Published in final edited form as:

Transplantation. 2020 October ; 104(10): 2113–2119. doi:10.1097/TP.0000000000003068.

Five-Year Outcomes of Pulmonary Hypertension with and without Elevated Left Atrial Pressure in Patients Evaluated for Kidney Transplantation

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Abstract

Background: Pulmonary hypertension (PH) is frequently reported in patients with advanced chronic kidney disease (CKD) and is associated with early allograft failure and death. However, the causes of PH are heterogeneous, and patient prognosis may vary by etiologic subtype.

Methods: Data from the UNC Cardiorenal Registry were examined to determine associations between pulmonary hypertension (PH), with or without elevated left atrial pressure (eLAP), and mortality in candidates for kidney transplantation. PH and eLAP were determined by Doppler echocardiography and by tissue Doppler imaging, respectively.

Results: From 2006-2013, 778 registry patients were screened preoperatively by echocardiography. Most patients were black (64%) and male (56%); the mean age was 56 years. PH was identified in 97 (12%) patients; of these, eLAP was prevalent in half. During a median follow up of 4.4 years, 179 (23%) received a kidney transplant, and 195 (25%) died. After adjustments for demographics, comorbidities, dialysis vintage and kidney transplantation, PH was associated with twice the 5-year mortality (HR = 2.11; 95% CI: 1.48 – 3.03), with stronger associations in the absence of eLAP (HR = 2.87; 95% CI: 1.83 – 4.49) than with eLAP (HR = 1.11; 95% CI: 0.57 – 2.17); *P* for interaction = 0.01.

Conclusion: The mortality risk associated with PH among patients with advanced CKD appears to differ by etiology. Patients with PH in the absence of eLAP are at high risk of death and in need of focused attention. Future research efforts should investigate potential strategies to improve outcomes for these patients.

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AUTHOR CONTRIBUTIONS

MCC performed the statistical analysis and wrote the manuscript. ALH conceptualized the study, interpreted the data and revised the manuscript critically. RKD, JAS, LJR, and AVK revised the manuscript critically.

Conflicts of Interest

The authors declare no conflicts of interest.

Introduction

A high prevalence of pulmonary hypertension (PH) has been reported in patients with late stages of chronic kidney disease (CKD).^{1–4} In these patients, PH has been associated with both pretransplant and posttransplant mortality,⁵ as well as allograft failure.⁶ However, the causes of PH are heterogeneous, and prognosis may vary by etiologic subtype. Advanced CKD is often complicated by myocardial fibrosis⁷ and volume expansion, which may lead to elevated left atrial and pulmonary venous pressures and “postcapillary” pulmonary hypertension.⁸ The prevalence of elevated left atrial pressure (eLAP) and its relationship to pulmonary hypertension in patients with advanced CKD has not been previously investigated, except in highly selected populations undergoing right heart catheterization.⁹ Echocardiography is noninvasive and suitable for hemodynamic evaluations in a broader range of patients, but to date, large screenings for PH have not discriminated between impaired left ventricular relaxation (stage 1 diastolic dysfunction) and impaired relaxation with eLAP (stage 2 diastolic dysfunction) in patients with advanced CKD.^{10,11} Further, pulmonary pressures have been shown to decrease following hemodialysis, suggesting PH secondary to eLAP may be reversible in some cases.⁹ In the absence of eLAP, PH in patients with advanced CKD may be attributable to “precapillary” pulmonary vascular remodeling and elevated pulmonary vascular resistance. We hypothesized that the associated mortality risk would differ for “postcapillary” PH due to eLAP vs. “precapillary” PH as a manifestation of pulmonary vasculature remodeling. To examine this, we analyzed 5-year longitudinal outcomes of 778 patients with advanced CKD who were enrolled in the University of North Carolina (UNC) Cardiorenal Registry.

Materials and Methods

The UNC Cardiorenal Registry

Initiated in 2006, the UNC Cardiorenal Registry is an ongoing collaborative effort of the Division of Cardiology and the Division of Nephrology and Hypertension. Registry enrollment is offered to all adult patients with stage 4 or 5 CKD referred for cardiovascular evaluation prior to kidney transplantation. Study participation is initiated at the time of referral for kidney transplantation, a clinically meaningful time point when assessments of prognosis will influence treatment decisions. In addition to standard medical care, registry participants undergo a comprehensive evaluation of cardiovascular risk, which includes a detailed medical history, laboratory studies, cardiac diagnostic testing (including echocardiography), anthropometry assessment, and standardized questionnaires of physical status and psychosocial wellbeing. All research activities were conducted with informed consent and approved by the UNC institutional review board.

