Cardiovascular Outcomes in Kidney Transplant Recipients With ADPKD

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Introduction: Cardiovascular disease leads to high morbidity and mortality in patients with kidney failure. Autosomal Dominant Polycystic Kidney Disease (ADPKD) is a systemic disease with various cardiac abnormalities. Details on the cardiovascular profile of patients with ADPKD who are undergoing kidney transplantation (KT) and its progression are limited.

Methods: Echocardiographic data within 2 years before KT (1993–2020), and major adverse cardiovascular events (MACEs) after transplantation were retrieved. The primary outcome is to assess cardiovascular abnormalities on echocardiography at the time of transplantation in ADPKD as compared with patients without ADPKD matched by sex (male, 59.4%) and age at transplantation (57.2 ± 8.8 years).

Results: Compared with diabetic nephropathy (DN, $n = 271$) and nondiabetic, patients without ADPKD (NDNA) ($n = 271$) at the time of KT, patients with ADPKD ($n = 271$) had lower rates of left ventricular hypertrophy (LVH) (39.4% vs. 66.4% vs. 48.6%), mitral (2.7% vs. 6.3% vs. 7.45) and tricuspid regurgitations (1.8% vs. 6.6% vs. 7.2%). Patients with ADPKD had less diastolic (25.3%) and systolic (5.6%) dysfunction at time of transplantation. Patients with ADPKD had the most favorable post-transplantation survival (median 18.7 years vs. 12.0 for diabetic nephropathy [DN] and 13.8 years for nondiabetic non-ADPKD [NDNA]; $P < 0.01$) and the most favorable MACE-free survival rate (hazard ratio = 0.51, $P < 0.001$). Patients with ADPKD had worsening of their valvular function and an increase in the sinus of Valsalva diameter post-transplantation (38.2 vs. 39.9 mm, $P < 0.01$).

Conclusion: ADPKD transplant recipients have the most favorable cardiac profile pretransplantation with better patient survival and MACE-free survival rates but worsening valvular function and increasing sinus of Valsalva diameter, as compared with patients with other kidney diseases.

ADPKD is the most common inherited kidney disease worldwide,[1] and the fourth leading cause of kidney failure.[2] It is mainly caused by mutations to the *PKD1* and *PKD2* genes. *PKD1* mutations cause a more severe disease course, leading to kidney failure 20 years earlier than patients with *PKD2* mutations.[2] ADPKD is characterized by extrarenal involvement in many organs, including liver, pancreas, colon, heart, and blood vessels.[1]

Cardiovascular complications remain a major cause of morbidity and mortality in patients with ADPKD.[3] Cardiovascular pathologies include increased left ventricular (LV) mass,[4] LVH,[3,5,6] valvular heart disease,[3,7] cardiac arrhythmias such as atrial fibrillation,[8] thoracic aortic aneurysms,[9] pericardial effusion,[10] structural diseases such as dilated, hypertrophic, and noncompaction cardiomyopathies,[4] and coronary vessel

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anomalies.[11,12] Mitral valve prolapse (MVP) is the most common cardiac manifestation in ADPKD, encountered in up to 20% of patients.[3,7]

Patients with ADPKD have a similar survival rate compared with the normal population.[13] Nevertheless, the long-term survival of patients with all kidney diseases following renal transplantation remains considerably below that of the general population.[14] The major cause of this finding is the increased risk of cardiovascular disease through all the stages of chronic kidney disease (CKD) preceding KT.[14]

Two previous studies assessed the prevalence of cardiovascular abnormalities in the ADPKD population and compared it to other patients with kidney failure at the time of transplantation, but the number of patients with ADPKD was limited.[15,16] In addition, the control groups of these studies did not include patients with diabetes, who are the most predisposed to cardiovascular disease among patients with patients with CKD.[17] Furthermore, results from studies evaluating post-transplantation cardiovascular outcomes in patients with ADPKD compared with nondiabetic kidney failure patients have been controversial.[18,19]

Kidney failure is a major risk factor for structural and ischemic heart disease.[20] Cardiovascular disease remains the leading cause of mortality in patients with kidney disease. Nevertheless, details on the prevalence of cardiovascular disease and its morbidity in patients with ADPKD with kidney failure undergoing KT and its progression following transplantation are limited.

Our study aimed to evaluate the prevalence of cardiovascular abnormalities on echocardiography in ADPKD at the time of transplantation compared with patients with other causes of kidney failure and examine the overall survival and risk of cardiovascular events post KT.

METHODS

Patient Selection
All adult patients who underwent KT at the Mayo Clinic in Minnesota, Florida, and Arizona in the United States were identified ($n = 3377$). This study included patients ≥18 years of age that had a kidney transplant between 1993 and 2021 and underwent at least 1 echocardiogram testing at Mayo Clinic within 2 years before transplantation ($n = 2736$). The end of the study was defined as the date of last follow-up, graft failure, or death. The diagnosis of ADPKD was based on Ravine's criteria in the presence of positive family history. In the absence of family history, the criteria for diagnosing ADPKD required bilateral kidney enlargement with at least 10 renal cysts in each kidney and absence of clinical features suggestive of other kidney

cystic diseases. Patients without ADPKD were categorized into 2 groups depending on the primary cause of their kidney failure: (i) DN or (ii) NDNA.

Outcome Definitions
The study's primary outcome is to assess the prevalence of cardiac abnormalities on echocardiogram in patients with ADPKD and compare it with the other 2 groups (DN, NDNA) at the time of KT. Secondary outcomes include assessing the following in the ADPKD group: (i) post-transplantation all-cause mortality (patient survival), (ii) post-transplantation MACE-free survival rate, and (iii) the evolution of cardiovascular abnormalities after KT.

Data Collection
Demographics, comorbidities, and clinical data were retrieved from the patients' electronic medical records. Date of birth, sex, race, and smoking history data were obtained using the Mayo Clinic Data Explorer. The remaining data that were obtained after a thorough medical chart review, include the following: dates of KT dialysis initiation, and last follow-up, body mass index at time of transplantation, history of diabetes mellitus and hypertension at the time of transplant, last serum creatinine value before undergoing dialysis or transplantation, and type and date of MACEs. MACE was defined as any incidence of the following events: cerebrovascular event (ischemic or hemorrhagic stroke, transient ischemic attack), myocardial infarction, hospitalization for heart failure, and coronary revascularization (by percutaneous intervention or bypass surgery). Patients with the first event before transplantation were excluded from the MACE analyses. The estimated glomerular filtration rate was calculated using the CKD Epidemiology Collaboration formula. This retrospective cohort study was conducted in accordance with the recommendations of the Mayo Clinic Institutional Review Board. Minnesota Research Authorization was provided for all participants. While conducting this study, we abided by guidelines laid out by the Declaration of Istanbul.

