

Original Article



Changes in Cardiac Structure and Function After Kidney Transplantation: A New Perspective Based on Strain Imaging

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ABSTRACT

BACKGROUND: We aimed to investigate left ventricular (LV) global longitudinal strain (GLS) in end-stage renal disease patients and its change after kidney transplantation (KT).

METHODS: We retrospectively reviewed patients who underwent KT between 2007 and 2018 at two tertiary centers. We analyzed 488 patients (median age, 53 years; 58% male) who had obtained echocardiography both before and within 3 years after KT. Conventional echocardiography and LV GLS assessed by two-dimensional speckle-tracking echocardiography were comprehensively analyzed. Patients were classified into three groups according to the absolute value of pre-KT LV GLS (|LV GLS|). We compared longitudinal changes of cardiac structure and function according to pre-KT |LV GLS|.

RESULTS: Correlation between pre-KT LV EF and |LV GLS| were statistically significant, but the constant was not high ($r = 0.292$, $p < 0.001$). |LV GLS| was widely distributed at corresponding LV EF, especially when the LV EF was $> 50\%$. Patients with severely impaired pre-KT |LV GLS| had significantly larger LV dimension, LV mass index, left atrial volume index, and E/e' and lower LV EF, compared to mildly and moderately reduced pre-KT |LV GLS|. After KT, the LV EF, LV mass index, and |LV GLS| were significantly improved in three groups. Patients with severely impaired pre-KT |LV GLS| showed the most prominent improvement of LV EF and |LV GLS| after KT, compared to other groups.

CONCLUSIONS: Improvements in LV structure and function after KT were observed in patients throughout the full spectrum of pre-KT |LV GLS|.

Keywords: Left ventricle; Global longitudinal strain; Kidney transplantation

INTRODUCTION

Chronic kidney disease (CKD) is a strong risk factor for cardiovascular (CV) disease and mortality.¹⁻⁴⁾ Both traditional CV risk factors and non-traditional CV risk factors (e.g., vascular calcification, inflammation, hemodynamic overload) contribute to the progression of CV disease and mortality in patients with CKD.^{5,7)} Kidney transplantation (KT) improves survival in patients with advanced CKD and end-stage renal disease (ESRD) compared to dialysis.⁸⁾ A previous study reported reverse cardiac remodeling and improved left ventricular (LV) ejection fraction (LVEF) following KT, with a corresponding improvement in long-term survival.⁹⁾

LVEF is a widely used surrogate marker for LV systolic function. However, LVEF is load-dependent and has a tendency to increase with LV concentric remodeling.^{10,11)} In addition, increased afterload may reduce the LVEF despite preserved LV contractility.¹²⁾ Therefore, LVEF may not be an adequate enough measure to assess myocardial intrinsic contractility in patients with ESRD, in whom changes in preloads and afterload status occur frequently. In this respect, LV global longitudinal strain (GLS) assessed by speckle-tracking echocardiography has been reported to more sensitively assess subclinical LV systolic dysfunction with better reproducibility compared to LVEF.¹³⁻¹⁵⁾ The aim of this study was to investigate the longitudinal change of cardiac structure and function in ESRD patients after KT according to pre-KT LV GLS values.

METHODS

Study subjects

We reviewed adult ESRD patients (≥ 19 years old) who underwent living-donor or cadaveric KT at two tertiary centers in Korea, Samsung Medical Center and Severance Hospital, between 2007 and 2018. Among them, patients who underwent echocardiography before and within 3 years after KT were selected. Patients who underwent heart transplantation, whose images were not analyzable, or who were lost during follow-up were excluded. All patients underwent baseline echocardiography within 3 months before KT and follow-up echocardiography within 3 years after KT. Finally, a total of 488 patients were analyzed. All patients received standardized protocol-driven immunosuppression medications, including cyclosporine, tacrolimus, mycophenolate mofetil, and prednisone. Our study complied with the Declaration of Helsinki and was approved by the Institutional Review Board of

Samsung Medical Center (IRB No. 2021-01-108) and Severance Hospital (IRB No. 4-2021-0543).