Echocardiography

Echocardiograms were performed by registered sonographers using a standardized protocol and a Philips iE33 ultrasound machine (Philips Medical; Boston, MA). Images were acquired the day before dialysis for patients receiving hemodialysis. All echocardiographic measurements and interpretations were made by the same cardiologist (A.L.H.) in accordance with a standardized protocol for reading clinical echocardiograms.

Left ventricular hypertrophy, left atrial dilation, and ejection fraction

Left ventricular diameter and wall thicknesses were measured in the parasternal long axis view at end-diastole. Left atrial area was measured in the apical 4-chamber view at end-systole. Based on 2-dimensional measurements and visual assessment, chamber dilation and hypertrophy were qualitatively scored as mild, moderate, or severe.¹² For the purposes of this analysis, a moderate or severe score was required for classification of left atrial dilation and left ventricular hypertrophy. Left ventricular ejection fraction was estimated by visually assessing ventricular contraction in the parasternal long axis, parasternal short axis, and apical views. If left ventricular systolic function was judged to be decreased, the ejection fraction was calculated using Simpson's biplane method of discs.¹² For the purposes of this analysis, moderate to severely reduced ejection fraction (<40%) was classified as left ventricular systolic dysfunction.

Mitral annular calcification, mitral regurgitation, diastolic dysfunction, and left atrial pressure

The mitral valve was visually inspected for echogenicity at the annulus suggesting calcification, and regurgitation was assessed by color flow and continuous wave Doppler. Based on the size and extent of the regurgitant jet, the vena contracta width, and the size of the flow convergence region, mitral regurgitation was categorized as mild, moderate, or severe.¹³ The transmitral early (E) and late (A) diastolic velocities were measured by pulse-wave Doppler, with the sample volume placed at the mitral valve tips. The early diastolic myocardial relaxation velocity (e') was quantified by tissue Doppler, with the sample volume placed at the septal mitral annulus. Grade 2 left ventricular diastolic dysfunction (impaired relaxation with eLAP) was defined by the presence of both a transmitral E/A ratio 0.8, and an E/e' ratio 15.⁸ We excluded 10 patients with severe mitral regurgitation and 4 with mitral valve prostheses, as these preclude accurate assessment of diastolic dysfunction and hemodynamics.⁸

Pulmonary hypertension

Tricuspid regurgitation was evaluated by continuous wave Doppler, in the parasternal short axis, right ventricular inflow, and apical 4-chamber views. Consistent with European Society of Cardiology recommendations, we considered a tricuspid regurgitant jet velocity (TRV) 2.9 m/s to be evidence of PH, with or without additional echocardiographic signs such as left ventricular septal flattening or dilated inferior vena cava.¹⁴ The relationship between the TRV and the pulmonary artery systolic pressure (PASP) is described by the modified Bernoulli equation ($PASP = 4 \times TRV^2 + \text{right atrial pressure}$). Thus, a TRV of 2.9 m/s represents a PASP of approximately 40 mmHg.

Clinical Covariates

Blood pressure, anthropometry, and detailed medical histories were acquired at the time of the index visit to the Cardiorenal Clinic. Comorbidities, medications, and laboratory values were abstracted from the medical record. Patient sex, race, age, education level, and smoking were self-reported.

Outcomes

As a member of the Organ Procurement and Transplantation Network, our hospital maintains a quality performance database for all patients referred for kidney transplantation. Occurrences and dates of kidney transplants and deaths are recorded, as is the date of last patient contact within our healthcare system. The United Network for Organ Sharing notifies the UNC Center for Transplant Care should kidney transplantation occur outside our healthcare system. Patients are classified as “removed”, “ineligible”, or “not followed” if no longer candidates for kidney transplantation; however, the database continues to collect deaths and dates of last contact within the healthcare system. For quality assurance, we additionally searched the electronic health records and online obituaries for dates of last contact and mortality outcomes. For our analysis, follow up time was censored at the date of last contact or 5 years following the index visit to the Cardiorenal Clinic, whichever came first.