Echocardiography
Transthoracic echocardiograms (TTE) performed within 2 years before KT and up to study end dates were identified through the Mayo Clinic Echocardiographic Laboratory Database. Echo measures were retrieved on excel sheets that were sent to the research team from Mayo Clinic Echocardiographic Laboratory Database. Measured variables were defined based on the Acute Dialysis Quality Initiative XI criteria.[21] LVH was defined as LV mass index > 47 g/m$^{2.7}$ for women and > 50 g/m$^{2.7}$ for men. Indexing LVM to height^7 was

used instead LVM indexed to body surface area to diagnose LVH, because it represents a more sensitive and more accurate method, especially in obese and overweight patients.[22–24] Increased LV end diastolic volume index was defined as >86 ml/m^2 at end of diastole left atrial enlargement was defined as left atrial volume index >34 ml/m^2. A diagnosis of LV systolic dysfunction was made for patients with a LV ejection fraction ≤45%, and right ventricular systolic dysfunction for patients with a lateral tricuspid annulus velocity (S') < 9.5 cm/sec. Other Acute Dialysis Quality Initiative XI criteria included diastolic dysfunction grade ≥2, mitral and/or aortic valvular disease with moderate to severe regurgitation (mitral valve regurgitation, aortic valve regurgitation). Prevalence of MVP and tricuspid valve disease with moderate to severe tricuspid regurgitation was also included in our study. The valvular regurgitation severity was classified based on the American Society of Echocardiography recommendations.[25] Right ventricular systolic pressure was also obtained. Measurements of the aortic root at the sinus of Valsalva, mid ascending aorta, and LV outflow tract diameters were also retrieved. TTE was performed according to American Society of Echocardiography and European Association of Echocardiography guidelines for the assessment of valves and chamber size and function.[26–29]

Genetic Analysis for Patients With ADPKD

The entire coding and flanking intronic regions of *PKD1* and *PKD2* were screened for pathologic variants by Sanger or next-generation sequencing.[30–33] Patients were classified as follows: *PKD1* truncating (*PKD1*^{T}), *PKD1* nontruncating (*PKD1*^{NT}), or *PKD2*.[34]

Statistical Analysis

Using propensity score matching, the 3 groups (ADPKD, DN, NDNA) were matched based on sex and age at KT using the recommended caliper size of 0.25 (SD) of the logit of the propensity score. Data were reported as mean ± SD for continuous variables or percentage for categorical variables. Variables were compared between ADPKD versus DN and ADPKD versus NDNA using paired t-tests for continuous variables and χ^2 test or Fisher exact test for categorical data. Cox proportional hazard regression models were used to estimate the effect of ADPKD on MACE after transplantation, adjusting for hypertension, smoking history, pre-emptive status and body mass index. Overall patient survival and MACE-free survival rates post-transplantation were analyzed using Kaplan-Meier methods, and comparison between groups was performed using log-rank test. McNemar test was used to compare categorical echocardiographic findings before

and after KT (until study end dates) in each group; and the first echocardiogram after transplantation that reported the presence of any categorical variable was used. Linear Mixed models (mixed effects) were used to analyze the progression of sinus of Valsalva diameter pretransplantation and post-transplantation; all available echocardiograms after transplantation were used in this analysis. Mixed models were used because the analysis was done on repeated measurements with missing values and taking into consideration patient to patient variations.[35] A 2-tailed $P < 0.05$ was considered statistically significant. All statistical analyses were conducted using the JMP Pro software version 14.1.0 (SAS Institute, Inc., Cary, NC) and GraphPad Prism version 9.2.0 (GraphPad Software, San Diego, CA). Propensity score matching was done using R version 4.1.1 (R Project, Vienna, Austria).

RESULTS

Baseline Characteristics

Among the 2736 kidney transplant patients with TTEs who met the inclusion criteria, 271 patients in each group (ADPKD, DN, and NDNA) were included after propensity matching for sex and age at transplantation (Figure 1). Baseline demographics, kidney and genetic characteristics are summarized in Table 1. In each of the 3 groups, 59.4% of the subjects were males, and the mean (SD) age at KT was 57.2 (8.8) years. A higher proportion of patients with ADPKD underwent pre-emptive KT (64%) as compared with patients with DN (55.0%, $P < 0.001$) or NDNA (39.5%, $P = 0.02$). Age at dialysis initiation and time spent on dialysis pretransplant were comparable among the 3 groups. Nevertheless, patients with ADPKD were more frequently hypertensive at the time of transplantation (94%) as compared with DN (88.1%, $P < 0.001$) or NDNA (80%, $P < 0.001$). Only 8.1% of ADPKD patients had diabetes at the time of transplant as compared with 19.9% in NDNA ($P < 0.001$). Among the 104 patients who underwent PKD genotyping, 50 (48.1%) had *PKD1* truncating variants, 39 (37.5%) had *PKD1* nontruncating variants, 8 (7.7%) with *PKD2* variants, and 7 (6.7%) with no pathogenic variants detected.

TTE Findings at the Time of KT

TTE findings among patients with kidney failure within 2 years before KT are presented in Table 2. The mean (±SD) age at TTE was similar among the 3 groups (56.5 ± 8.8 years). The mean time between the first TTE and KT was also similar. LVH was frequently seen in patients with ADPKD (30.9%); however, it was more prevalent in patients with DN (66.4%, $P < 0.001$) and patients with NDNA (48.6%, $P = 0.05$). Left atrial
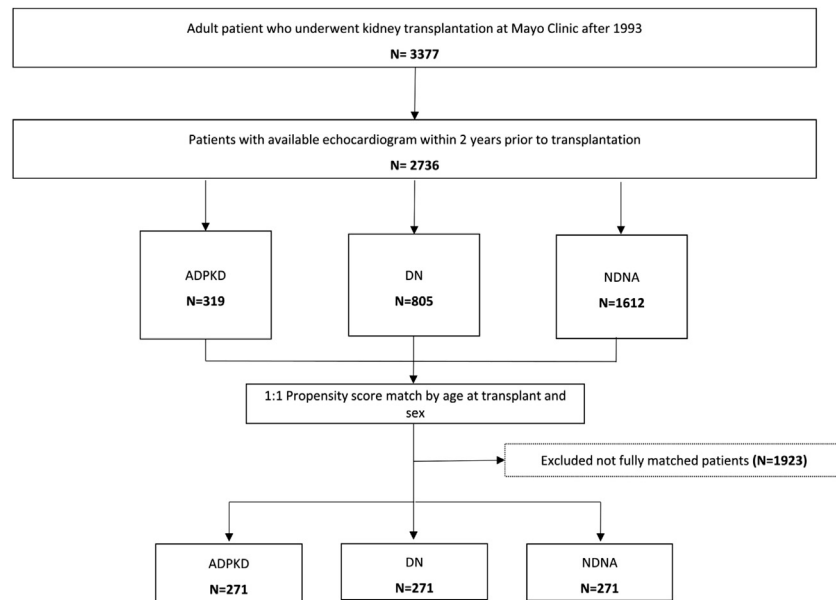
Figure 1. Overview of study flow chart and cohort selection depicting patient exclusions and group assignment based on cause of kidney failure. Using propensity score matching, the 3 groups (ADPKD, DN, NDNA) were matched based on sex and age at kidney transplantation. ADPKD, autosomal dominant polycystic kidney disease; DN, diabetic nephropathy; NDNA, nondiabetic non-ADPKD.

enlargement was seen in 39.3% of ADPKD subjects, compared with 62.6% in DN ($P = 0.001$) and 51.8% in NDNA ($P = 0.08$). LV mass index, LV end-diastolic volume index, left atrial volume index, and right ventricular systolic pressure measurements are summarized in Figure 2a-d.