Echocardiography

Two-dimensional and Doppler echocardiography were performed using a commercially available ultrasound machine (Siemens, Munich, Germany; GE Vingmed Ultrasound, Horten, Norway; or Phillips, Amsterdam, Netherlands) with a 2.5–3.5 MHz probe before and after KT. All patients underwent comprehensive two-dimensional echocardiography with Doppler and tissue Doppler imaging according to existing guidelines.¹⁶⁾ LVEF was measured using the biplane Simpson's method in apical four- and two-chamber views. The left atrial (LA) volume index was measured using the biplane method as the end of ventricular systole and indexed to the body surface area. From the mitral inflow velocities, we obtained data on the peak velocity of early (E) and late filling and the deceleration time of E velocity. Early diastolic (e') velocities were measured at the septal mitral annulus.

For strain analysis, we used a vendor-independent program. Digitally acquired echocardiographic images in DICOM format were uploaded to the TomTec imaging system (TOMTEC Imaging Systems GmbH, Munich, Germany) for further deformational analyses.¹⁷⁾ To quantify LV GLS, two-dimensional speckle-tracking analyses were performed on standard routine greyscale images of the apical 2-, 3-, and 4-chamber views, and the mean LV GLS was calculated from three apical GLS curves. The absolute value of LV GLS was presented as $|\text{LV GLS}|$. Change of $|\text{LV GLS}|$ before and after KT was defined as $\Delta|\text{LV GLS}|$ ($\text{post-KT } |\text{LV GLS}| - \text{preKT } |\text{LV GLS}|$).

Statistical analysis

Data are described as median (interquartile range [IQR]) or number (%). Continuous variables were compared using the Mann–Whitney *U* test, while categorical variables were compared using the chi-squared test or Fisher's exact test as appropriate. Patients were classified three groups according to pre-KT $|\text{LV GLS}|$ tertiles (T1 = lowest tertile, severely impaired pre-KT $|\text{LV GLS}|$, T2 = middle tertile, moderately impaired pre-KT $|\text{LV GLS}|$, T3 = highest tertile, severely impaired pre-KT $|\text{LV GLS}|$). Pre- and Post-KT clinical characteristics were compared among groups according to pre-KT $|\text{LV GLS}|$. Univariable linear regression analysis was used to analyze the association between clinical variables and the changes in LVGLS (ΔLVGLS). Statistical analyses were performed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). All analyses were 2-tailed, and $p < 0.05$ was considered to be statistically significant.

RESULTS

Baseline characteristics

Table 1 shows the baseline characteristics of the study population and the group comparison according to the pre-KT |LV GLS|. Of 488 patients, the median age was 53 years and 58% were male. All patients were dialysis-dependent (80% on hemodialysis), and the median dialysis duration was 37 (IQR, 8–78) months. A total of 297 (61%) patients underwent living-donor KT and 14 (3%) patients underwent simultaneous pancreas or liver transplantation. Patients with severely impaired pre-KT |LV GLS| (T1) had significantly higher prevalence of diabetes, coronary artery disease, heart failure, atrial fibrillation, and revascularization history, compared to patients in T2 and T3 groups. The median age, sex, and duration of dialysis were similar among three groups. Before KT, patients with severely impaired pre-KT |LV GLS| (T1)

had significantly larger LV end-diastolic/systolic dimension, LV mass index, and LA volume index, higher E/e', and lower LV EF, when compared to other groups (T2 and T3).

LV reverse remodeling and systolic function

The median duration between pre- and post-KT echocardiography was 17 (range, 8–30) months. **Table 2** presents the echocardiographic parameters before and after KT. During the pre-KT assessment, the median LVEF and |LV GLS| were 62% (IQR, 56–67%) and 14.3% (IQR, 11.3–17.8%), respectively. Among our cohort, 76% (n = 371) had reduced |LV GLS| (< 18%), while 83% (n = 406) of patients had preserved EFs (> 50%) before KT. Although modest, there was a significant correlation between pre-KT LV EF and |LV GLS| (r = 0.292, p < 0.001) (**Figure 1**). |LV GLS| was widely distributed at corresponding LVEF, especially when the LVEF was > 50%.

