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Reduced global longitudinal strain is associated with increased risk of cardiovascular events or death after kidney transplant

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Abstract

Background: Patients with chronic kidney disease are at increased risk of cardiovascular disease (CVD). Even after kidney transplant, the rate of CVD events and death remain elevated. Early detection of patients at risk would be helpful for guiding aggressive preventive therapy. The purpose of this study was to evaluate global longitudinal strain (GLS) as a predictor of CVD events and death after kidney transplant.

Method: Among patients with successful kidney transplant between 3/2009 and 12/2012 at our institution, 111 individuals had an echocardiogram within 6 months of the transplant. Medical records were evaluated for demographics and patient characteristics. Echocardiograms were analyzed for conventional measurements, and GLS was assessed using speckle-tracking analysis.

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Statement of authorship

Kana Fujikura takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Bradley Peltzer takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Results: The median age of the study sample was 54 years. Overall, 60% were men; 35% were non-Hispanic black, and 50% Hispanic. After a mean follow-up of 3.8 ± 0.5 years, there were 21 cardiovascular events or deaths. Patients who experienced an event were older, more frequently had a history of coronary artery disease, and had higher LV filling/longitudinal diastolic annular velocity (E/e') than those who did not. GLS was significantly associated with event-free survival even after adjusting for age, sex, race-ethnicity, hypertension, diabetes, history of coronary artery disease or heart failure, and E/e' .

Conclusion: Reduced GLS peri-transplant is significantly associated with increased CVD events or death after kidney transplant. Larger studies are required to determine the incremental predictive value of GLS over clinical and other echocardiographic parameters for adverse CVD events following renal transplantation.

Keywords

Echocardiogram; Speckle-tracking; Global longitudinal strain; Kidney transplant; Post-transplant events

1. Background

Cardiovascular disease (CVD) remains the leading cause of mortality in the United States, accounting for 611,105 deaths in 2013 [1]. Chronic kidney disease (CKD) is a common condition with a prevalence of 15.2% among American adults, and has long been identified as a risk factor for CVD [2]. The prevalence of CVD is 69.6% among patients aged 66 and older who have CKD, compared to 34.7% among without CKD [3]. Moreover, CVD is a significant comorbidity for patients along the entire spectrum of CKD and end-stage renal disease (ESRD) [4].

Successful kidney transplant is associated with improved long-term outcomes in patients with CKD. Over 17,000 kidney transplants were performed in the United States in 2013 [2]. However, even after transplant, CVD remains a leading cause of death [5]. Improved detection of individuals at higher risk for CVD at the time of kidney transplant could allow identification of those who might benefit from closer cardiovascular follow-up and more aggressive preventive therapies.

Left ventricular (LV) strain analysis by speckle-tracking echocardiography (STE) is an increasingly adopted modality for assessment of myocardial function [3],[6],[7],[8]. STE has shown utility in identifying LV dysfunction even in the context of normal LV ejection fraction in such disorders as ischemic heart disease, cardiomyopathies, and cardiotoxicity following chemotherapy, along with various other pathophysiological processes of the heart [9],[10]. STE has also been related to long-term outcomes in patients with amyloidosis, type 2 diabetes mellitus, and heart failure with preserved ejection fraction, as well as in the general population [11],[12],[13, 14]. Recently, STE was also linked to cardiovascular mortality in patients with end-stage renal disease [15].

The aim of this study was to examine whether STE global longitudinal strain (GLS), used as a measure of subclinical LV dysfunction, is associated with CVD events or death in patients

undergoing kidney transplantation at a large urban health system serving a population predominantly composed of race-ethnic minority groups.

2. Methods

2.1. Study population

After receiving institutional review board approval, we conducted a retrospective cohort study involving adult patients (age 18 or older) undergoing successful kidney transplant between March 2009 and December 2012 at Montefiore Medical Center. The onset of the study period was timed to the installation of an updated clinical echocardiographic data storing system at our institution, which was the beginning of 2009. Patients who completed a clinically indicated echocardiogram within 6 months before or after kidney transplant were evaluated for STE. Demographic and clinical variables were extracted using the hospital's proprietary electronic patient information database (Looking Glass™ Clinical Analytics, Streamline Health, Atlanta, GA) [16]. This database integrates clinical data from all inpatient and outpatient encounters, home care, and community service programs within the Montefiore system. Extractions using Looking Glass™ Clinical Analytics were further verified with manual crosschecking of the data by chart review. Clinical information during the follow-up, including admissions for acute coronary syndromes (ACS) and heart failure (HF), were obtained by query of diagnostic discharge codes (Looking Glass™ Clinical Analytics), supplemented by manual chart review. ACS was defined as unstable angina requiring hospitalization, non-ST elevated myocardial infarction, and ST elevated myocardial infarction. CVD events were defined as a combination of ACS and HF admissions. The primary endpoint was the occurrence of CVD requiring hospitalization or death, ascertained by reviewing all medical charts. Follow-up was extended through December 2015.