LV systolic dysfunction was detected in 5.6% of the ADPKD cohort, which was significantly lower

Table 1. Clinical characteristics for patients with ADPKD, DN, and NDNA at time of kidney transplantation

Clinical Characteristics	ADPKD	Diabetic Nephropathy	Nondiabetic, non-ADPKD	P-value ADPKD vs. DN	P-value ADPKD vs. NDNA
n	271	271	271		
Male, n (%)	161 (59.4)	161 (59.4)	161 (59.4)	1.00	1.00
Caucasians, n (%)	250 (92.2)	242 (89.3)	230 (84.5)	0.23	0.007
BMI in kg/m^2, mean (SD)	28.8 (6.2)	30.7 (7.8)	29.3 (6.3)	0.002	0.43
Age at last follow-up in years, mean (SD)	66.9 (10.7)	67.6 (10.4)	66.8 (11.1)		
Age at KT, yrs, mean (SD)	57.2 (8.8)	57.2 (8.8)	57.2 (8.8)		
eGFR closest to RRT in ml/min per 1.73 m^2, mean (SD)	13.3 (6.5)	14.1 (7.3)	13.6 (8.3)	0.47	0.22
Pre-emptive KT, n (%)	174 (64.2)	149 (55.0)	107 (39.5)	<0.001	0.02
Age at dialysis start in years, mean (SD)	56.9 (8.6)	56.2 (9.0)	55.3 (9.1)	0.35	0.57
Time patient spent on dialysis before KT in months, mean (SD)	18.5 (21.9)	21.1 (22.5)	23.0 (25.9)	0.34	0.41
Patients who underwent a second RRT, n (%)	24 (8.9)	36 (13.3)	33 (12.2)	0.005	0.10
Age at second RRT in yrs, mean (SD)	64.2 (7.9)	62.9 (8.6)	63.8 (6.8)	0.78	0.51
Hypertension at time of transplant, n (%)	257 (94.8)	236 (88.1)	216 (80.0)	<0.001	<0.001
Diabetes at time of transplant, n (%)	22 (8.1)	271 (100.0)	54 (19.9)	<0.001	<0.001
PKD genotype, n (%)	104 (38.3)				
PKD1 truncating, n (%)	50 (48.1)				
PKD1 nontruncating, n (%)	39 (37.5)				
PKD2 truncating, n (%)	8 (7.7)				
NMD, n (%)	7 (6.7)				
Causes of kidney failure, (%)	ADPKD (100)	Diabetes mellitus (100)	GN/AI (41.0)		
			Urological (15.8)		
			HTN renal disease (12.9)		
			Unknown (12.3)		
			Cancer/chemo related (10.3)		
			Miscellaneous and genetic syndromes (6.6)		

ADPKD, autosomal dominant polycystic kidney disease; AI, autoimmune; BMI, body mass index; Chemo, chemotherapy; DN, diabetic nephropathy; eGFR, estimated glomerular filtration rate; GN, glomerulonephritis; HTN, hypertension; KT, kidney transplant; NDNA, nondiabetic nephropathy, non-ADPKD; NMD, no mutation detected; PKD, polycystic kidney disease; RRT, renal replacement therapy.

Table 2. Echocardiogram findings among kidney failure patients at time of transplantation based on the Acute Dialysis Quality Initiative proposed criteria

Echocardiogram Variables	ADPKD n = 271	DN n = 271	NDNA n = 271	P-value ADPKD vs. DN	P-value ADPKD vs. NDNA
Age at TTE in yrs, mean (SD)	56.5 (8.8)	56.5 (8.8)	56.5 (8.8)		
Time between TTE and kidney transplant in mo, mean (SD)	8.8 (6.2)	9.3 (6.4)	8.4 (6.1)		
LV size, n	221	214	216		
LV hypertrophy present by LVM/height$^{2.7}$ measurement, n (%)	87 (39.4)	142 (66.4)	105 (48.6)	< 0.001	0.05
LVMI overall in g/m^2, mean (SD)	103.1 (30.9)	116.5 (31.0)	113.0 (60.4)	0.001	0.01
LV volume index, n	22	33	44		
LV volume index diastole >86 ml/m^2, n (%)	11 (50.0)	16 (48.5)	17 (38.6)	0.91	0.37
LV volume index diastole in ml/m^2, mean (SD)	80.2 (19.0)	83.6 (16.8)	82.6 (20.8)	0.53	0.64
LA size, n	84	107	108		
LA enlargement present, n (%)	33 (39.3)	67 (62.6)	56 (51.8)	0.001	0.08
LA volume index in ml/m^2, mean (SD)	33.7 (11.8)	38.9 (12.2)	37.1 (14.3)	0.007	0.07
Diastolic function, n	71	52	54		
Diastolic dysfunction present, n (%)	18 (25.3)	27 (51.9)	23 (42.6)	0.002	0.04
Mitral valve study, n	225	238	231		
Mitral valve prolapse, n (%)	13 (5.8)	3 (1.3)	5 (2.2)	0.008	0.04
≥Moderate mitral valve regurgitation, n (%)	6 (2.7)	15 (6.3)	17 (7.4)	0.06	0.02
Aortic valve study, n	182	153	174		
≥Moderate aortic valve regurgitation, n (%)	5 (2.7)	2 (1.3)	6 (3.4)	0.84	0.70
Tricuspid valve study, n	220	226	236		
≥Moderate tricuspid valve regurgitation, n (%)	4 (1.8)	15 (6.6)	17 (7.2)	0.01	0.006
LVEF, n	230	212	226		
LVEF ≤45%, n (%)	13 (5.6)	31 (14.6)	29 (12.8)	0.002	0.008
Right ventricular pressure, n	192	194	190		
RVSP in mm Hg, mean (SD)	30.7 (8.5)	38.3 (12.1)	33.9 (9.5)	< 0.001	< 0.001
S' in m/sec, n	42	40	64		
S'<9.5 m/sec, n (%)	2 (4.8)	14 (35.0)	7 (10.9)	0.006	0.26

ADPKD, autosomal dominant polycystic kidney disease; DN, diabetic nephropathy; LA, left atrium; LV, left ventricle; LVEF, left ventricular ejection fraction; LVM, left ventricular mass; LVMI, left ventricular mass index; NDNA, nondiabetic non-ADPKD; RVSP, right ventricular systolic pressure; S', Lateral tricuspid annulus peak systolic velocity; TTE, transthoracic echocardiography.

compared with the DN group (14.6%, $P = 0.002$) and NDNA group (12.8%, $P = 0.008$). Similarly, ADPKD had the lowest prevalence of left ventricle diastolic dysfunction among the 3 groups. Left ventricle diastolic dysfunction grade ≥ 2 was reported in 25.3% of patients with ADPKD, compared with 51.9% in DN ($P = 0.002$) and 42.6% in NDNA ($P = 0.04$) (Figure 3a).

ADPKD had the highest prevalence of MVP (5.8%) between the 3 groups (Table 2). The most frequently encountered valvular abnormalities in ADPKD were mitral valve regurgitation and aortic valve regurgitation. The prevalence of mitral valve regurgitation was lower in the ADPKD group (2.7%) compared with 6.3% in DN and 7.4% in NDNA ($P = 0.06$ and $P = 0.02$, respectively). Tricuspid regurgitation prevalence was significantly the lowest in the ADPKD cohort (1.8% vs. 6.6% in DN and 7.2% in NDNA, $P = 0.01$ and $P = 0.006$ respectively) (Figure 3b). Patients with ADPKD had significantly larger sinus of Valsalva, mid ascending aorta, and LV outflow tract diameters irrespective of the sex (Table 3 and Figure 4a–c).