Statistical Analysis

All statistical analyses were carried out using SAS 9.4 (SAS Institute; Cary, NC). Continuous variables were assessed for normality and compared using 2-sample t-tests or Wilcoxon rank sums tests, as appropriate. Categorical variables were compared using χ^2 tests. The association between PH and 5-year hazard of death was analyzed using Cox regression, adjusting for baseline variables (age, race, sex, body mass index, diabetes mellitus, coronary artery disease, stroke, dialysis vintage) as well as kidney transplantation (which was treated as a time-varying covariate).¹⁵ Modification of the mortality hazard ratio by PH type was assessed by constructing separate models for patients with and without eLAP, and by testing multiplicative interaction.

Results

From 2006-2013, a total of 1018 patients enrolled in the UNC Cardiorenal registry. Of these, 799 (78%) were evaluated by transthoracic echocardiography within 6 months of the registry clinical visit, as part of the preoperative workup. After the exclusion of 4 patients with mitral valve replacement, 10 with severe mitral regurgitation, and 7 patients with no linking records in the UNC Center for Transplant Care quality performance database, a total of 778 remained. The selection flow chart is shown in Figure S1. At baseline, the mean age was 56 years. Most patients were black (64%) and male (56%). The median follow-up time was 4.4 (IQR: 2.2 – 5.0) years overall, and 5.0 (IQR: 3.1 – 5.0) years for patients without a recorded death. A total of 179 (23%) received a kidney transplant within 5 years of the index visit to the Cardiorenal Clinic, with a median wait time of 2.1 (IQR: 0.9 – 3.2) years after the cardiorenal registry visit. A quarter of the patients (n=195) died during the observation period.

PH was identified in 97 (12%) patients, with a mean TRV of 3.2 m/s (estimated PASP = 50 mmHg). Demographics, comorbidities, and medications were largely similar between patients with and without PH (Table 1). However, patients with PH more often had CKD necessitating dialysis (85% vs. 72%) and atrial fibrillation (20% vs. 6%). Patients with PH also had a greater prevalence of echocardiographic abnormalities, including moderate or

severe left ventricular hypertrophy (39% vs. 21%), eLAP [or equivalently, grade 2 diastolic dysfunction] (45% vs. 16%), moderate or severe left atrial dilation (44% vs. 11%), and mitral annular calcification (56% vs. 24%). Left ventricular systolic dysfunction was rare, but more common in patients with PH (6% vs. 2%). As unadjusted longitudinal outcomes, patients with PH were slightly less likely to receive a kidney transplant (15% vs. 24%) and had nearly twice the mortality (41% vs. 23%).

Among the subset of patients identified with eLAP, PH was associated with lower body mass index (28 vs. 30 m/kg²) and less prevalent diabetes mellitus (57% vs. 77%), but greater prevalence of atrial fibrillation (18% vs. 7%), Table 2. In the absence of eLAP, comorbidities were comparable irrespective of PH, except atrial fibrillation, which was likewise more prevalent with PH (21% vs. 6%).

Mean TRV values among patients with PH did not differ by presence of eLAP (3.2 m/s for both groups). Similarly, extreme TRV values ≥ 3.5 m/s were equally distributed among patients with PH, irrespective of eLAP (Figure S2). Left ventricular hypertrophy was comparable for patients with PH with vs. without eLAP (41% and 38%). However, left atrial dilation was more prevalent for PH with eLAP, compared to PH without eLAP (52% vs. 38%).

As unadjusted longitudinal outcomes, kidney transplantation (20% vs. 17%) and death (34% vs. 31%) were comparable among patients with eLAP, irrespective of PH. However, in the absence of eLAP, patients with PH less often received kidney transplantation (11% vs. 25%) and had higher mortality (47% vs. 21%). As shown in Figure 1, the best 5-year survival was observed for patients with neither PH nor eLAP. Survival was lower in patients with eLAP, irrespective of PH; however, the worst survival was observed among patients with PH in the absence of eLAP.

After adjustments for baseline factors (age, race, sex, body mass index, diabetes mellitus, coronary artery disease, stroke, and dialysis vintage) as well as kidney transplantation (which was treated as a time-varying covariate), PH was associated with twice the hazard of 5-year mortality (HR = 2.11; 95% CI: 1.48 – 3.03). The association between PH and mortality was stronger in the absence eLAP (HR = 2.87; 95% CI: 1.83 – 4.49) than in patients with eLAP (HR = 1.11; 95% CI: 0.57 – 2.17); *P* for interaction = 0.01. When compared to a reference group of patients with neither PH nor eLAP, the highest adjusted mortality was observed for patients with PH without eLAP (HR = 2.96; 95% CI: 1.90 – 4.61), followed by patients with PH and eLAP (HR = 1.65; 95% CI: 0.95 – 2.86), and eLAP in the absence of PH (1.53; 95% CI: 1.03 – 2.27).

