant adjusted clinical correlates (Table 1). Patterns were also similar considering secondary P-HTN as the outcome measure, except that connective tissue disease history was also associated with secondary P-HTN after transplant (aHR, $_{1.02}1.20_{1.42}$) (**Table S3, SDC**, http://links.lww.com/TP/C229).

Associations of Posttransplant P-HTN With Death and Graft Loss

In time-varying analysis, a posttransplant diagnosis of P-HTN independently predicted subsequent death (aHR, $_{2.57}2.84_{3.14}$) and all-cause graft failure (aHR, $_{2.42}2.64_{2.88}$) within the first 3 y posttransplant (Figure 1). The prognostic impact of newly diagnosed P-HTN was slightly stronger, predicting approximately 3 times the risk of subsequent death (aHR, $_{2.77}3.10_{3.48}$) and all-cause graft failure (aHR, $_{2.62}2.88_{3.18}$). After accounting for the impact of P-HTN, risks of death and all-cause graft failure were also significantly higher for recipients with posttransplant P-HTN who had limited baseline physical capacity, diabetes mellitus, history of coronary artery disease/AMI, valvular disease, peripheral vascular disease or venous thromboembolism, longer dialysis duration, previous organ transplant, or who received a deceased donor kidney with higher Kidney Donor Profile Index, had delayed

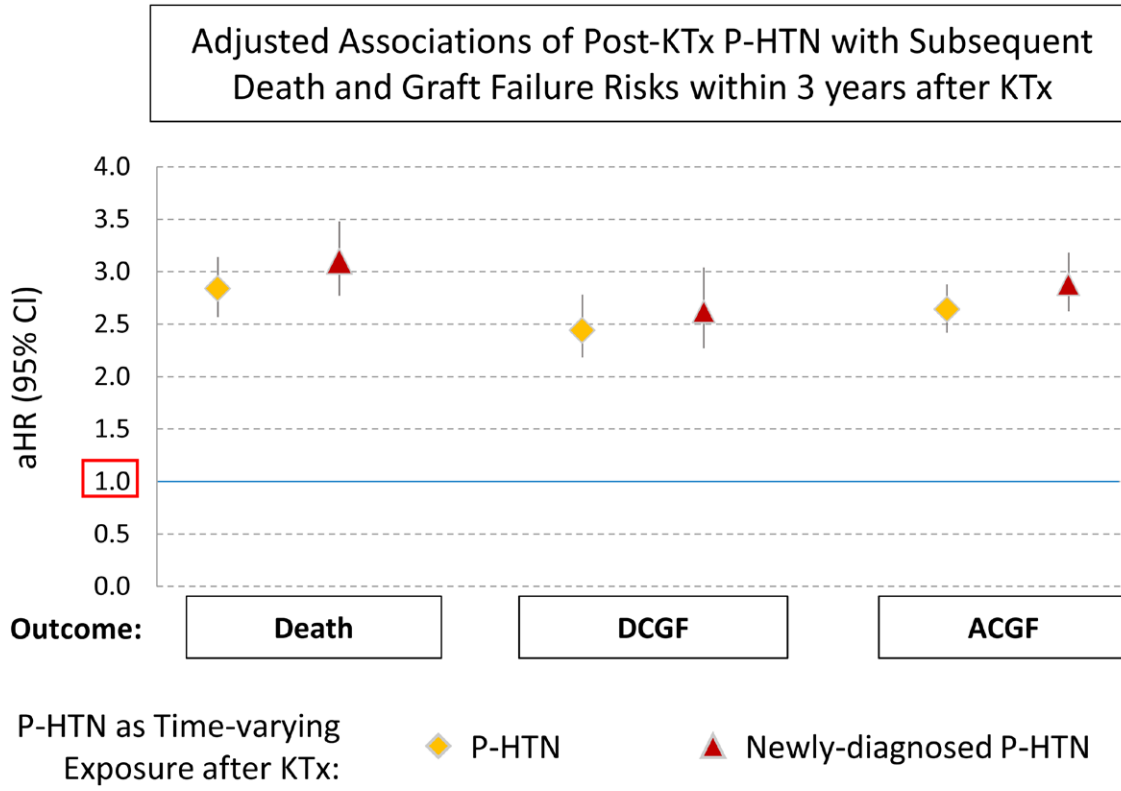

FIGURE 1. Adjusted associations of posttransplant P-HTN with subsequent death and graft failure risk within 3 y after kidney transplant. Effect estimates reflect impact of P-HTN and newly diagnosed P-HTN after transplant as time-varying predictors of subsequent, death, DCGF, and ACGF. ACGF, all-cause graft failure; aHR, adjusted hazard ratio; CI, confidence interval; DCGF, death-censored graft failure; KTx, kidney transplant; P-HTN, pulmonary hypertension.