A sensitivity analysis was performed to compare the patients' characteristics for the patients that were excluded from the main analysis due to unavailable match (Supplementary Table S1).

Post-transplantation Overall Survival and MACE-Free Survival

Patient survival post KT was plotted for each of the 3 groups (N = 271). Pateints with ADPKD had a more favorable survival as compared with patients with DN or NDNA ($P < 0.001$) (Figure 5). The median survival post KT was 18.7 years (CI 16.9-N/A) for patients with ADPKD, 12.0 years (CI 10.2–13.7) for patients with DN, and 13.8 years (CI 11.7–15.3) for NDNA. Patients with ADPKD had a lower risk of death compared with patients without ADPKD at any time post KT (hazard ratio = 0.43, CI 0.34–0.55, $P < 0.001$). A total of 63 patients with ADPKD (21.3%) died after transplantation at a mean age of 70.0 ± 8.3 years, compared with 137 patients (46.3%) with DN at a mean age of 64.6 ± 8.8 years and 96 (32.4%) patients with NDNA at a mean age of 67.2 ± 9.4 years.

MACE-free survival post KT was analyzed for all 3 groups by excluding patients who already developed MACE pre-KT (35 patients with ADPKD, 115 patients with DN, and 64 patients with NDNA). Overall,
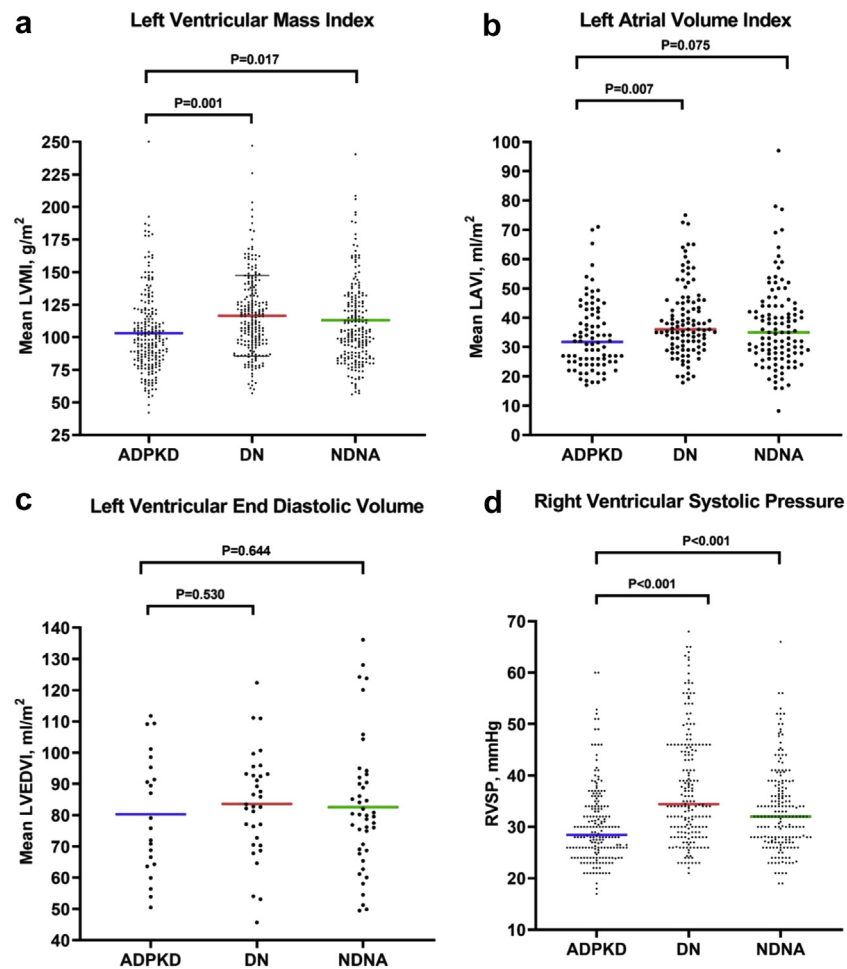
Figure 2. Echocardiography measurements before kidney transplantation comparing patients with ADPKD, DN and NDNA. (a) Mean left ventricular mass index is the lowest in ADPKD group, (b) mean left atrial volume index is the lowest in ADPKD group, (c) LVEDI was similar among all 3 groups, and (d) mean RVSP was lowest in ADPKD group. ADPKD, autosomal dominant polycystic kidney disease; DN, diabetic nephropathy; LVEDI, left ventricular end diastolic volume index; NDNA, nondiabetic non-ADPKD; RVSP, right ventricular systolic pressure.

patients with ADPKD have a more favorable MACE-free survival at any time post transplantation compared with the 2 other groups ($P < 0.001$) (Figure 6 and Table 4).

In the Cox proportional hazard model, having ADPKD was associated with lower risk of MACE during follow-up [hazard ratio = 0.51, 95% CI (0.37–0.70), $P < 0.001$]. This association remained consistent after adjustment for hypertension, smoking history before transplantation, pre-emptive transplant status, and body mass index [hazard ratio = 0.43, 95% CI (0.29–0.63), $P < 0.001$]. The univariable and multivariable Cox proportional hazard models for cumulative MACE and individual events are presented in Table 4.

TTE Findings Pretransplantation Versus Post-transplantation

To compare changes in TTE findings between pre and post KT, patients with 1 TTE before KT and 1 after KT were included. LV systolic and diastolic dysfunction,

