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Patterns of Left Ventricular Geometry and Risk of Cardiovascular Events in a Cohort of Kidney Transplant Patients

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Abstract

Background: Left ventricular hypertrophy is an independent risk factor for cardiovascular morbimortality. There is a clear association between patterns of left ventricular hypertrophy and volume load and myocardial abnormalities in hypertensive patients. The aim of the study is to evaluate the association between pre-transplant echocardiographic left ventricular abnormalities and post-transplant cardiovascular events.

Methods: Observational, retrospective cohort study, including 229 consecutive kidney transplant patients between 2010 and 2013. We investigated the association between pre-transplant left ventricular parameters and post-transplant cardiovascular events (Congestive heart failure, acute coronary syndrome, cardiac sudden death, ictus and aortic aneurysm rupture) after adjusting for confounders. Renal outcomes and mortality were analyzed.

Results: Concentric hypertrophy was associated with an increased risk of cardiovascular events after kidney transplant (HR 2.334; CI 1.191-4.571 p=0.01). Every 10 g/m^2 increase on left ventricular mass index over population mean represents a 9% higher risk for cardiovascular events (HR 1.009 per 1 g/m^2 p=0.003).

Conclusion: Pre-transplant left ventricular geometry is a useful parameter to assess cardiovascular risk in kidney recipients. Concentric hypertrophy was a powerful predictor of cardiovascular post-transplant events and should be used to identify renal transplant recipients at high cardiovascular risk.

Keywords: Cardiovascular events risk; Echocardiography; Concentric hypertrophy; Left ventricular hypertrophy; Kidney transplant

Abbreviations: AS: Aortic Stenosis; AVF: Arteriovenous Venous Fistula; BP: Blood Pressure; CKD: Chronic Kidney Disease; CVD: Cardiovascular Disease; ESRD: End Stage Renal Disease; GFR: Glomerular Filtration Rate; iMtor: Inhibitors of Mammalian Target of Rapamycin; IVSd: Interventricular Septal Thickness at End-Diastole; KT: Kidney Transplantation; LV: Left Ventricular; LVEDD: LV End-Diastolic Dimensions; LVH: Left Ventricular Hypertrophy; LVIDd: End Diastolic Left Ventricular Internal Diameter; LVM: Left Ventricular Mass; LVMi: Left Ventricular Mass Index; PWTd: Diastolic Posterior Wall Thickness; RWT: Relative Wall Thickness

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Introduction

The prevalence of left ventricular hypertrophy (LVH) ranges between 40-75% in end stage renal disease (ESRD) patients and is of multifactorial cause [1]. Elevated systolic and diastolic arterial blood pressure (BP) and decreased large-vessel compliance cause increased afterload, myocardial cell thickening, and concentric left

ventricular hypertrophy (LVH) [2]. Volume overload, anemia and high-flow arteriovenous fistulas (AVF) increase preload, which leads to myocardial cell lengthening and eccentric or asymmetric LV hypertrophy. However, this adaptation is more complex than expected [3].

Concentric hypertrophy is a risk factor for cardiovascular events (CVE) on the general population [4]. Paoletti et al. demonstrated that LVH in chronic kidney disease (CKD) patients correlates to a higher CVE risk [5]. Cardiovascular disease (CVD) is the leading cause of mortality in kidney transplant (KT) patients, and cardiovascular (CV) death with functioning kidney is the first cause of graft loss [6,7]. The prevalence of CVE at 36 months after KT in this population almost reaches 40%, and the most frequent CVE registered is congestive heart failure (CHF). Chronic exposure to immunosuppressive therapy aggravates hypertension, diabetes and dyslipidemia in KT population [7]. Tacrolimus increases the incidence of diabetes after KT, and prednisone clearly aggravates CV risk, but steroid-free protocols are not feasible in all patients [7,8].

Rigatto et al. described for the first time that LVH is an independent risk factor for CVE after transplantation, although no data regarding to LV geometry is available. Gu et al. reported that CVE risk was higher in patients with mild and severe abnormalities compared to normal echocardiogram, although ventricular geometry was not taken into account [9,10]. On the contrary, Delville et al. described that pre-transplant LVH was not associated with a higher incidence of CVE during the first year after KT [11].