Table 1. Baseline characteristics of the study population according to post-KT |LV GLS|

Variables	All patients (n = 487)	T1 (n = 165)	T2 (n = 161)	T3 (n = 162)	p-values
Clinical characteristics					
Age at transplant (years)	53 (43–60)	52 (43–60)	53 (43–61)	53 (44–60)	0.861
Male sex	284 (58)	108 (66)	97 (60)	90 (56)	0.067
BMI (kg/m ²)	22.6 (20.4–25.0)	23.1 (20.4–25.0)	22.4 (20.4–25.0)	22.3 (20.5–25.3)	0.795
Systolic BP (mmHg)	135 (125–149)	137 (132–153)	133 (122–146)	134 (125–151)	0.181
Hemodialysis	391 (80)	142 (86)	121 (76)	128 (79)	0.054
AV fistula	246 (51)	86 (52)	76 (48)	84 (52)	0.648
Dialysis duration (months)	37 (8–78)	30 (8–69)	39 (8–84)	44 (15–79)	0.177
Living donor KT	297 (61)	101 (61)	102 (63)	94 (58)	0.614
Comorbidities					
Glomerulonephritis	179 (37)	47 (29)	60 (38)	72 (44)	0.011
PKD	14 (3)	3 (2)	7 (4)	4 (3)	0.360
Hypertension	432 (89)	146 (89)	146 (91)	140 (86)	0.389
Diabetes mellitus	189 (39)	75 (46)	70 (44)	44 (27)	0.001
Dyslipidemia	78 (16)	22 (13)	25 (16)	31 (19)	0.355
AF	23 (5)	14 (9)	6 (4)	3 (2)	0.014
CAD	74 (15)	42 (26)	22 (14)	10 (6)	< 0.001
Revascularization Hx	39 (8)	20 (12)	14 (9)	5 (3)	0.010
Heart failure	52 (11)	36 (22)	11 (7)	5 (3)	< 0.001
Pre-KT echocardiography					
LV EDD	53 (50–57)	55 (51–61)	53 (50–57)	52 (48–54)	< 0.001
LV ESD	34 (30–38)	37 (31–45)	34 (30–38)	32 (29–35)	< 0.001
LV mass index	126 (106–158)	147 (113–169)	125 (108–155)	126 (106–158)	< 0.001
LA volume index	38.8 (30.0–50.9)	41.9 (30.3–57.5)	38.8 (30.9–50.0)	36.3 (28.9–45.5)	< 0.001
E/e'	12.0 (9.4–15.9)	14.1 (10.2–17.5)	12.0 (9.0–15.6)	11.4 (9.0–14.7)	0.001
RVSP	29 (24–37)	31 (25–40)	28 (24–36)	29 (24–36)	0.193
LV EF	62 (56–67)	57 (43–64)	61 (59–68)	66 (60–70)	< 0.001
LV GLS (%)	14.3 (11.3–17.8)	9.7 (7.5–11.2)	14.2 (13.5–15.1)	18.8 (17.7–20.9)	< 0.001
Medications					
ARB/ACEi	168 (34)	44 (27)	54 (33)	70 (43)	0.007
CCB	225 (46)	84 (51)	76 (47)	65 (40)	0.142
BB	263 (54)	81 (49)	85 (53)	97 (60)	0.139

Values are presented as number (%) or median (interquartile range).

ACEi: angiotensin converting enzyme inhibitor, AF: atrial fibrillation, ARB: angiotensin receptor blocker, AV: arteriovenous, BB: beta blocker, BMI: body mass index, BP: blood pressure, CAD: coronary artery disease, CCB: calcium channel blocker, EDD: end diastolic dimension; EF: ejection fraction, ESD, end systolic dimension, Hx: history, KT: kidney transplantation, LA: left atrial, LV: left ventricular, PKD: polycystic kidney disease.

T1 = severely impaired pre-KT |LV GLS|, lowest tertile; T2 = moderately impaired pre-KT |LV GLS|, middle tertile T3 = mildly impaired pre-KT |LV GLS|, highest tertile.

Cardiac Function After Kidney Transplantation

Table 2. Changes in echocardiographic parameters in subgroups according to pre-KT |LV GLS| tertiles