LVH and valvular abnormalities are summarized in Table 5 and Figure 7a-e. Patients with ADPKD had more LVH post-KT compared with pre-KT (58.2% vs. 46.6%, $P = 0.03$). The same finding was seen in patients with NDNA when LVH comparing pre and post-KT (66.3% vs. 56.3%, $P < 0.001$). Nevertheless, LVH was similar pre-KT and post-KT in DN (64.6% vs. 65.4%, $P = 0.86$; Figure 7c). All 3 groups had an improved LV systolic function after KT, and the results were statistically significant among the 2 control groups but not in ADPKD ($P = 0.53$) (Figure 7a). Interestingly, only patients with ADPKD had an improved LV diastolic function post-KT. LV diastolic dysfunction (LVDD) grade ≥ 2 was seen in only 22.7% of the patients post-KT compared with 50.0% pre-KT ($P = 0.001$). Patients with DN had an increase in LVDD post-KT (70.6% vs. 58.8%, $P = 0.03$), similarly to the NDNA group (41.2% vs. 35.3%, $P = 0.004$) (Figure 7b). In contrast, all groups had greater regurgitation post-transplant for at least 1 of the mitral, tricuspid, or aortic valves. Patients with ADPKD
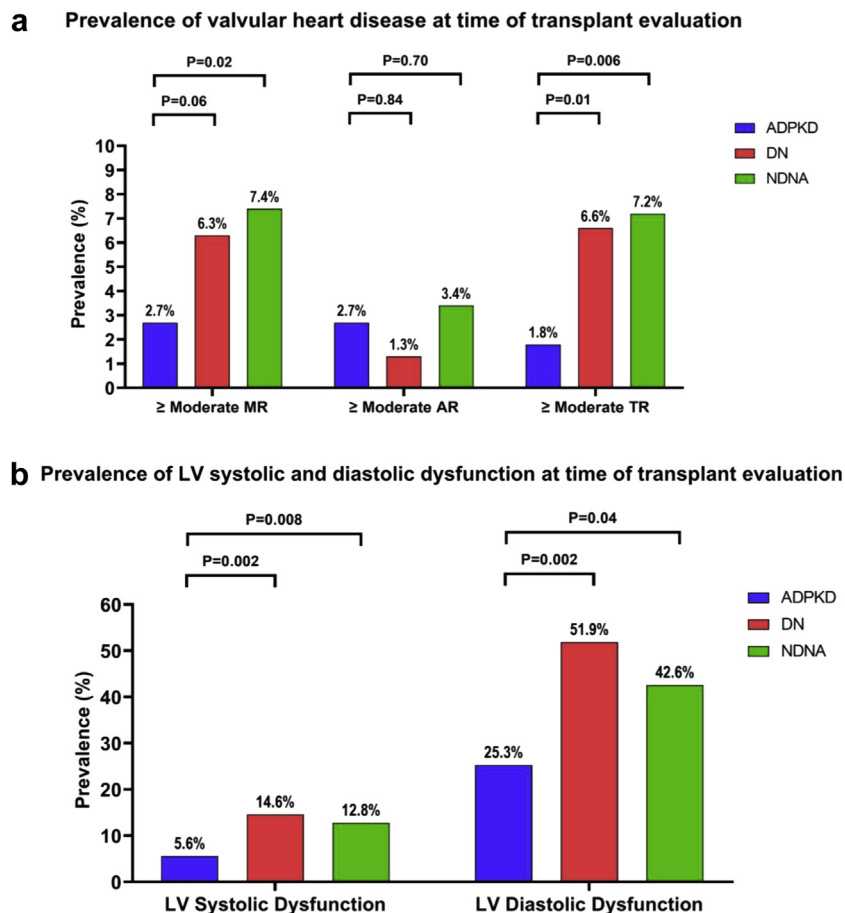
Figure 3. Prevalence of valvular and left ventricular dysfunction comparing the 3 groups, ADPKD, DN, and NDNA at time of transplantation. (a) Prevalence of mitral, aortic, and tricuspid regurgitation. (b) Patients with ADPKD had lower prevalence of moderate to severe mitral valve regurgitation or tricuspid regurgitation but similar aortic valve regurgitation prevalence. Patient with ADPKD had lower prevalence of both left ventricular systolic and diastolic dysfunction as compared to the 2 control groups. ADPKD, autosomal dominant polycystic kidney disease; DN, diabetic nephropathy; NDNA, nondiabetic non-ADPKD.

had the greatest increase in dysfunction post-transplantation among the 3 groups, and it was apparent for the 3 valves (Figure 7d, e, and f). Sinus of Valsalva and mid ascending aortic diameters increased significantly only in ADPKD post-transplantation (Table 6).

DISCUSSION

In this large cohort of age-matched and sex-matched patients, cardiovascular abnormalities identified on echocardiography at the time of kidney transplant evaluation were less common in patients with ADPKD as compared with DN and other kidney disease patients. For example, LV and RV systolic dysfunction, LVH, and tricuspid regurgitation were less prevalent in the ADPKD group as compared with the other kidney disease groups. On the other hand, ADPKD had the largest aortic root and ascending aortic diameters. Overall, patients with ADPKD had a much more favorable outcome for both patient survival and MACE-free survival as compared with the diabetic and

nondiabetic kidney disease groups even after adjustment for potential confounders. Furthermore, patients with ADPKD had an improved systolic and diastolic dysfunction post KT but worsening valvular function.

Structural and functional cardiac abnormalities in ADPKD have been the subject of extensive research over recent decades. The importance of LVH relies on being an independent predictor of poor outcome and all-cause mortality,[3,36] especially in patients with kidney failure.[37–39] The association of ADPKD with LVH remains controversial. Numerous studies indicated an increased LVM and higher prevalence of LVH in ADPKD patients.[4,40] On the other hand, previous studies comparing patients with ADPKD to nondiabetic kidney failure patients on dialysis or after transplantation showed no significant difference in the LVH prevalence.[15,16] In our study, we found that at time of transplantation, patients with ADPKD had less LVH and lower LV mass index as compared with patients without ADPKD. Furthermore, when comparing cardiovascular findings before and after transplantation, we observed an increase in LVH rates post-KT in all

Table 3. Echocardiography measurements before kidney transplantation comparing patients with ADPKD, DN, and NDNA including Sinus of Valsalva diameter, mid ascending aortic diameter, and left ventricular outflow tract diameter

	ADPKD	DN	Nondiabetic, non-ADPKD	P-value	
Echocardiogram Variables	n = 271	n = 271	n = 271	ADPKD vs. DN	ADPKD vs. NDNA
SOV diameter in mm					
Overall, mean (SD)	38.2 (3.8)	33.8 (4.7)	35.9 (5.8)	<0.001	0.004
Males, mean (SD)	40.0 (3.1)	35.7 (4.3)	36.9 (6.4)	<0.001	0.002
Females, mean (SD)	35.0 (2.9)	30.2 (2.9)	34.1 (4.0)	<0.001	< 0.001
Mid ascending aorta diameter in mm					
Overall, mean (SD)	36.5 (4.2)	34.1 (4.2)	35.4 (4.7)	<0.001	0.006
Males, mean (SD)	37.5 (4.1)	34.9 (4.3)	36.2 (5.2)	<0.001	0.04
Females, mean (SD)	34.7 (3.7)	32.6 (3.4)	34.3 (3.7)	<0.001	0.01
LVOT diameter in cm					
Overall, mean (SD)	2.4 (0.2)	2.2 (0.2)	2.2 (0.2)	<0.001	<0.001
Males, mean (SD)	2.5 (0.2)	2.3 (0.2)	2.3 (0.2)	<0.001	<0.001
Females, mean (SD)	2.2 (0.2)	2.0 (0.1)	2.1 (0.1)	<0.001	<0.001

ADPKD, autosomal dominant polycystic kidney disease; DN, diabetic nephropathy; LVOT, left ventricular outflow tract; NDNA, nondiabetic non-ADPKD; SOV, sinus of Valsalva.

groups except DN, who already had a very high prevalence of LVH pretransplantation.