In general population, CVE risk prediction models properly stratify patients depending on the probability of presenting an event. The validity of these models in KT patients is inconclusive. Mansell et al. conducted a systematic review of 6 studies investigating the validity of CVE risk prediction models in KT population, and they found that they underestimated the real CVE risk [6]. Although Soveri et al. developed a model on a KT cohort, external validation was retrospective in patients with an unusual immunosuppressive regimen (belatacept) [12,13].

The primary goal of our study was to determine whether the pattern of left ventricular geometry is a predictor of CVE post KT. We used echocardiographically derived left ventricular mass (LVM) and relative wall thickness to define the patterns of ventricular geometry. To our knowledge, the effect of LV morphology on cardiovascular outcomes has not been previously tested in this population.

Materials and Methods

Study population

This is a retrospective, observational and single-center study. Kidney allograft recipients between 2010 and 2013 at Bellvitge University Hospital were eligible for the study. The inclusion criteria were: age ≥18 years, available echocardiography within the 12 months prior to KT and clinical follow-up in our center. Patients were excluded if echocardiogram was performed by an external cardiology team and/or when its quality was poor for technical reasons (poor acoustic window). Patients were also excluded if they received a combined transplant and/or if they experienced an early (< 1 month) graft loss (due to transplantectomy or primary non-functioning graft). Patients with severe valvulopathy or severe cardiac dysfunction (ejection fraction <25%) were not included. All patients were followed at the outpatient's clinic after the KT, and all medical records were fully available.

The Bellvitge University Hospital Institutional Review Board approved the study protocol. All procedures were in accordance with institutional guidelines. Inclusion criteria flowchart is shown in **Figure 1**.

Clinical outcomes

CVE were identified retrospectively from medical records, and validated by a second independent observer. We included all episodes diagnosed as congestive heart failure, acute coronary syndrome, stroke, aortic dissection or aneurysm rupture, and cardiac death. We defined a congestive heart failure episode as the appearance of dyspnea, decreased exercise tolerance, fatigue and signs of volume overload or organ hypo-perfusion requiring therapeutic intervention, with a concordant chest x-ray and elevated serum pro-brain natriuretic peptide. Acute coronary syndrome was diagnosed by clinical symptoms, electrocardiography, biomarkers or coronarography abnormalities, and included silent myocardial infarction, acute coronary syndrome with or without S-T elevation, requiring or not percutaneous coronary intervention. Stroke was defined as acute episode of focal or global neurological dysfunction caused by hemorrhage or infarction. Sudden death was defined as unexpected death not following a myocardial infarction, without the suspicion of an extra-cardiac cause. We also recorded cardiovascular mortality and all-cause mortality.

We recorded demographic variables, immunosuppressive therapy, and history of diabetes, hypertension, prior cardiovascular events and tobacco use prior to KT. We registered dialysis vintage prior to KT, history of previous KT, and incidence of delayed graft function (DGF) and acute rejection after KT. We measured glomerular filtration rate (GFR) according to CKD-EPI equation. BP was recorded at the time of echocardiography, using an oscillometric-validated device, and the procedure was executed according to the recommendations of the American Heart Association [14]. Blood pressure was analyzed as pulse pressure as a marker of arterial stiffness.

Echocardiogram study

Two-dimensional spectral and color flow Doppler transthoracic echocardiogram was performed. In hemodialysis patients, echocardiogram was performed in a midweek non-dialysis day, 24 hours after the last session and in the target dry weight in order to avoid inaccuracies [15]. End diastolic left ventricular internal diameter (LVIDd), diastolic posterior wall thickness (PWTd) and diastolic septal wall thickness were measured according to the recommendations of the American Society of Echocardiography [16]. LVM was calculated using LV end-diastolic dimensions (LVEDD), interventricular septal thickness at end-diastole (IVSd), relative wall thickness (RWT) calculated as septal wall thickness + posterior wall thickness divided by LV diastolic diameter, and LV

outflow tract diameter PWd through the formula:

$$LV\ mass = 0.8\left(1.04\left(\left(LVEDD + IVSd + PWd\right)^3\right)\right) + 0.6$$

$$RWT = 2 \times PWd / LVEDD$$

Left ventricular mass was standardized to body surface area (BSA), constituting the left ventricular mass index (LVMi) [17]. We defined LVH as LVMi ≥ 95 g/m² for women or ≥ 115 g/m² for men. The severity of the hypertrophy was defined according to the current guidelines [18]. We considered normal geometry RWT ≤ 0.42 and LVMi ≤ 95 g/m² for women or ≤ 115 g/m² for men. We classified patients as concentric remodeling when RWT ≥ 0.42 and LVMi ≤ 95 g/m² for women or ≤ 115 g/m² for men. We defined concentric hypertrophy as RWT ≥ 0.42 and LVMi ≥ 95 g/m² for women or ≥ 115 g/m² for men, while eccentric hypertrophy as RWT ≤ 0.42 and LVMi ≥ 95 g/m² for women or ≥ 115 g/m² for men [19].