graft function, or received nontriple maintenance immunosuppressant therapy except tacrolimus and mycophenolic acid/azathioprine (**Table S4, SDC**, http://links.lww.com/TP/C229). Posttransplant P-HTN (aHR, $_{2.14}2.44_{2.78}$) and newly diagnosed P-HTN (aHR, $_{2.27}2.62_{3.04}$) were also associated with increased risk of death-censored graft loss.

Mortality implications were similar considering secondary P-HTN as a time-varying predictor of subsequent death and graft failure (**Table S5, SDC**, http://links.lww.com/TP/C229). Reported causes of death in patients with P-HTN included slightly more common attribution to cardiovascular disease compared with deaths among patients without P-HTN (17.6% versus 16.2%), although other and unknown causes were common in these data (**Figure S1, SDC**, http://links.lww.com/TP/C229).

Ancillary Analysis of Kidney Transplantation on Risk of P-HTN After Listing

Considered from the perspective of continued waiting without transplant, KTx was associated with increased likelihood of P-HTN diagnosis within 6 mo of transplant. Associated short-term risks ranged from a 70% increase for patients aged <45 y (aHR, $_{1.49}1.70_{1.93}$) to 3 times the risk in patients aged ≥60 y (aHR, $_{2.82}3.11_{3.43}$) (Figure 2A). In contrast, beyond 6 mo, KTx was associated with 47% reduction in the likelihood of P-HTN compared with continued waiting in patients younger than age 45 y (aHR, $_{0.46}0.53_{0.61}$) and a 25% reduction in those aged 45–60 y (aHR, $_{0.67}0.75_{0.44}$), but no nonsignificant impact in older candidates (Figure 2B). Patterns were similar for newly diagnosed P-HTN.

DISCUSSION

In this large retrospective study of Medicare-insured KTx recipients, we found that P-HTN within 3 y posttransplant was diagnosed in 10.6%, with a higher proportion in those with versus without pretransplant P-HTN (38.7% versus 8.1%). Posttransplant P-HTN was correlated with certain baseline factors including older age, female sex, longer dialysis duration, hemodialysis, more recent transplant era, and baseline comorbidities including coronary artery disease, valvular heart disease, peripheral vascular disease, COPD, and obstructive sleep apnea. A diagnosis of P-HTN was also associated with >2.5-fold increased risk of subsequent mortality and graft loss. Ancillary analysis suggested that compared with continued waiting without transplant, KTx may be associated with longer-term reduction in risk of P-HTN after the perioperative period, at least among candidates younger than age 60 y.

In our study, 8.2% of recipients had a diagnostic code for P-HTN in the 2 y before transplant, much lower than the pooled prevalence of 33% reported in a systematic review of kidney patients by Bolignano et al,[14] but more similar to the estimate of 12% in a recent study of KTx candidates captured in the University of North Carolina Cardiorenal Registry.[17] The lower frequency of P-HTN in our cohort can be attributed, in part, to selection bias, in that dialysis patients with severe P-HTN may be less likely to undergo transplant. Also, the recipients in our observational cohort may have undergone cardiac investigations to assess P-HTN as part of their evaluations, but not necessarily within the 2 y before transplant. In the 3 y after transplant, we found that 1 in 10 recipients had a diagnostic