ADPKD is associated with activation of the renin-angiotensin-aldosterone system and the renal sympathetic nervous system,[40] that increase remodeling and thus increasing LVM and LVH.[41] In addition, LVH and increased LVM were widely attributed to the presence of hypertension in the vast majority of patients with ADPKD,[42] and rigorous blood pressure control was associated with a steeper decline in LV mass index compared with patients with a more lenient blood pressure control.[43] Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers remain the cornerstone of hypertension treatment in ADPKD.[44] These medications play a major role in the regression of LVH.[45] The early and aggressive management of hypertension with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers is reported to be the main reason why the prevalence of LVH may be lower in ADPKD compared with other patients with CKD. The HALT PKD trial reported only a 4% prevalence of LVH in its large cohort of hypertensive patients with ADPKD. This finding could be explained by the evolving trend, including earlier detection and treatment of hypertension, more rigorous blood pressure control, and an increased use of renin-angiotensin-aldosterone system antagonists.[46–48] The increase of LVH post transplantation could be attributed to age as LVH correlates directly with LVM which is strongly associated with age increase.[49]

MVP has been heavily linked to ADPKD.[3] Different studies showed that MVP was more common in ADPKD compared with the normal population. Nevertheless,
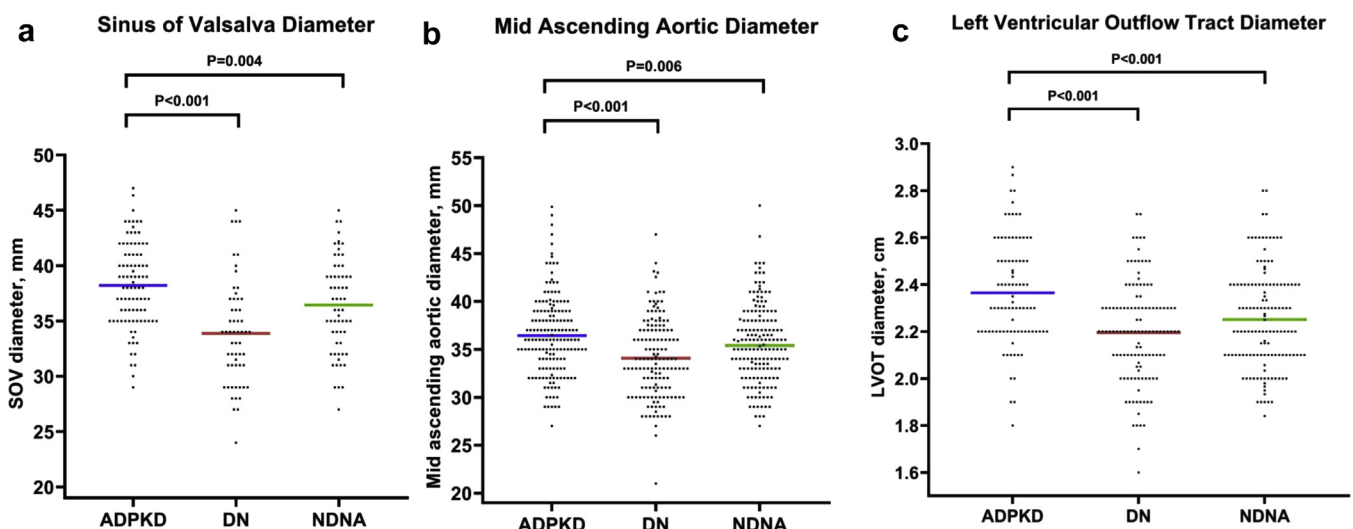

Figure 4. Echocardiography measurements before kidney transplantation comparing patients with ADPKD, DN and NDNA. SOV diameter was larger in (a) patients with ADPKD, (b) mid ascending aortic diameter was larger in ADPKD, and (c) LVOT diameter was also larger in ADPKD. ADPKD, autosomal dominant polycystic kidney disease; DN, diabetic nephropathy; LVOT, left ventricular outflow tract; NDNA, nondiabetic non-ADPKD; SOV, Sinus of Valsalva.
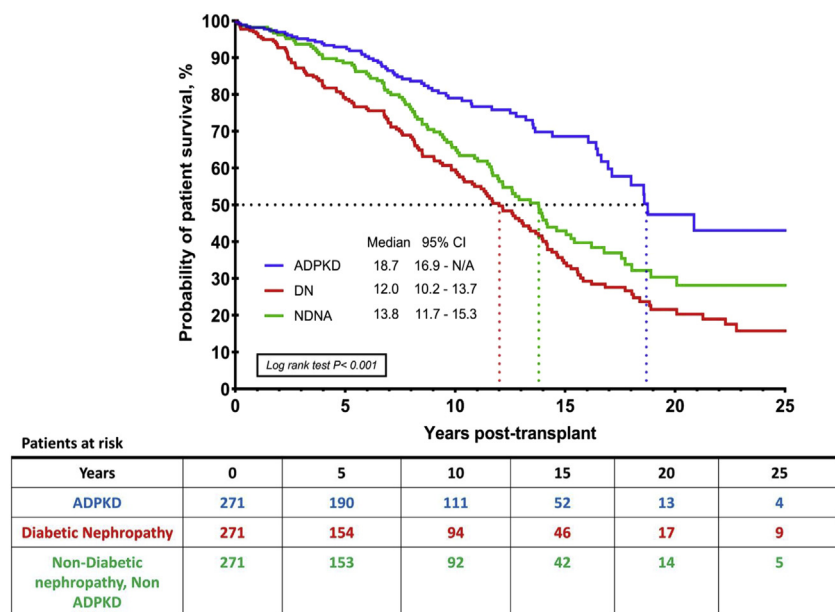
Figure 5. Patient's survival rate from time of kidney transplantation was significantly better in ADPKD as compared with the control groups (DN and NDNA). ADPKD, autosomal dominant polycystic kidney disease; DN, diabetic nephropathy; N/A, not applicable; NDNA, nondiabetic non-ADPKD.

the reported prevalence of MVP was inconsistent, and ranged from 6% to 26%, compared with relatively small control groups.[7,50–52] Our study confirms the higher prevalence of MVP in ADPKD when compared with the largest cohort with age-matched and sex-matched control. Mitral, tricuspid, and aortic regurgitations are common in kidney failure patients.[53,54] ADPKD has also been associated with an increased risk of valvular regurgitation compared with the normal population.[7,50] Our study showed that patients with ADPKD at time of KT have a lower frequency of moderate to severe valvular regurgitation compared with the other control groups.

Our findings are consistent with previous studies that described the association of ADPKD with mild to moderate valvular regurgitation[7,50] and not moderate to severe.[50] Moreover, we demonstrate that patients with ADPKD have a significantly higher aortic root diameter size compared with other patients, which is consistent with previous reports.[55] One possible explanation for the milder valvular findings in patients with ADPKD is the natural history of this progressive disease where
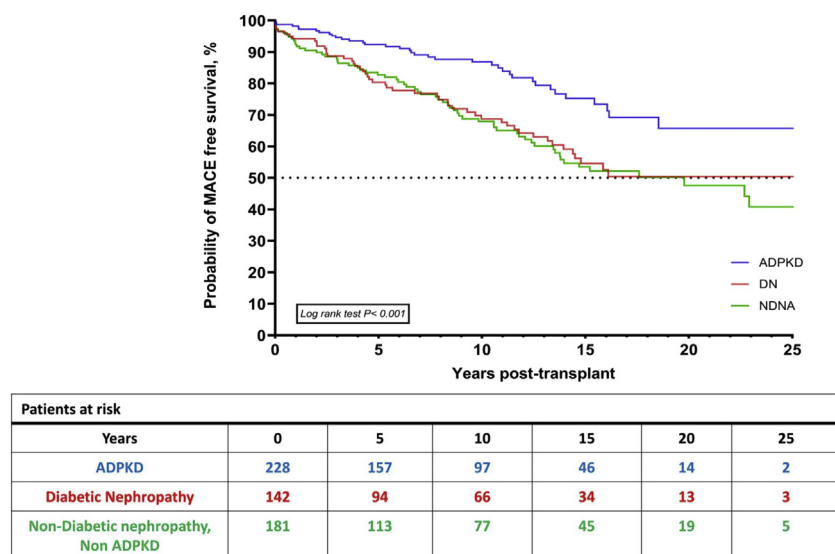

Figure 6. MACE-free survival rate after kidney transplantation was significantly better for ADPKD as compared with the control groups (DN and NDNA). Patients who developed MACE before kidney transplantation were excluded from this analysis. ADPKD, autosomal dominant polycystic kidney disease; DN, diabetic nephropathy; MACE, major adverse cardiovascular event; NDNA, nondiabetic non-ADPKD.