Variables	All patients (n = 487)	T1 (n = 165)	T2 (n = 161)	T3 (n = 162)
LVEF (%)				
Pre-KT	62 (56–67)	57 (43–64)	61 (59–68)	66 (60–70)
Post-KT	64 (58–69)	60 (54–66)	64 (59–68)	67 (62–71)
p-value	< 0.001	< 0.001	0.002	0.089
LV EDD (mm)				
Pre-KT	53 (49–57)	55 (51–61)	53 (50–57)	52 (48–54)
Post-KT	50 (46–54)	53 (47–56)	50 (46–54)	50 (46–53)
p-value	< 0.001	< 0.001	< 0.001	< 0.001
LV ESD (mm)				
Pre-KT	34 (30–38)	37 (31–45)	34 (30–38)	32 (29–35)
Post-KT	32 (28–35)	33 (29–38)	32 (28–34)	30 (28–34)
p-value	< 0.001	< 0.001	< 0.001	< 0.001
LV mass index (g/m²)				
Pre-KT	126 (106–158)	147 (113–169)	125 (108–155)	117 (100–140)
Post-KT	116 (98–141)	124 (104–153)	114 (93–138)	114 (94–134)
p-value	< 0.001	< 0.001	< 0.001	0.020
E/e'				
Pre-KT	12.0 (9.4–15.9)	14.1 (10.2–17.5)	12.0 (9.0–15.6)	11.4 (9.0–14.7)
Post-KT	11.5 (8.6–14.8)	12.5 (9.0–15.5)	10.9 (8.0–14.7)	11.3 (9.2–13.9)
p-value	0.002	0.004	0.202	0.413
LA volume index (mL/m²)				
Pre-KT	38.8 (30.0–50.9)	41.9 (30.3–57.5)	38.8 (30.9–50.0)	36.3 (28.9–45.5)
Post-KT	36.0 (38.8–46.1)	36.6 (29.7–47.7)	36.0 (28.8–45.9)	34.9 (27.8–46.0)
p-value	< 0.001	0.003	0.002	0.469
RVSP (mmHg)				
Pre-KT	29 (24–37)	31 (25–40)	28 (24–36)	29 (24–36)
Post-KT	28 (24–35)	28 (23–35)	28 (24–35)	29 (25–35)
p-value	0.008	0.035	0.162	0.393
 LV GLS (%)				
Pre-KT	14.3 (11.3–17.8)	9.7 (7.5–11.2)	14.2 (13.5–15.1)	18.8 (17.7–20.9)
Post-KT	15.8 (13.2–18.6)	14.6 (11.8–16.6)	16.0 (13.8–18.2)	18.3 (15.8–20.2)
p-value	< 0.001	< 0.001	< 0.001	0.001

Values are presented as median (interquartile range).

EDD: end diastolic dimension, EF: ejection fraction, ESD: end systolic dimension, GLS: global longitudinal strain, KT: kidney transplantation, LA: left atrium, LV: left ventricle, RVSP: right ventricular systolic pressure.

T1 = severely impaired |LV GLS|; T2 = moderately impaired |LV GLS|; T3 = mildly impaired |LV GLS|.

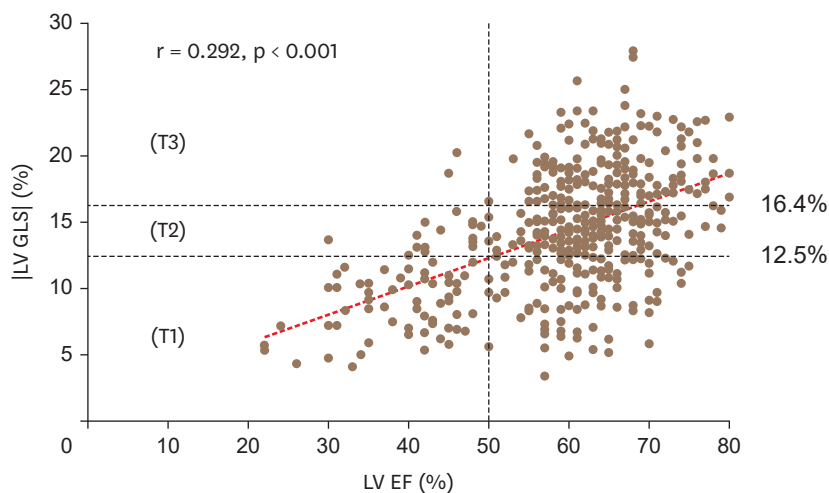


Figure 1. Correlation between pre-kidney transplantation |LV GLS| and LVEF. EF: ejection fraction, GLS: global longitudinal strain, LV: left ventricle. T1 = lowest tertile, T2 = middle tertile, T3 = highest tertile.

All patients in three groups showed numerical improvement of LV structure and function (**Table 2**). Notably, patients with severely impaired pre-KT |LV GLS| values (T1) showed significant improvement of LV EF, LV mass index, E/e', LA volume index, |LV GLS|, and RV systolic pressure after KT. In addition, patients with severely impaired pre-KT |LV GLS| (T1) showed the most prominent improvement of LV EF and |LV GLS| after KT, compared to other groups (**Figure 2**). In linear regression analysis, Δ |LV GLS| showed significant negative correlation with change of LV end-systolic dimension and pre KT |LV GLS| (**Table 3**).