Pulmonary Artery Pressure (PAP) was estimated from the calculated systolic trans-tricuspid gradient and the right atrial pressure. Pulmonary artery hypertension (PAH) was analyzed as dichotomy variable with a PAP cut off ≥ 40 mmHg. Severity of aortic stenosis was defined according to current guidelines [20].

Statistical analysis

Normally distributed data were described using mean and standard deviation. Non-normally distributed data were described using median and range. Student *t*-test was used to compare means of normally distributed continuous variables, and χ^2 and Pearson test to compare the incidence of an event among different groups. Kruskal–Wallis or Mann–Whitney *U* test was used to compare non-normally distributed variables. Cardiovascular events free survival time was compared using Kaplan-Meier curves and log-rank test. Cox's regression model was used to estimate hazard ratios for first cardiovascular event. We adjusted potential confounders by performing two multivariate models, depending on whether we included geometry (model 1) or mass (model 2) of the left ventricle. Just variables that were significant ($p < 0.05$) at univariate level were introduced in the multivariate model for the final analysis. The inter-observer reliability for echocardiography measurements of parameters of left ventricular hypertrophy was assessed through with the intra-class correlation coefficient (ICC). An ICC >0.8 indicated the good liability of the test. All p-values were two-tailed and statistical significance level was fixed at $p<0.05$. SPSS20.0 software (SPSS Inc., Chicago, IL) and GraphPad Prism version 6.0 (GraphPad Software, La Jolla, CA) were used for data management and analysis.

Results

Demographic characteristics

We included 229 consecutive patients undergoing a KT. Mean follow-up was 51.8 ± 15.07 months (range 4-84 months). Echocardiographic evaluation was performed 8.3 ± 1.1 months before KT. Baseline demographics for the overall cohort and by ventricular geometry are reported in **Table 1**.

Echocardiographic evaluation

Echocardiographic parameters are shown in **Supplementary Table 1**. Mean LVMi was 130.4 ± 42.2 g/m². LVH was observed in 166 patients (72,5%), normal geometry in 41 patients (17.9%), concentric remodeling in 22 patients (9.6%). Among hypertrophic patterns, concentric hypertrophy was detected in 85 patients (37.1%) and eccentric hypertrophy in 81 patients (35.4%). LVMi was higher in concentric hypertrophy compared to eccentric hypertrophy ($p<0.001$).

The intra-class correlation coefficient between the two cardiologists (E.C. and A.M) who performed echocardiograms for IVSd, LVEDD and PWTd were 0.93 (IC 0.83-0.97), 0.95 (IC 0.87-0.98) and 0.88 (IC 0.72-0.94) respectively.

Cardiovascular events and mortality

Forty-one patients (17.9%) had a CV event, and the mean survival time free of events was 51 months. The most frequently registered CV event was heart failure **(Table 2)**. The majority of CVE (87.8%) occurred beyond the first 6 months after transplantation.

The prevalence of CVE was higher in patients with LVH (10% vs 21.1%; P= 0.09). LVMi was significantly higher in patients who suffered a CV event compared to those who did not (152.1 ± 64 g/m² *vs.* 125.7 ± 33 g/m² respectively; p=0.001) **(Supplementary Table 2)**. CVE were more frequent in the concentric group compared with the eccentric group (27% vs. 13.5%; p=0.035) **(Supplementary Table 3)**.

Figures 2 and 3 show CVE-free survival time depending on left ventricle geometry and severity of ventricular mass hypertrophy. Patients with concentric hypertrophy showed statistically significant lower CVE-free survival time (log-rank p=0.002). Severity of ventricular hypertrophy was not associated to a different CVE-free survival time (log-rank p=0.125).