Table 4. Univariable and Multivariable Cox Proportional Hazard Analysis comparing patients with ADPKD to without ADPKD for adverse events

Clinical Variables	Univariable		Multivariable[a]	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Cumulative MACE	0.51 (0.37–0.70)	< 0.001	0.43 (0.29–0.63)	<0.001
Stroke	0.48 (0.26–0.87)	0.02	0.46 (0.25–0.85)	0.01
Myocardial infarction	0.71 (0.40–1.28)	0.26	0.69 (0.22–0.38)	0.69
Revascularization (PCI or CABG)	0.53 (0.28–1.00)	0.05	0.49 (0.26–0.93)	0.03
Hospitalization for congestive heart failure	0.22 (0.08–0.57)	<0.001	0.21 (0.08–0.54)	<0.01

ADPKD, autosomal dominant polycystic kidney disease; CABG, Coronary Artery Bypass Grafting; HR, hazard ratio; MACE, major adverse cardiovascular event; PCI, percutaneous coronary intervention.
[a]Adjusted for hypertension, smoking history, body mass index, pre-emptive transplant status.

patients with ADPKD are typically monitored frequently early in their disease process as compared with patients with other kidney disease, allowing rigorous cardiovascular risk factor management and hypertension control which are essential in valvular regurgitation management.[56]

Interestingly, our study demonstrated that all groups had worsening valvular regurgitation after KT. Nevertheless, the interval decline in valvular function was more pronounced in ADPKD as compared with diabetic and noncystic patients. In addition, only

Table 5. Evolution of LV systolic and diastolic dysfunction, hypertrophy and valvular regurgitation post kidney transplantation for patients with ADPKD, DN, and NDNA

Echocardiogram variables	Before kidney transplant[a]	After kidney transplant	P-value
LV systolic dysfunction n (%)			
ADPKD n = 113	9 (7.96)	7 (6.20)	0.53
DN n = 150	26 (17.33)	25 (16.67)	<0.001
Non-DN, non-ADPKD n = 121	19 (15.7)	15 (12.4)	0.02
LV Diastolic dysfunction n (%)			
ADPKD n = 22	11 (50.00)	5 (22.73)	0.001
DN n = 17	10 (58.82)	12 (70.59)	0.03
Non-DN, non-ADPKD n = 17	6 (35.29)	7 (41.18)	0.004
LVH n (%)			
ADPKD n = 103	48 (46.60)	60 (58.25)	0.03
DN n = 133	87 (65.41)	86 (64.66)	0.86
NDNA n = 110	62 (56.36)	73 (66.36)	<0.001
≥Moderate mitral valve regurgitation, n (%)			
ADPKD n = 110	4 (3.64)	11 (10.00)	0.03
DN n = 166	13 (7.83)	15 (9.04)	0.66
Non-DN, Non-ADPKD n = 124	13 (10.48)	13 (10.48)	1.00
≥Moderate aortic valve regurgitation, n (%)			
ADPKD n = 65	5 (7.69)	11 (16.92)	0.03
DN n = 49	2 (4.08)	2 (4.08)	1.00
Non-DN, non-ADPKD n = 65	6 (9.23)	7 (10.77)	<0.001
≥Moderate tricuspid valve regurgitation, n (%)			
ADPKD n = 102	2 (1.96)	8 (7.84)	0.01
DN n = 155	9 (5.81)	25 (16.13)	<0.001
Non-DN, non-ADPKD n = 127	14 (11.02)	20 (15.75)	<0.001

ADPKD, autosomal dominant polycystic kidney disease; DN, diabetic nephropathy; LV, left ventricular; LVH, left ventricular hypertrophy; NDNA, nondiabetic non-ADPKD.
[a]Within 2 years before kidney transplantation.

patients with ADPKD had an increase in aortic root diameter at the sinus of Valsalva. Sinus of Valsalva enlargement is associated with significant aortic regurgitation.[57,58] The pronounced enlargement of sinus of Valsalva in patients with ADPKD could be explained by the role of abnormal polycystins in altering smooth muscle and endothelial cell functions[9,40]; and in altering the extracellular matrix which could worsens valvular function and aortic root size over time.[9,59] Hypertension plays a role because elevated systolic blood pressure proportionally correlates with an increased risk of valvular heart disease and aortic root dilatation.[60,61] Blood pressure control prevents and halts progression of aortic root disease.[62,63] Thus, early aggressive management of hypertension in ADPKD is essential in preventing the progression of dilated aortic root into aneurysms and dissections.

All patients with kidney disease in our cohort had an improved LV systolic function after transplantation, but only patients with ADPKD had a concomitant improvement in LV diastolic function. Diastolic dysfunction indicates poor ventricular filling and is associated with worse survival and increased heart failure hospitalization.[64] Diastolic function has been reported to worsen throughout CKD stages, especially in ADPKD.[65] KT reduces LVH and improves systolic function; however diastolic dysfunction persisted and even worsened in a proportion of patients post-transplantation.[66–70] Therefore, the finding of improvement in diastolic dysfunction in patients with ADPKD only is intriguing. However, due to the very limited number of patients who underwent a LVDD study pre-KT and post-KT, this finding cannot be generalized, especially considering patients with ADPKD had an increase in LVH post-KT. Further studies evaluating a larger, more uniform group of patients with LVDD evaluation post KT is required to conclude on whether overall characteristics of ADPKD can be attributed to an improvement in LVD function.

In another significant finding in this study, ADPKD is associated with more favorable patient survival and post-transplant MACE-free survival. Prior studies have demonstrated that the overall survival of patients with ADPKD is equivocal to that of the normal population.[13] Our study showed that the survival for patients with ADPKD is significantly greater as compared with other patients without ADPKD with kidney failure despite both groups receiving KT at the same age. This finding confirms what is well known that patients with ADPKD have a good post-transplant course.