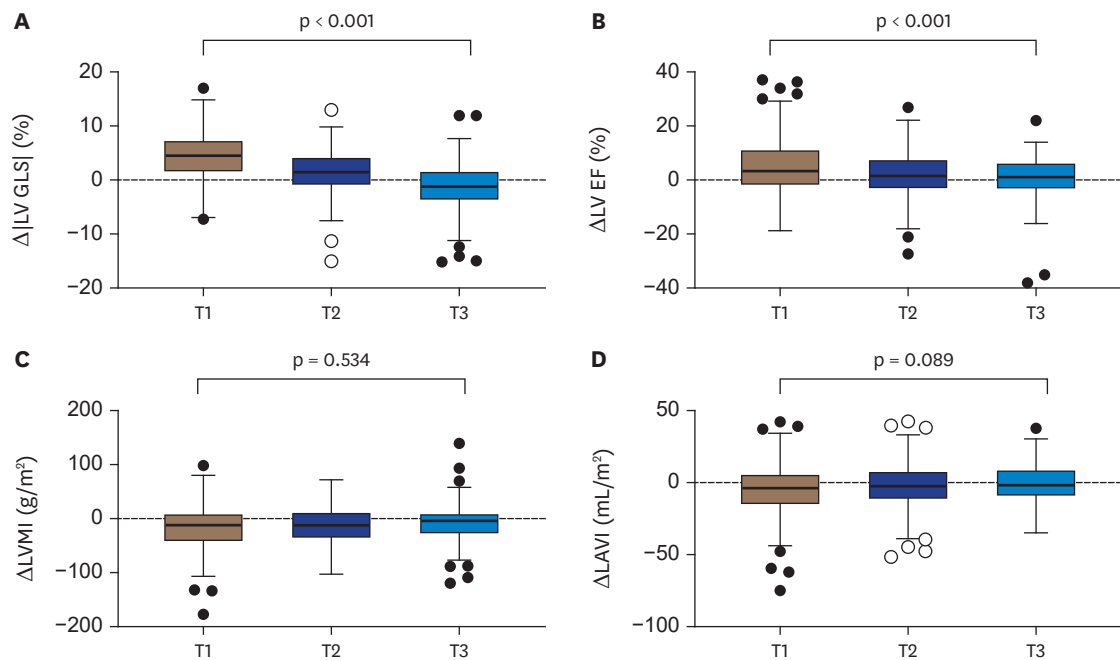


Figure 2. Change of LV function, LV mass index and LA volume index after KT according to pre-KT |LV GLS| tertiles. EF: ejection fraction, GLS: global longitudinal strain, LA: left atrium, LV: left ventricle, MI: mass index, VI: volume index. T1 = lowest tertile, T2 = middle tertile, T3 = highest tertile.

Table 3. Correlation between clinical variables and pre KT |LV GLS|*

Variables	Pre-KT LV GLS	
	Coefficient (95% CI)	p-value
Age at transplant	-0.008 (-0.058 to 0.041)	0.744
Δ LV EDD	0.032 (-0.189 to 0.254)	0.773
Δ LV ESD	-0.315 (-0.420 to -0.209)	0.600
Δ LV GLS	-0.315 (-0.420 to -0.209)	< 0.001
Post-KT LVEF	0.122 (0.077 to 0.166)	< 0.001
Post-KT LV GLS	0.300 (0.207 to 0.392)	< 0.001
Post-KT LV EDD	-0.147 (-0.256 to -0.037)	0.009
Post-KT LV mass index	-0.003 (-0.012 to 0.006)	0.581
Post-KT E/e'	-0.023 (-0.483 to 0.629)	0.629
Post-KT LA volume index	-0.009 (-0.044 to 0.026)	0.623
6-month post-KT eGFR	-0.003 (-0.017 to 0.010)	0.608
Δ hemoglobin	0.036 (-0.010 to 0.010)	0.994
6-month post-KT hemoglobin	0.007 (-0.196 to 0.211)	0.943
Δ systolic blood pressure	-0.029 (-0.021-0.015)	0.764

CI: confidence interval, EDD: end-diastolic dimension, EF: ejection fraction, eGFR: estimated glomerular filtration rate ESD: end-systolic dimension, GLS: global longitudinal strain, KT: kidney transplantation, LA: left atrium, LV: left ventricle, RVSP: right ventricular systolic pressure.