Because physiology and outcomes may differ by dialysis status, we constructed separate survival analyses for patients who were on dialysis at the time of referral for kidney transplantation (N=577), and the subset (N=201) who had not yet initiated dialysis at the study start. Among the patients who were on dialysis at the index visit, 156 (27%) deaths occurred, and 119 (21%) received kidney transplantations. In mortality models adjusted identically to the primary analysis, PH was associated with an increased risk of death (HR = 1.77; 95% CI: 1.20 – 2.74), with stronger associations in the absence of eLAP (HR = 2.54;

95% CI: 1.52 – 4.24) than with eLAP (HR = 0.92; 95% CI: 0.45 – 1.89); P for interaction = 0.03. Kaplan-Meier survival curves are shown in Figure S3. Of the 201 patients who were not on dialysis at the cardiorenal registry visit, 43 subsequently transitioned to hemodialysis. Censoring follow up at the time of dialysis initiation yielded a median 3.5 (IQR: 1.2 – 5.0) years of observation for patients not yet on dialysis. During this time, 35 (17%) deaths occurred, and 32 (16%) patients received kidney transplants. Mortality was high for patients with PH, both in the absence of eLAP (6 deaths out of 12 total patients, 50%), and for PH with eLAP (2 deaths of 3 total patients, 67%); however, stratified sample sizes and numbers of events were too small to analyze comprehensively. Kaplan Meier Survival curves are shown in Figure S4.

Finally, we examined posttransplantation outcomes associated with PH and eLAP. Among the 179 kidney transplant recipients, a total of 17 deaths occurred during a median 1.2 (IQR: 0.3 – 1.9) years posttransplantation. The lowest mortality was observed among patients with neither PH nor eLAP (11 deaths out of 146 recipients, 8%), with comparable mortality among patients with PH with eLAP (2 deaths out of 9 recipients, 22%), PH without eLAP (1 death out of 6 recipients, 17%), and eLAP without PH (3 deaths out of 18 recipients, 17%). Posttransplantation Kaplan Meier curves are shown in Figure S5. However, the stratified sample sizes and numbers of events were too low to examine comprehensively in adjusted models.

Discussion

In this analysis of 778 patients who were evaluated for kidney transplantation, we identified PH in 12%, with a mean TRV of 3.2 m/s. Nearly half (45%) of the patients presenting with PH had evidence of eLAP. During the 5-year follow up period, 23% of patients received a kidney transplant and 25% died. After adjustments, PH was associated with twice the hazard of 5-year mortality. However, the mortality risk associated with PH was only noteworthy in patients without eLAP (HR = 2.87; 95% CI: 1.83 – 4.49). There was no mortality risk associated with PH in patients with eLAP (HR = 1.11; 95% CI: 0.57 – 2.17).

The diverse etiology of PH in patients with severe CKD may explain the heterogeneity in mortality risk. By consensus of the World Health Organization, PH is divided into 5 distinct groups based on the underlying pathologies.¹⁶ These include true pulmonary vascular arteriopathy (group 1), PH secondary to left heart disease (group 2), PH secondary to lung disease (group 3), PH secondary to pulmonary artery obstruction (group 4), and miscellaneous causes (group 5). Reflecting the multiple mechanisms responsible for PH in association with impaired renal function, PH in patients with CKD is classified as Type 5.¹⁶ Previous research suggests that PH observed in advanced CKD is often associated with left heart disease.^{1–4} Hypertension, volume overload, and uremic toxins accompanying advanced CKD are known to promote left ventricular remodeling, fibrosis, and diastolic dysfunction,⁷ which may lead to eLAP,¹⁷ high pulmonary venous pressures, and subsequent elevation in pulmonary arterial pressures.⁸ Longstanding eLAP may also be associated with pulmonary venous remodeling, contributing further to high PASP.¹⁸