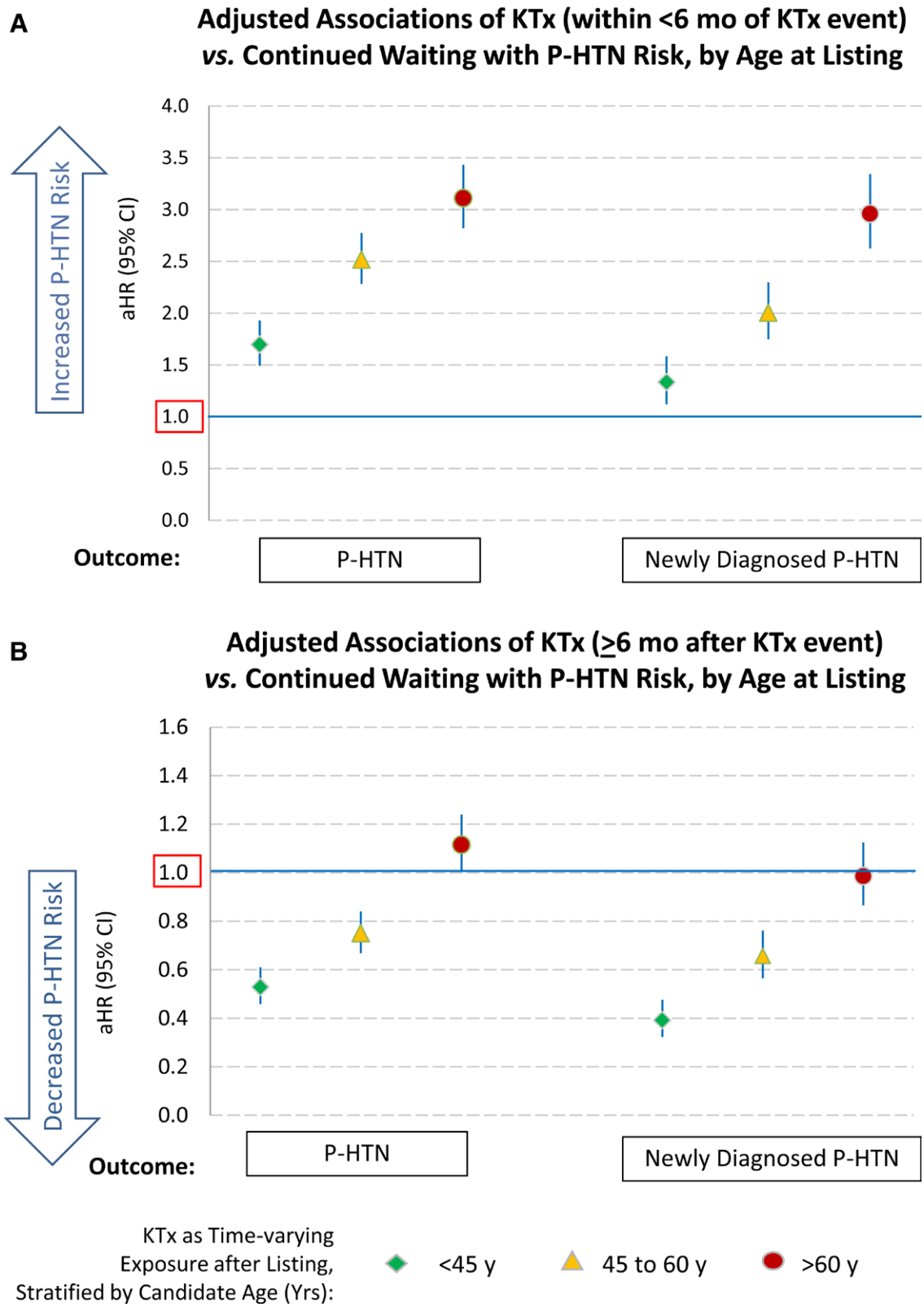

FIGURE 2. A, Adjusted association of kidney transplant (within <6 mo post-KTx) with risk of P-HTN after listing vs continued waiting, by age at listing. B, Adjusted association of kidney transplantation (>6 mo post-KTx) with risk of P-HTN after listing vs continued waiting, by age at listing. Effect estimates reflect impact of kidney transplantation as a time-varying predictor of subsequent P-HTN. P-HTN risk associated with KTx vs waiting was partitioned by exposure time into within <6 mo and ≥6 mo of the transplant event and stratified by candidate age at listing. aHR, adjusted hazard ratio; CI, confidence interval; KTx, kidney transplant; P-HTN, pulmonary hypertension.

code for P-HTN. In the literature, prevalence of P-HTN in KTx recipients ranges from 5% to 18%.[10,16,22-24] The wide variation reflects the heterogenous diagnostic definition of P-HTN, including investigation modality (echocardiogram versus right heart catheterization) and abnormal pulmonary artery pressure thresholds, which can range from

25 to ≥45 mm Hg.[15] Our study used diagnostic codes to identify P-HTN cases, which allowed for a generalizable national assessment of P-HTN, including associated demographic and clinical factors and subsequent outcomes, but at the expense of potential misclassification of disease and lack of information on etiology, severity, and treatment of P-HTN.[20] Potential misclassification may occur as diagnostic codes are often based on noninvasive testing (ie, echocardiography) to diagnose P-HTN, instead of a gold-standard right heart catheterization.