MACE is a strong predictor of overall mortality and morbidity.[71–73] Interestingly, patients with ADPKD had also improved MACE-free outcome after
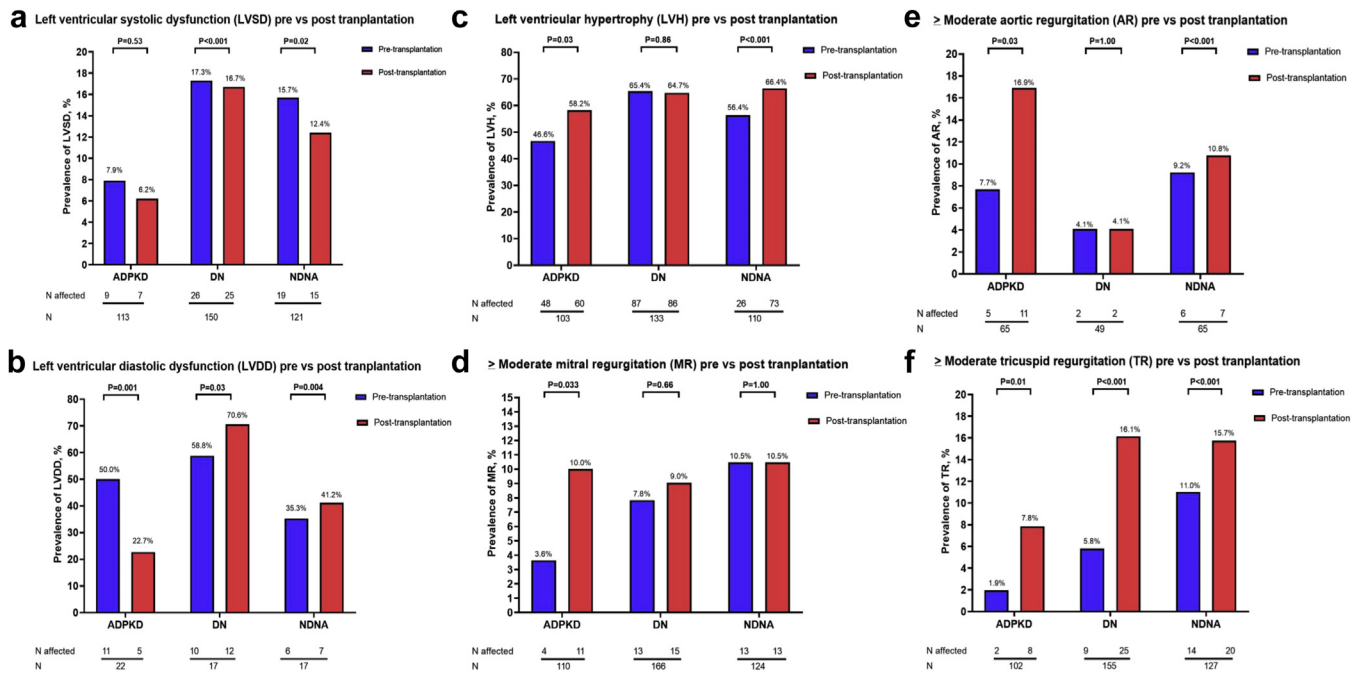
Figure 7. Evolution of the echocardiogram findings before and after transplantation for each of the 3 groups ADPKD, DN and NDND. (a) LV systolic dysfunction has improved post transplantation in patients with ADPKD as well as DN and NDNDA, (b) LV diastolic dysfunction has significantly improved in patients with ADPKD but worsened in patient with DN and NDND, (c) left ventricular hypertrophy has worsened in ADPKD and NDNA but slightly improved in DN group, (d) the prevalence of Moderate to severe mitral valve regurgitation has significantly worsened for patients with ADPKD. Similarly, for the (e) aortic regurgitation, and (f) tricuspid regurgitation. ADPKD, autosomal dominant polycystic kidney disease; DN, diabetic nephropathy; LV, left ventricular; NDNA, nondiabetic non-ADPKD.

transplantation as compared with other kidney failure patients. These findings were previously reported.[18] Our study takes these findings further by also showing that patients with ADPKD have better outcomes when it comes to single events, such as stroke, revascularization, and heart failure hospitalization independent of confounders. On the other hand, Florijn *et al.*[19] reported that patients with ADPKD are at increased risk of fatal myocardial infarctions and cerebrovascular events. This study was published in 1994, and because then major changes have been made in the management of KT, as well as cardiovascular disease treatment and prevention.[74,75]

Improved MACE-free survival, lower rates of LVH, LV systolic dysfunction and diastolic dysfunction, and improvement of diastolic function after KT could

certainly explain the lower risk of death at any time post-KT in ADPKD as compared with all other KT patients. Furthermore, this also can be attributed to the fact that ADPKD is a predictable disease with relatively early diagnosis, thereby allowing for optimization of preventative measures and aggressive management of cardiovascular risk factors.

Our study has several strengths and limitations. The major strengths of our study are the large number of patients with ADPKD included in our cohort, and the use of using propensity score matching to identify age and sex matched control groups. The control group included patients with DN who have been excluded in many prior studies. Another key strength is the large number of echocardiograms performed during evaluation for KT and several years post transplantation

Table 6. Evolution of SOV diameter post kidney transplantation for patients with ADPKD, DN and NDNA

Echocardiogram Variables	Mean SOV diameter within 2 yrs pretransplant	Mean SOV diameter post-transplant	Mean difference in diameter post transplantation, mm [95% CI]	T ratio	*P*-value
SOV					
ADPKD (*n* = 271)	38.2	39.9	+1.74 [1.09–2.39]	5.59	<0.01
DN (*n* = 271)	33.8	34.1	+0.24 [−0.65 to 1.31]	0.45	0.65
Non-DN, non-ADPKD (*n* = 271)	35.9	36.6	+0.72 [−0.29 to 2.10]	1.04	0.29
Mid ascending aorta					
ADPKD (*n* = 271)	36.5	37.1	+0.62 [0.23–1.01]	3.16	0.002
DN (*n* = 271)	34.1	34.1	+0.0 [−0.41 to 0.32]	0.23	0.81
Non-DN, non-ADPKD (*n* = 271)	35.4	36.0	+0.53 [−0.11 to 1.18]	1.62	0.10

ADPKD, autosomal dominant polycystic kidney disease; DN, diabetic nephropathy; NDNA, nondiabetic non-ADPKD; SOV, Sinus of Valsalva.

which facilitates a comprehensive representation of cardiac findings through time. An inherent limitation to retrospective analysis is the reliability on available clinical data. Nevertheless, the Mayo Clinic electronic system and Mayo Clinic PKD database have been comprehensive in their available data for >2 decades. Timing of echocardiograms was not uniform for all patients especially in post-transplantation follow-up. However echocardiograms are commonly obtained during transplant evaluation, thereby mitigating this limitation for the primary objective of this study. In addition, the limited number of patients undergoing LVDD evaluation limits the generalization of our findings regarding this measurement. Furthermore, some patients with ADPKD might have moved their long-term follow-up to local nontertiary centers, thereby lowering the number of available post-transplantation echocardiograms. Our study findings would be applicable to patients with ADPKD undergoing KT workup in a tertiary center.

In conclusion, despite more frequent worsening of valvular function and an increase in the sinus of Valsalva diameter, ADPKD transplant recipients have the most favorable cardiac profile pretransplantation with favorable patient survival and MACE-free survival rates as compared with kidney transplant patients with other causes of kidney failure. The predictability of ADPKD's clinical course and aggressive management of risk factors likely play a role in these favorable outcomes.

DISCLOSURE

Data Sharing Statement

The data that support the findings of this study are not publicly available because they contain information that could potentially compromise the privacy of the research participants and are however available from the corresponding author FTC on reasonable request.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Comparison of echocardiogram findings at time of transplantation between APDKD included in the study and ADPKD patients not fully matched.

The RECORD statement–checklist of items, extended from the STROBE statement.

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