In our registry patients, left heart disease was a common etiology of PH, with approximately half the patients with PH showing evidence of eLAP. Left atrial pressures rise with severe mitral regurgitation, volume expansion due to renal insufficiency, and elevations in left ventricular diastolic filling pressure, which may be related to myocardial fibrosis and impaired left ventricular relaxation. To date, the reported prevalence of eLAP in patients with PH and advanced CKD has been limited to highly selected populations undergoing right heart catheterization. An example of this, the Prevalence of Precapillary Pulmonary Arterial Hypertension in Patients with End-Stage Renal Disease (PEPPER) study, examined 62 patients with advanced CKD and symptoms of dyspnea.⁹ In contrast to this small invasive study, we examined 778 patients by echocardiography, which is appropriate for screening a broader range of patients. We identified eLAP by a transmitral E/A > 0.8 and an E/e' > 15, which together correspond to grade 2 diastolic dysfunction (impaired left ventricular relaxation with eLAP). Other large echocardiographic screenings of PH inferred diastolic dysfunction by an E/A ratio <1 and either isovolumic relaxation time > 110 ms or an E-wave deceleration time > 240 ms,¹⁰ or by left ventricular mass.¹¹ These definitions do not discriminate between impaired left ventricular relaxation (stage 1 diastolic dysfunction) and impaired relaxation with eLAP (stage 2 diastolic dysfunction).⁸

In patients with advanced CKD, chronic volume overload is a recognized cause of eLAP, hypertension, left ventricular remodeling, arrhythmias, and death.^{17,19} We observed worse survival in patients with eLAP, which is consistent with previous studies examining volume expansion in patients with advanced CKD.^{20,21} In our registry, the patients with the best 5-year survival had neither PH nor eLAP. When compared to this group, patients with eLAP had an increased risk of mortality, irrespective of PH presence. However, the worst survival was observed for patients with PH in the absence of eLAP. It is possible that PH without eLAP may reflect more severe pulmonary vascular disease, with less influence from volume overload. In a single study, right heart catheterization before and after hemodialysis demonstrated a contributory role of volume from interdialytic weight gain to PH with eLAP. On average, pulmonary artery systolic pressures were reported to decrease 7 mmHg following dialysis, and in a few cases, PH resolved following hemodialysis.⁹ Although some investigators advocate echocardiography assessments immediately after dialysis,⁴ interdialytic assessments may be a more durable reflection of the PH burden over time. Additionally, volume overload may persist following dialysis, with nearly a third of hemodialysis patients routinely dialyzed above their specified target weight.²¹ Hemodialysis patients in our registry were imaged the day before their dialysis session. Our study results suggest that echocardiographic evaluations 1 day prior to hemodialysis effectively stratify the mortality risk associated with PH, with greater risk associated with PH in the absence of eLAP.

The causes of PH without eLAP in patients with advanced CKD are likely multifactorial. Potential contributors may include vasculopathies (eg, intimal hyperplasia, medial fibrosis, or medial calcification) leading to arteriosclerosis and increased pulmonary vascular resistance. Although we did not have measures of endothelial activation, previous research suggests endothelin-1 and asymmetric dimethylarginine are elevated in the setting of advanced CKD.²² This may contribute to PH by diminishing bioavailability of nitric oxide and impairing endothelial regulation of vascular tone. Parathyroid hormone is associated

with cellular calcium uptake, and calcifications of the lung, pulmonary vessels, heart, and kidney are commonly observed in patients with hyperparathyroidism secondary to ESRD.²³ Fibroblast growth factor 23, a regulator of phosphorus and vitamin D homeostasis, may also contribute to arterial stiffening in patients with advanced CKD; however, its role in vascular calcification is not well established.^{24,25} In our registry patients, mitral annular calcification was more prevalent with PH, which may suggest a contributory role of extraosseous calcification in PH. Alternatively, a hyperdynamic cardiac output may contribute to high PASP. Anemia, a common comorbidity of advanced CKD, is compensated by increased cardiac stroke volume, which augments blood flow and pressure in the pulmonary artery. Surprisingly, we did not observe a difference in hematocrit levels among patients with vs. without PH in our registry. Elevated stroke volume has also been reported with arteriovenous fistulas,^{26,27} possibly explaining the greater prevalence of PH among hemodialysis patients in our registry. However, the role of arteriovenous shunts in the development of PH remains controversial.^{28,29} Because kidney transplantation is contraindicated for patients with significant respiratory illness, interstitial lung disease is not a likely cause of PH in our registry patients. However, microbubbles originating from the dialyzer have been postulated to increase pulmonary vascular resistance, by obstructing pulmonary capillaries and inducing ischemia.³⁰ Another potential cause may be chronic pulmonary embolism, possibly from platelet aggregation in the fistula graft or dialysis lines.³¹