By multivariate Cox regression analysis, we found an increased CVE risk in patients with concentric hypertrophy compared to the rest of geometric patterns (HR 2.334; CI 95% 1.191-4.571 p=0.01). Every g/m² of increased LVMi (compared to the mean of our population) represents a 0.9% risk (HR 1.009 CI95% 1.003-1.015 p=0.003) (**Table 3**).

Overall mortality was 13.97% without differences according LV geometry. Despite the absence of differences in LV geometry depending on hemodialysis vascular access, patients with proximal AVF showed an increased risk for congestive heart failure, (at cox regression multivariate analysis for congestive heart failure AFV (proximal vs distal location) HR 5.201, CI 1.001-27.003; p=0.05), with no significant differences in other CVE.

Graft function

Prevalence of delayed graft function (DGF) and acute rejection was 37.1% and 13.1% respectively. Twenty-five patients (10,9%) returned to dialysis after KT during follow-up. Mean eGFR at 3 months was 46.3 ± 17.3 ml/min **Supplementary Table 4** shows transplant characteristics and analytic parameters 3 months after KT. Prevalence of DGF was not different depending on the presence or absence of LVH (39.8% *vs.* 30.2% respectively, p=0.13). Moreover, prevalence of DGF was similar among the 4 different LV geometric patterns (31%, 31%, 35% and 43% for normal, concentric remodeling, concentric and eccentric

Table 1 Baseline characteristics of the population.

Characteristic	All (n=229)	Normal (n=41)	CR (n=22)	EH (n=81)	CH (n=85)	p value
Sex Male/Female (%)	63.3/36.7	65.8/34.2	50/50	59.2/40.8	69.4/30.6	0.29
Age, mean ± SD	58 ± 12.5	54.3 ± 12.2	53.5 ± 13.2	57.5 ± 13.2	61.4 ± 11*	**0.003**
BSA, mean ± SD	1.81 ± 0.19	1.85 ± 0.22	1.84 ± 0.25	1.77 ± 0.17	1.83 ± 0.17	0.09
Smoking (Never/Ex or active)%	52.4/47.6	56.1/43.9	40.9/59.1	56.8/32.1	49.4/50.6	0.50
Previous CVE, n (%)	33 (14.4)	3 (1.3)	2 (0.9)	13 (5.7)	15 (6.6)	0.38
Pulse Pressure (mean ± SD)	64 ± 17	65 ± 13****	52 ± 14**	62 ± 18^{+}	69 ± 17***	**0.001**
Hypertension before KT n (% total)	210 (91.7)	35 (15.3)	20 (8.7)	75 (32.8)	80 (34.9)	0.40
Diabetes before KT, n (% total)	46 (20.1)	4 (1.7)	3 (1.3)	12 (5.2)**	27 (11.8)**	**0.008**
Type of RRT (DP/HD/Pre-emp)%	10.2/81.4/8.4	15/75/10	4/86/10	11/80/9	8.3/84.5/7.2	0.85
Time on Dialysis (Mean ± DS)	32.9 ± 41.9	27.1 ± 31.3	41.6 ± 55.6	33.2 ± 36.8	33.1 ± 47.0	0.63
Number Transplant (1st/2nd/3rd)%	85.2/13.1/1.7	83/14.6/2.4	90.2/9.8/0	89/10/1	81/16/3	0.81

CR: Concentric Remodeling; EH- Eccentric Hypertrophy; CH – Concentric Hypertrophy; SD – Standard Deviation; BSA: Body Surface Area; CVE: Cardiovascular Events; DP: Peritoneal Dialysis; HD: Hemodialysis; Pre-Emp: Pre-emptive transplant; RRT: Renal Replacement Therapy. *p<0.05 *vs.* Normal and remodeling group; **p<0.05 *vs.* all others group ***p<0.01 *vs.* remodeling and eccentric group ****p<0.01 *vs.* remodeling $^{+}$p<0.01 *vs.* remodeling and concentric group.

Table 2 Total number and percentage of cardiovascular events and mortality at the study population.