Approximately 40% of recipients with pretransplant P-HTN were diagnosed with posttransplant P-HTN within 3 y, whereas 60% had no evidence of a diagnostic code. P-HTN in these recipients may have stabilized or improved posttransplant, such that it did not require medical care within the first 3 y after transplant. Another possibility is that pretransplant P-HTN resolved with a functioning allograft, which has been reported in the literature.[25-28] For example, 1 study compared pretransplant and 1-y posttransplant P-HTN in 35 KTx recipients and found a significant reduction in diagnosed P-HTN (49% versus 14%, $P = 0.01$) and measured pulmonary arterial systolic pressure (52 versus 36 mm Hg, $P < 0.03$).[27] KTx can lead to improvement or reversal of many dialysis-related complications that contribute to or worsen P-HTN, including elevated systemic blood pressure, left ventricle (LV) hypertrophy, LV systolic and diastolic dysfunction, volume overload, AVF flow, and anemia.[10,29-33] In an ancillary analysis of the current dataset, we found a reduction in P-HTN risk among listed candidates aged <60 y after KTx, beyond 6 mo following the KTx event. Risk of P-HTN diagnosis was increased within the first 6 mo posttransplant, consistent with patterns for other cardiovascular conditions like congestive heart failure and ischemic heart disease,[7,34,35] which may reflect hemodynamic stressors in the perioperative period and/or impacts of closer clinical surveillance early after surgery.

Only a few studies have assessed clinical correlates of posttransplant P-HTN in KTx recipients. These studies generally report no significant differences in demographic factors between recipients with and without P-HTN, possibly due to small sample sizes.[23,24] To our knowledge, ours is one of the largest studies to assess clinical correlates of P-HTN after KTx, including newly diagnosed P-HTN. The demographic factors correlated with posttransplant P-HTN were similar to those reported for pretransplant P-HTN in other studies, including older age,[16,24] obesity,[24,28] and longer dialysis duration.[16,36] Similar to our findings, prior studies have also reported associations of hemodialysis with P-HTN,[16,37,38] which may be impacted by vascular access. Compared to patients managed with peritoneal dialysis or catheter-based dialysis, hemodialysis patients with an AVF had higher prevalence of P-HTN (40% versus 10%) in 1 small series.[25] Although AVF have been implicated as a correlate or exacerbating factor for P-HTN progression in some hemodialysis cohorts,[39-42] other studies have shown no significant relationship.[43] Resolution of symptomatic P-HTN including normalization of pulmonary hemodynamics after revision or ligation of high-flow AVF has been described in case reports and small series,[44,45] including after KTx,[46-48] while a recent small randomized trial showed mixed results on hemodynamic parameters.[49] Our data captured dialysis modality but did not allow classification of pretransplant dialysis access, as this is not recorded in the registry and the access may have been placed >2 y before KTx. Further study of the impact of AVF ligation on P-HTN risk after KTx is warranted. Using diagnostic claims among a large sample, we also identified associations of baseline comorbidities with P-HTN after transplant including cardiovascular and pulmonary conditions, which may help identify patients at-risk for P-HTN after KTx. The explanation for increased posttransplant P-HTN in more recent years of the study is speculative but may reflect increased diagnostic scrutiny, differences in clinical awareness, and changes in patient characteristics including older age and higher BMI.