This large registry of patients evaluated for kidney transplantation has some limitations. Dry weight was not measured as part of our cardiorenal registry. We also lacked information concerning pulmonary arterial hypertension medications. Echocardiograms were performed and interpreted in a clinical, “real world” setting, and included visual assessments typical in clinical echocardiography. Mitral annular calcification severity was not reported and may have influenced tissue Doppler measurements in some patients. On the other hand, all echocardiograms were interpreted by the same cardiologist, contributing standardization to these data. Although echocardiography is a valuable method for characterizing hemodynamics in large patient cohorts, right heart catheterization remains the “gold standard” for measurement of PASP and left atrial pressure.

In conclusion, the mortality risk associated with PH in patients evaluated at the initial referral for kidney transplantation appears to differ by its etiologic subtype. Patients with PH in the absence of eLAP are at high risk of death and in need of focused attention. Future research efforts should investigate the causes of PH without eLAP, and potential strategies to improve outcomes for these patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments:

The authors thank the participants of the UNC Cardiorenal Registry.

Financial Disclosures

This project was supported by the National Center for Advancing Translational Sciences (NCATS), National Institutes of Health, through Grant Award Number UL1TR001111. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

References:

1. Bolignano D, Rastelli S, Agarwal R, et al. Pulmonary hypertension in CKD. *Am J Kidney Dis*. 2013;61(4):612–622. [PubMed: 23164943]
2. Kavar B, Ellam T, Jackson C, et al. Pulmonary hypertension in renal disease: epidemiology, potential mechanisms and implications. *Am J Nephrol*. 2013;37(3):281–290. [PubMed: 23548763]
3. Sise ME, Courtwright AM, Channick RN. Pulmonary hypertension in patients with chronic and end-stage kidney disease. *Kidney Int*. 2013;84(4):682–692. [PubMed: 23739239]
4. 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(1):166–181. [PubMed: 26985742]
5. Tang M, Batty JA, Lin C, et al. Pulmonary hypertension, mortality, and cardiovascular disease in CKD and ESRD patients: a systematic review and meta-analysis. *Am J Kidney Dis*. 2018;72(1):75–83. [PubMed: 29429751]
6. 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(9):3090–3096. [PubMed: 20299337]
7. Middleton RJ, Parfrey PS, Foley RN. Left ventricular hypertrophy in the renal patient. *J Am Soc Nephrol*. 2001;12(5):1079–1084. [PubMed: 11316868]
8. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2016;29(4):277–314. [PubMed: 27037982]
9. Pabst S, Hammerstingl C, Hundt F, et al. Pulmonary hypertension in patients with chronic kidney disease on dialysis and without dialysis: results of the PEPPER-study. *PLoS One*. 2012;7(4):e35310. [PubMed: 22530005]
10. Bozbas SS, Akcay S, Altin C, et al. Pulmonary hypertension in patients with end-stage renal disease undergoing renal transplantation. *Transplant Proc*. 2009;41(7):2753–2756. [PubMed: 19765426]
11. Agarwal R. Prevalence, determinants and prognosis of pulmonary hypertension among hemodialysis patients. *Nephrol Dial Transplant*. 2012;27(10):3908–3914. [PubMed: 22290987]
12. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification. *Eur J Echocardiogr*. 2006;7(2):79–108. [PubMed: 16458610]
13. Zoghbi WA, Enriquez-Sarano M, Foster E, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr*. 2003;16(7):777–802. [PubMed: 12835667]
14. Bossone E, D'Andrea A, D'Alto M, et al. Echocardiography in pulmonary arterial hypertension: from diagnosis to prognosis. *J Am Soc Echocardiogr*. 2013;26(1):1–14. [PubMed: 23140849]
15. Allison PD. *Survival Analysis Using SAS: A Practical Guide*, Second Edition. 2nd ed. Cary, NC: SAS Institute; 2010:324.
16. Simonneau G, Robbins IM, Beghetti M, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol*. 2009;54(1 Suppl):S43–S54. [PubMed: 19555858]
17. Ritz E, Wanner C. The challenge of sudden death in dialysis patients. *Clin J Am Soc Nephrol*. 2008;3(3):920–929. [PubMed: 18372318]
18. Fayyaz AU, Edwards WD, Maleszewski JJ, et al. Global pulmonary vascular remodeling in pulmonary hypertension associated with heart failure and preserved or reduced ejection fraction. *Circulation*. 2018;137(17):1796–1810. [PubMed: 29246894]
19. Zoccali C, Benedetto FA, Tripepi G, et al. Cardiac consequences of hypertension in hemodialysis patients. *Semin Dial*. 2004;17(4):299–303. [PubMed: 15250922]