Cardiovascular events and mortality (n (%))	
Cardiovascular events	41/229 (17.9%)
Class of cardiovascular event	
Cardiac sudden death	7/41 (17.1%)
Acute coronary syndrome	7/41 (17.1%)
Congestive Heart Failure	16/41 (39%)
Stroke	4/41 (9.7%)
Aneurysmal dissection	7 (17.1%)
Time to cardiovascular event after KT	
<1 month	2/41 (4.9%)
1 to 6 months	3/41 (7.3%)
>6 months	36/41 (87.8%)
Overall mortality	32/229 (13.97%)
Cardiovascular mortality	17/229 (7.4%)
Note: KT-kidney transplantation	

hypertrophy respectively; p=0.18). DGF was associated with a higher risk of CVE **(Table 3)**.

eGFR at 3 months was not different depending on LVH or left ventricular geometric pattern. eGFR data at 12 months was available from 202 patients (27 patients were censored because of death, graft loss or lost follow-up or lack of eGFR at this time point). Again no 12-month eGFR differences were observed between groups.

Table 3 Cox regression logistic multivariate analysis for cardiovascular events.

Analysis	Model 1			Model 2		
	p Value	HR	CI 95%	p Value	HR	CI95%
Age	0.094	1.032	0.995-1.072	0.054	1.037	0.999-1.076
Previous diabetes (yes *vs.* not)	0.012	2.442	1.215-4.907	0.053	1.990	0.991-3.993
Time on dialysis	0.048	1.006	1.000-1.013	0.050	1.006	1.000-1.012
Previous CVE (yes *vs.* not)	0.002	3.082	1.520-6.248	0.000	3.834	1.982-7.416
Pulse pressure	0.92	1.001	0.981-1.022	0.7	1.004	0.983-1.024
PHT (yes *vs.* not)	0.007	2.990	1.353-6.608	0.022	2.547	1.141-5.682
AS (yes *vs.* not)	0.05	3.400	1.846-3.173	0.011	2.930	1.275-6.730
DGF (yes *vs.* not)	0.012	2.395	1.456-7.937	0.008	2.571	1.286-5.138
Proximal AVF (*vs.* distal or no fistula)	0.13	1.664	0.854-3.241	0.09	1.749	0.911-3.357
Concentric LVH (*vs.* others patterns)	--	--	--	0.01	2.334	1.191-4.571
LVMi	0.003	1.009	1.003-1.015	--	--	--

CVE: Cardiovascular Events, PHT: Pulmonary Hypertension, AS: Aortic Stenosis DGF: Delayed Graft Function, AVF: Arteriovenous Fistula, LVH: Left Ventricular Hypertrophy, LVMi: Left Ventricular Mass Index, HR: Hazard Ratio, CI: Confidence Interval. Note: Just variables significant at univariate level ($p<0.05$) were introduced in the models.

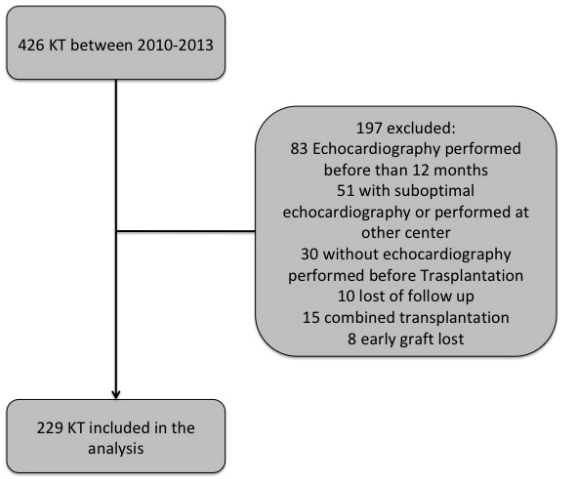

Figure 1 Patients flowchart.

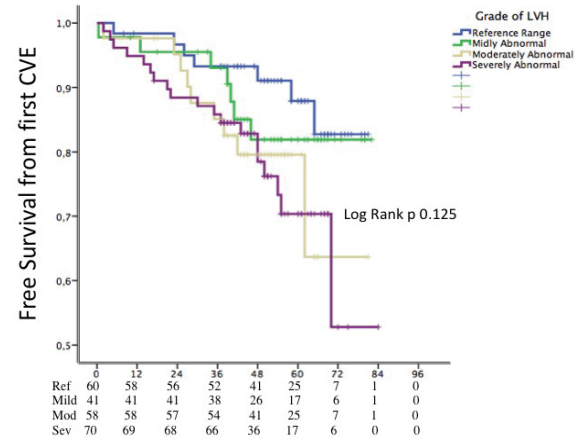

Figure 3 CVE-free survival time according to grade of left ventricular hypertrophy.