Previous studies have described the association of pretransplant P-HTN with posttransplant outcomes, including delayed graft function,[36] graft dysfunction,[38,50] graft failure,[51] and mortality.[36,52] In 1 retrospective study of 363 KTx recipients, Jarmi et al reported that survival for recipients with P-HTN diagnosed intraoperatively at the time of transplant by right heart catheterization was significantly shorter than for recipients without P-HTN (aHR, ${}_{1.04}1.98_{3.74}$, $P = 0.04$).[36] These studies highlight the importance of identifying P-HTN in KTx candidates, as it may affect posttransplant patient and graft survival and morbidity. In our study, we found that posttransplant P-HTN was associated with a >2.5-fold increased risk of subsequent death and graft failure within the first 3 y posttransplant. This association was significant for recipients with and without pretransplant P-HTN, suggesting that newly diagnosed P-HTN also portends poor outcomes. As in the general population and the dialysis population, the risk of death associated with P-HTN in KTx recipients may be mediated through LV dysfunction. Similarly, graft failure in recipients with P-HTN may be due to allograft hypoperfusion related to hemodynamic changes and increased vascular stiffness and resistance.[10,23,38] One study suggests that altered levels of vasoactive substances may have resulted in allograft vasoconstriction and ischemia–reperfusion injury leading to graft dysfunction.[36,38]

Our study furthers the description of P-HTN epidemiology in a large, national sample of KTx recipients. It substantiates the associated risk factors and outcome implications of P-HTN in this population. The study also has limitations. Our sample of Medicare beneficiaries differs in some baseline characteristics from the full sample of US KTx recipients, and findings may not generalize to those in private insurance systems. We relied on diagnostic codes to identify pre- and posttransplant P-HTN cases, and we lacked data on how the diagnosis was made. The gold standard and standard of care definition is according to results of the right heart catheterization. Some of the diagnoses were established by echocardiographic findings only. Thus, there is likely heterogeneity with regard to the clinical presentation and pathological thresholds for identifying P-HTN based on clinician diagnosis. As described above, this may result in misclassification bias and lacks the granularity to assess P-HTN severity and etiology. In addition, misclassification bias may be due to differential billing practices and referral patterns. Reassuringly, our P-HTN incidence rates were similar to those reported in smaller single-center studies, as were our clinical correlates. We also lacked information on concurrent treatments for P-HTN, which may modify associations with outcomes.

Because of the observational nature of our study, we can describe only associations, not causations. Nonetheless, description grounded in large-sample epidemiology can provide a framework to help inform future clinical studies. The study is intended to complement, not to replace, prospective and interventional study designs.

In summary, in this national study of Medicare-insured KTx recipients, we found that posttransplant P-HTN is diagnosed in 1 in 10 KTx recipients within the first 3 y after transplant and is associated with a >2.5-fold increased risk of subsequent mortality and graft loss. When P-HTN is identified, the primary goal should be to identify reversible causes and optimize hemodynamics, ideally with care of those with moderate-to-severe P-HTN, in a specialized P-HTN clinic. At this time, the efficacy of P-HTN management strategies in patients with ESKD before and after KTx is largely unproven. We advocate for future research including large-scale, well-designed observational studies with low bias risk to confirm the need for clinical attention to P-HTN and to define benefits of appropriate therapeutic approaches in the KTx population.

ACKNOWLEDGMENTS

The authors include members of the AST KPCOP Cardiovascular Consensus work group, and we thank the AST Education Committee for review and approval of the manuscript. The authors thank SRTR colleague Nan Booth, MSW, MPH, ELS, for article editing. The US Government (and others acting on its behalf) retains a paid-up, nonexclusive, irrevocable, worldwide license for all works produced under the SRTR contract, and to reproduce them, prepare derivative works, distribute copies to the public, and perform publicly and display publicly, by or on behalf of the Government. The data reported here have been supplied by the HHRI as the contractor for 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, the US Government, or funding sources.