Δ = post-KT value – pre-KT value.

*By linear regression.

DISCUSSION

The main findings of the current study are as follows: 1) improvements in LV structure and function were observed in patients throughout the full spectrum of pre-KT |LV GLS|; 2) reverse remodeling and improvements in LV systolic function

was most prominently observed in patients with severely reduced |LV GLS| compared to those with mildly or moderately reduced |LV GLS|.

The prevalence of HF with reduced LVEF was reported to be approximately 25% among patients on the waiting list for KT.¹⁸⁾ Because previous studies have reported a strong association between pre-KT LVEF and mortality after KT, ESRD patients with reduced LVEF are considered to be at high risk for transplantation.¹⁹⁾ However, previous single-center data described improved LV systolic function and improved HF symptoms even in patients with reduced LVEFs after KT.⁹⁾¹⁹⁾ Similar to this previous study, our study reported improvements in LV structure and systolic and diastolic functions after KT, even in patients with severely reduced pre-KT |LV GLS|.

In patients with ESRD and CKD, cardiac remodeling occurs with myocardial hypertrophy, fibrosis, and capillary loss and is associated with mortality.²⁰⁾²¹⁾ The pathogenesis of LV remodeling in ESRD is considered to be multi-factorial. Mechanical and humoral factors, including uremic toxin and oxidative stress, at play during the progression of CKD are known to cause myocardial fibrosis and facilitate LV diastolic dysfunction.²²⁾ Hemodynamic overload from hypertension, atherosclerosis, and anemia and volume overload results in cardiomyocyte hypertrophy and the development of LV hypertrophy.²³⁾²⁴⁾

Overactivation of the sympathetic nervous system and renin–angiotensin–aldosterone system in CKD is a well-known pathogenesis of cardiac remodeling in CKD.²⁵⁾²⁶⁾ Alterations in mineral metabolism and increased systemic inflammation in CKD lead to activation of the profibrotic signaling pathway, which results in myocardial hypertrophy and fibrosis.²⁷⁾²⁸⁾ The overall adverse effect of uremic cardiac remodeling seems to be more sensitively assessed by LV GLS than LVEF. Although 84% of our cohort had preserved EF (> 50%) (n = 410) at pre-transplantation, only 22% of patients (n = 105) had preserved LV GLS (|LV GLS| > 18%). Similarly, a previous study reported that all CKD patients had reduced LV deformation or early myocardial relaxation abnormalities, and the extent and severity of functional LV impairment were underestimated with LVEF.²⁹⁾

The benefit of cardiac reverse remodeling has been previously suggested by a single-center study reporting improvements in LVEF and LV mass following KT.⁹⁾ In our study, improvement of LV function and structure was observed even in those with severely reduced pre-KT |LV GLS|. Regarding LV systolic function, patients with severely reduced pre-KT |LV GLS| showed significant improvement of LV EF and |LV GLS| compared to patients with mildly and moderately reduced pre-KT |LV GLS|. Our study extends previous findings by demonstrating improvement of cardiac structure and LV mechanics in a multi-center cohort with a longer median hemodialysis duration before KT. The current study provides an important attribution to the existing knowledge regarding improved cardiac structure and function after successful KT.

The major limitation of this study is that this was a retrospective investigation involving selected patients who were able to undergo follow-up echocardiography after KT at tertiary centers. However, unlike the previous study, this study analyzed the longitudinal change of cardiac mechanics in a large number of patients enrolled from tertiary centers. So far, this study has included the largest number of KT patients with serial echocardiography data. Our study did not include metabolic parameters or inflammatory markers that are relevant to uremic cardiomyopathy. The improvement of |LV GLS| may accompany an improvement in uremic milieu with KT. Future studies that include alterations in mineral metabolism, insulin resistance, and uremic toxin after KT are needed to understand reverse cardiac remodeling after KT.

Improvements in LV structure and function after KT were observed in patients throughout the full spectrum of pre-KT |LV GLS|. The current study provides an important attribution to the existing knowledge regarding improved cardiac structure and function after successful KT.

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Conflict of Interest

The authors have no financial conflicts of interest.

Author Contributions

Conceptualization: Kim D; Formal analysis: Kim D; Resources: Kim D, Kim M, Park JB, Lee J, Huh KH, Hong GR, Ha JW; Supervision: Choi JO, Shim CY; Writing - original draft: Kim D; Writing - review & editing: Choi JO, Shim CY.

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