20. Movilli E, Camerini C, Gaggia P, et al. Magnitude of end-dialysis overweight is associated with all-cause and cardiovascular mortality: a 3-year prospective study. *Am J Nephrol*. 2013;37(4):370–377. [PubMed: 23548380]
21. Flythe JE, Kshirsagar AV, Falk RJ, et al. Associations of posthemodialysis weights above and below target weight with all-cause and cardiovascular mortality. *Clin J Am Soc Nephrol*. 2015;10(5):808–816. [PubMed: 25862779]
22. Zoccali C The endothelium as a target in renal diseases. *J Nephrol*. 2007;20 Suppl 12:S39–S44. [PubMed: 18050141]
23. 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(4):353–360. [PubMed: 16775448]
24. Bundy JD, Chen J, Yang W, et al. Risk factors for progression of coronary artery calcification in patients with chronic kidney disease: the CRIC study. *Atherosclerosis*. 2018;271:53–60. [PubMed: 29459266]
25. Lunyera J, Scialla JJ. Update on chronic kidney disease mineral and bone disorder in cardiovascular disease. *Semin Nephrol*. 2018;38(6):542–558. [PubMed: 30413250]
26. 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(8):1686–1692. [PubMed: 15840664]
27. 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(25):2809–2818. [PubMed: 31045455]
28. 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(2):49–53. [PubMed: 19124358]
29. 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(4):398–402. [PubMed: 20854331]
30. Yigla M, Abassi Z, Reisner SA, et al. Pulmonary hypertension in hemodialysis patients: an unrecognized threat. *Semin Dial*. 2006;19(5):353–357. [PubMed: 16970730]
31. Wang IK, Shen TC, Muo CH, et al. Risk of pulmonary embolism in patients with end-stage renal disease receiving long-term dialysis. *Nephrol Dial Transplant*. 2017;32(8):1386–1393. [PubMed: 27448674]

Figure 1:

Unadjusted 5-year survival probabilities since the time of referral for kidney transplantation, comparing patients with vs. without pulmonary hypertension and present vs. absent elevated left atrial pressure. The UNC Cardiorenal Registry.

+PH +eLAP = pulmonary hypertension with elevated left atrial pressure

+PHT -eLAP = pulmonary hypertension without elevated left atrial pressure

-PHT +eLAP = no pulmonary hypertension but elevated left atrial pressure

-PHT -eLAP = no pulmonary hypertension and normal left atrial pressure

Table 1:

Baseline demographics and clinical characteristics of patients evaluated for kidney transplantation, stratified by presence of pulmonary hypertension*. The UNC Cardiorenal Registry, 2006-2013.