REFERENCES

1. Hart A, Lentine KL, Smith JM, et al. OPTN/SRTR 2019 annual data report: kidney. *Am J Transplant*. 2021;21(Suppl 2):21–137.
2. Axelrod DA, Schnitzler MA, Xiao H, et al. An economic assessment of contemporary kidney transplant practice. *Am J Transplant*. 2018;18:1168–1176.
3. Lentine KL, Gheorghian A, Axelrod D, et al. The implications of acute rejection for allograft survival in contemporary U.S. kidney transplantation. *Transplantation*. 2012;94:369–376.
4. Schnitzler MA, Lentine KL, Gheorghian A, et al. Renal function following living, standard criteria deceased and expanded criteria deceased donor kidney transplantation: impact on graft failure and death. *Transpl Int*. 2012;25:179–191.
5. Lentine KL, Hurst FP, Jindal RM, et al. Cardiovascular risk assessment among potential kidney transplant candidates: approaches and controversies. *Am J Kidney Dis*. 2010;55:152–167.
6. Lentine KL, Costa SP, Weir MR, et al; American Heart Association Council on the Kidney in Cardiovascular Disease and Council on Peripheral Vascular Disease; American Heart Association; American College of Cardiology Foundation. Cardiac disease evaluation and management among kidney and liver transplantation candidates: a scientific statement from the American Heart Association and the American College of Cardiology Foundation: endorsed by the American Society of Transplant Surgeons, American Society of Transplantation, and National Kidney Foundation. *Circulation*. 2012;126:617–663.
7. Lentine KL, Xiao H, Brennan DC, et al. The impact of kidney transplantation on heart failure risk varies with candidate body mass index. *Am Heart J*. 2009;158:972–982.
8. Mathur AK, Chang YH, Steidley DE, et al. Patterns of care and outcomes in cardiovascular disease after kidney transplantation in the United States. *Transplant Direct*. 2017;3:e126.
9. Adeseun GA, Rivera ME, Thota S, et al. Metabolic syndrome and coronary artery calcification in renal transplant recipients. *Transplantation*. 2008;86:728–732.
10. 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.
11. McLaughlin VV, Archer SL, Badesch DB, et al; American College of Cardiology Foundation Task Force on Expert Consensus Documents; American Heart Association; American College of Chest Physicians; American Thoracic Society Inc; Pulmonary Hypertension Association. ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc; and the Pulmonary Hypertension Association. *J Am Coll Cardiol*. 2009;53:1573–1619.
12. Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J*. 2019;53:1801913.
13. Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol*. 2013;62(25 Suppl):D34–D41.
14. Bolignano D, Pisano A, Coppolino G, et al. Pulmonary hypertension predicts adverse outcomes in renal patients: a systematic review and meta-analysis. *Ther Apher Dial*. 2019;23:369–384.
15. Bolignano D, Pisano A, D'Arrigo G. Pulmonary hypertension: a neglected risk condition in renal patients? *Rev Cardiovasc Med*. 2018;19:117–121.
16. Abedini M, Sadeghi M, Naini AE, et al. Pulmonary hypertension among patients on dialysis and kidney transplant recipients. *Ren Fail*. 2013;35:560–565.
17. Caughey MC, Detwiler RK, Sivak JA, et al. Five-year outcomes of pulmonary hypertension with and without elevated left atrial pressure in patients evaluated for kidney transplantation. *Transplantation*. 2020;104:2113–2119.
18. American Society of Transplantation (AST) Kidney Pancreas Community of Practice (KPCOP). *Consensus Conference: Improving Cardiovascular Disease Care in Solid Organ Transplant Recipients: Controversies, Common Goals and Future Directions*. Washington, DC, USA; 2019. Available at https://www.myast.org/communities-practice/kidney-pancreas-community-practice-kpcop. Accessed March 23, 2021.
19. Link J, Glazer C, Torres F, et al. International Classification of Diseases coding changes lead to profound declines in reported idiopathic pulmonary arterial hypertension mortality and hospitalizations: implications for database studies. *Chest*. 2011;139:497–504.
20. Gillmeyer KR, Lee MM, Link AP, et al. Accuracy of algorithms to identify pulmonary arterial hypertension in administrative data: a systematic review. *Chest*. 2019;155:680–688.
21. Lentine KL, Alhamad T, Cheungpasitporn W, et al. Impact of functional status on outcomes of simultaneous pancreas-kidney transplantation: risks and opportunities for patient benefit. *Transplant Direct*. 2020;6:e599.
22. Frost AE. The intersection of pulmonary hypertension and solid organ transplantation. *Methodist Debakey Cardiovasc J*. 2016;12(4 Suppl):10–13.
23. Bal Z, Sezer S, Uyar ME, et al. Pulmonary hypertension is closely related to arterial stiffness in renal transplant patients. *Transplant Proc*. 2015;47:1186–1189.
24. 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.
25. Yigla M, Nakhoul F, Sabag A, et al. Pulmonary hypertension in patients with end-stage renal disease. *Chest*. 2003;123:1577–1582.
26. Bozbas SS, Kanyilmaz S, Akcay S, et al. Renal transplant improves pulmonary hypertension in patients with end stage renal disease. *Multidiscip Respir Med*. 2011;6:155–160.