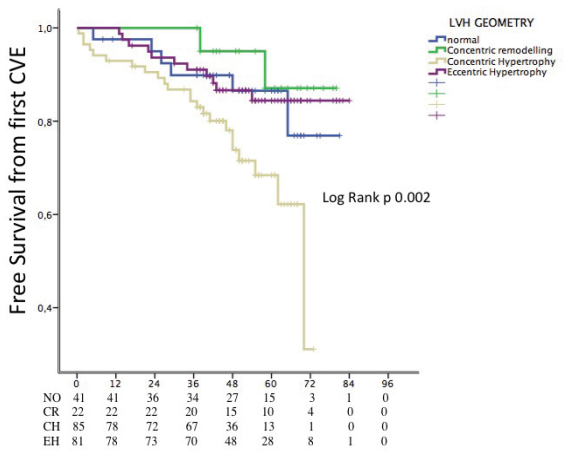

Figure 2 CVE-free survival time according to left ventricular geometric pattern.

Discussion

CVE are the leading cause of death and graft loss in KT population. Predicting events in this population is challenging because the methods used in the general population are not applicable [6].

LVH is an independent risk factor for CVE and mortality in general and CKD population [5,21]. In addition, concentric hypertrophy is an independent CV risk factor in certain populations such as hypertensive and elderly patients [22,23]. Until now, no study has analyzed the impact of pre-transplant geometric pattern type and/or LVMi on CVE after KT.

We found a prevalence of 72,5% of LVH in our cohort, similar to the previously described prevalence of LVH in dialysis patients [24,25]. The mean LVMi observed in our patients was higher compared to general population, indicating the need to further refine the echocardiographic evaluation in order to estimate the

CVE risk. Nevertheless, in our cohort, pre-transplant LVMi was clearly associated with post-transplant CVE. In fact, each g/m^2 above the mean conferred an increased risk of 0.9% for major CVE in our cohort. Grading hypertrophy according to the current guidelines based on general population failed to predict the real risk of CVE in our cohort, evidencing the need for new risk classification tools in KT patients [19]. Contrary, the assessment of the geometric pattern was key to correctly stratify CVE risk in our KT population.

At the multivariate Cox model analysis, classic CV risk factors, such as pre-transplant diabetes, previous CVE, time on dialysis, but not age, were confirmed. Probably all others variables define the real biological status of patients and make the chronological age not predictive. Moreover, DGF was associated with a higher risk of CVE and mortality, as other authors already reported [26]. As expected, patients with concentric hypertrophy had higher pulse pressure values compared to others groups, nonetheless pulse pressure was not predictive for CVE at multivariate cox model analysis.

The main finding in our study was that pre-transplant LV geometry is an independent risk factor for CVE and mortality after KT. We observed a 2.3-fold probability of CVE for concentric hypertrophy compared to the other geometries in the cox multivariate model. We propose LV geometry as a marker to identify KT recipients with a higher risk of CVE. LV geometry is easy to obtain from two simple echocardiographic measurements and is divided into 4 clearly differentiated categories, being an easy-to-interpret tool for the daily clinical practice.

Our study has some important limitations. First of all, the retrospective design could lead to a selection bias. We only included patients with an echocardiographic evaluation performed during the 12 months before transplantation, and echocardiographic evaluation in younger and healthier patients is not routinely performed at our center. Because of this, the results of our study cannot be universally applied until validated in an independent cohort. Regression of LVH was not evaluated in our study, but our data indicate an urgent need for new studies looking at geometric pattern modification after transplantation.

Conclusion

In conclusion, LVH with concentric pattern is a risk factor for the occurrence of CVE after transplantation. Concentric hypertrophy, detected at echocardiogram screening for waiting list inclusion, strongly indicates the need for a tighter follow-up of these patients in order to prevent new CVE after transplantation. Further studies are needed to evaluate whether other echocardiographic parameters of diastolic dysfunction or systolic ventricular function (such as global longitudinal strain) or biomarkers (such as n-terminal type B natriuretic propeptide) are related with geometric pattern and/or cardiovascular events after kidney transplantation.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Disclosure

The authors declare no conflict of interest.

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