Characteristic	Pulmonary Hypertension (N=97)	No Pulmonary Hypertension (N=681)	P-value
<i>Demographics</i> No. (%) or Mean $\pm$ S.D.			
Age (years)	57 $\pm$ 12	56 $\pm$ 10	0.2
Male	58 (60%)	379 (56%)	0.4
Black	67 (70%)	427 (63%)	0.2
<i>Medical History</i>			
Current smoker	12 (12%)	65 (10%)	0.4
Body mass index (kg/m ²)	29 $\pm$ 7	30 $\pm$ 6	0.3
Systolic blood pressure (mmHg)	149 $\pm$ 29	146 $\pm$ 28	0.2
Diastolic blood pressure (mmHg)	82 $\pm$ 16	83 $\pm$ 14	0.8
Dialysis	82 (85%)	495 (72%)	0.01
Hemodialysis	74 (90%)	399 (81%)	0.04
Peritoneal dialysis	8 (10%)	96 (19%)	0.04
Dialysis vintage (years)	3.5 $\pm$ 2.9	2.9 $\pm$ 2.6	0.07
Diabetes mellitus	51 (53%)	396 (58%)	0.3
Coronary artery disease	23 (24%)	126 (19%)	0.2
Stroke	17 (18%)	82 (12%)	0.1
Atrial fibrillation	19 (20%)	43 (6%)	<0.0001
Hematocrit (%)	35 $\pm$ 5	36 $\pm$ 5	0.1
<i>Echocardiography</i>			
Ejection fraction (%)	56 $\pm$ 10	58 $\pm$ 7	0.05
Left ventricular systolic dysfunction	6 (6%)	15 (2%)	0.02
Left ventricular hypertrophy	38 (39%)	142 (21%)	<0.0001
Elevated left atrial pressure	44 (45%)	106 (16%)	<0.0001
Left atrial dilation	43 (44%)	74 (11%)	<0.0001
Mitral annular calcification	54 (56%)	163 (24%)	<0.0001
<i>Medications</i>			
ACE inhibitor	40 (41%)	227 (33%)	0.1
Angiotensin receptor blocker	16 (16%)	128 (19%)	0.6
Aspirin	53 (55%)	361 (53%)	0.8
Beta blocker	69 (71%)	412 (61%)	0.04
Diuretic	30 (31%)	207 (30%)	0.9
Antihypertensive	90 (93%)	596 (88%)	0.1
Statin	37 (38%)	352 (52%)	0.01

* Pulmonary hypertension defined by a tricuspid regurgitant jet velocity $\geq$ 2.9 m/s

S.D. = standard deviation, ACE = angiotensin converting enzyme

Baseline demographics and clinical characteristics of patients evaluated for kidney transplantation, stratified by presence of pulmonary hypertension with or without elevated left atrial pressure. The UNC Cardiorenal Registry, 2006-2013.

Table 2:

With Elevated Left Atrial Pressure			Without Elevated Left Atrial Pressure			
	PHT N=44	No PHT N=106	P-value	PHT N=53	No PHT N=575	P-value
No. (%) or Mean ± S.D.						
<i>Demographics</i>						
Age (years)	57 ± 12	55 ± 10	0.2	57 ± 13	56 ± 10	0.4
Male	25 (57%)	57 (54%)	0.7	33 (62%)	322 (56%)	0.4
Black	26 (59%)	67 (63%)	0.6	41 (77%)	360 (63%)	0.03
<i>Medical History</i>						
Current smoker	7 (16%)	12 (11%)	0.4	5 (9%)	53 (9%)	1.0
Body mass index (kg/m ²)	28 ± 5	30 ± 6	0.05	30 ± 8	30 ± 6	1.0
Systolic blood pressure (mmHg)	151 ± 29	155 ± 27	0.5	148 ± 29	144 ± 28	0.4
Diastolic blood pressure (mmHg)	81 ± 16	82 ± 12	0.8	84 ± 16	83 ± 14	0.8
Dialysis	41 (93%)	91 (86%)	0.4	41 (77%)	404 (70%)	0.3
Diabetes mellitus	25 (57%)	82 (77%)	0.01	26 (49%)	314 (55%)	0.4
Coronary artery disease	13 (30%)	28 (26%)	0.7	10 (19%)	98 (17%)	0.7
Stroke	10 (23%)	16 (15%)	0.3	7 (13%)	66 (11%)	0.7
Atrial fibrillation	8 (18%)	7 (7%)	0.03	11 (21%)	36 (6%)	0.0001
Hematocrit (%)	35 ± 4	36 ± 5	0.5	36 ± 5	36 ± 5	0.3
<i>Echocardiography</i>						
Ejection fraction (%)	57 ± 10	56 ± 9	0.5	55 ± 10	58 ± 7	0.02
Left ventricular systolic dysfunction	2 (5%)	5 (5%)	1.0	4 (8%)	10 (2%)	0.02
Left ventricular hypertrophy	18 (41%)	31 (29%)	0.2	20 (38%)	111 (19%)	0.006
Left atrial dilation	23 (52%)	26 (25%)	0.001	20 (38%)	48 (8%)	<0.0001
Mitral annular calcification	27 (61%)	41 (39%)	0.01	27 (51%)	122 (21%)	<0.0001

PHT = pulmonary hypertension, defined by a tricuspid regurgitant jet velocity ≥ 2.9 m/s

S.D. = standard deviation