27. 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.
28. Reddy YN, Lunawat D, Abraham G, et al. Progressive pulmonary hypertension: another criterion for expeditious renal transplantation. *Saudi J Kidney Dis Transpl*. 2013;24:925–929.
29. 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.
30. Rigatto C, Foley RN, Kent GM, et al. Long-term changes in left ventricular hypertrophy after renal transplantation. *Transplantation*. 2000;70:570–575.
31. 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.
32. 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.
33. Rakhit DJ, Zhang XH, Leano R, et al. Prognostic role of subclinical left ventricular abnormalities and impact of transplantation in chronic kidney disease. *Am Heart J*. 2007;153:656–664.
34. Lentine KL, Schnitzler MA, Abbott KC, et al. De novo congestive heart failure after kidney transplantation: a common condition with poor prognostic implications. *Am J Kidney Dis*. 2005;46:720–733.
35. Lentine KL, Brennan DC, Schnitzler MA. Incidence and predictors of myocardial infarction after kidney transplantation. *J Am Soc Nephrol*. 2005;16:496–506.
36. Jarmi T, Doumit E, Makdisi G, et al. Pulmonary artery systolic pressure measured intraoperatively by right heart catheterization is a predictor of kidney transplant recipient survival. *Ann Transplant*. 2018;23:867–873.
37. Kosmadakis G, Aguilera D, Carceles O, et al. Pulmonary hypertension in dialysis patients. *Ren Fail*. 2013;35:514–520.
38. 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.
39. MacRae JM, Pandeya S, Humen DP, et al. Arteriovenous fistula-associated high-output cardiac failure: a review of mechanisms. *Am J Kidney Dis*. 2004;43:e17–e22.
40. 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.
41. Yigla M, Banderski R, Azzam ZS, et al. Arterio-venous access in end-stage renal disease patients and pulmonary hypertension. *Ther Adv Respir Dis*. 2008;2:49–53.
42. Beigi AA, Sadeghi AM, Khosravi AR, et al. Effects of the arteriovenous fistula on pulmonary artery pressure and cardiac output in patients with chronic renal failure. *J Vasc Access*. 2009;10:160–166.
43. Unal A, Tasdemir K, Oymak S, et al. The long-term effects of arteriovenous fistula creation on the development of pulmonary hypertension in hemodialysis patients. *Hemodial Int*. 2010;14:398–402.
44. Clarkson MR, Giblin L, Brown A, et al. Reversal of pulmonary hypertension after ligation of a brachiocephalic arteriovenous fistula. *Am J Kidney Dis*. 2002;40:E8.
45. Bhatia S, Morrison JF, Bower TC, et al. Pulmonary hypertension in the setting of acquired systemic arteriovenous fistulas. *Mayo Clin Proc*. 2003;78:908–912.
46. Kabitz HJ, Walterspacher S, Geyer M, et al. Reversible pulmonary hypertension in a kidney transplant with patent A-V fistula. *Clin Kidney J*. 2012;5:347–349.
47. Gkotsis G, Jennings WC, Malik J, et al. Treatment of high flow arteriovenous fistulas after successful renal transplant using a simple precision banding technique. *Ann Vasc Surg*. 2016;31:85–90.
48. Schier T, Göbel G, Bösmüller C, et al. Incidence of arteriovenous fistula closure due to high-output cardiac failure in kidney-transplanted patients. *Clin Transplant*. 2013;27:858–865.
49. Rao NN, Stokes MB, Rajwani A, et al. Effects of arteriovenous fistula ligation on cardiac structure and function in kidney transplant recipients. *Circulation*. 2019;139:2809–2818.
50. Wang SC, Garcia R, Torosoff M, et al. Influence of mildly and moderately elevated pulmonary artery systolic pressure on post-renal transplantation survival and graft function. *Echocardiography*. 2019;36:22–27.
51. Foderaro AE, Baird GL, Bazargan-Lari A, et al. Echocardiographic pulmonary hypertension predicts post-transplantation renal allograft failure. *Transplant Proc*. 2017;49:1256–1261.
52. Issa N, Krowka MJ, Griffin MD, et al. Pulmonary hypertension is associated with reduced patient survival after kidney transplantation. *Transplantation*. 2008;86:1384–1388.