2.2. Echocardiographic studies

Echocardiograms performed for clinical indications at MMC were acquired using either Philips iE33 xMATRIX or CX50 xMATRIX (both from Philips Healthcare, Andover, MA). Performance of scans at MMC follow a standardized clinical protocol involving 2D imaging, as well as pulsed wave, continuous wave and color Doppler, in accordance with recommendations of the American Society of Echocardiography [17][18][19]. LV volumes and ejection fraction (EF) were calculated by the biplane Simpson's method. Doppler indices of LV diastolic function, including pulsed-wave Doppler of mitral inflow (E), Doppler tissue imaging (TDI) of the lateral mitral annulus (e'), and E/e' were also obtained from the clinical echocardiogram reports. Echocardiographic cine loops comprising 2 cardiac cycles and stored in Xcelera (Philips Healthcare, Andover, MA) were retrospectively processed to analyze STE using TomTec software (TomTec Imaging Systems Corporation, Unterschleissheim, Germany). STE analysis was performed by an experienced echocardiographer (K.F.) The speckle-tracking analysis was performed using two apical views (apical four-chamber (4ch) and two-chamber (2ch) views), with GLS calculated as their average (Fig. 1) [13]. The endocardial border was traced manually, and the region of interest was adjusted to include the entire myocardium and exclude the pericardium by aligning the epicardial border [20]. The integrity of tracking was visually confirmed as well

as ascertained from the credibility of the strain curves. If necessary, the region of interest was readjusted. Patients with echocardiograms of poor quality not allowing satisfactory tracking were excluded from the study. The frame rate of image acquisition was 42.1 ± 6.7 for apical 4-chamber images and 43.5 ± 9.3 for apical 2-chamber images. Intra-observer variability for GLS showed an intraclass correlation coefficient of 0.87, consistent with high reproducibility.

2.3. Definition of covariates

Race-ethnicity was defined by self-report. Hypertension was defined by a blood pressure $\geq 140/90$ mmHg, use of antihypertensive medication, or by documented history. Diabetes was defined by fasting blood glucose of ≥ 126 mg/dl, HbA1c $\geq 6.5\%$, use of anti-hyperglycemic medication, or by documented history. Smoking was defined by current or ever smoking as recorded in the medical history. Family history of premature CAD was defined by first-degree relative with CAD before age 55 years in male and age 65 years in female as reported in the medical history. History of CAD and heart failure was based on documentation in the medical record. Dependence on peritoneal dialysis or hemodialysis was defined by medical history prior to renal transplant. Use of specific medications was based on documentation in the medical record.

2.4. Statistical analysis

Comparison of demographic, clinical and echocardiographic characteristics in those who did and did not experience CVD or death was performed with the chi-square or Fisher's exact test, or with the Wilcoxon rank-sum test, as appropriate. The unadjusted association of GLS with time to CVD event or death was examined by the Kaplan-Meier method. For this analysis, GLS was dichotomized at the previously reported mean value of -20% [21] and differences assessed by the log-rank test. Cox proportional hazards models were used to evaluate the association of GLS with incident CVD or death after adjustment for covariates. An initial model adjusted for demographic factors (age, sex, and race/ethnicity), while a subsequent model adjusted for all covariates related to outcome at $p < 0.20$. Sensitivity analyses evaluated the association of GLS with incident CVD or death in two subgroups: patients who underwent echocardiography pre-transplant, and those in whom echocardiography was obtained within 100 days pre- or post-transplant. A two-tailed $p < 0.05$ was used to define statistical significance. All statistical analyses were performed using SAS version 9.4 (Cary, North Carolina).

3. Results

There were 153 adult patients who underwent kidney transplant during the study period, along with echocardiography within 6 months of the transplant. Two patients were excluded because of irregular heart rhythm at the time of echocardiography. Twenty-three patients did not have complete data available for STE analysis. In seventeen patients, the transplanted graft failed and hemodialysis was initiated prior to conduct of the echocardiogram. Overall, 111 patients undergoing echocardiography within 6 months of transplant were included in this study. Most echocardiograms (87 patients [78.4%]) were performed within 100 days of

renal transplant. Of the total sample of 111 patients, 65 (58.6%) received echocardiography prior to renal transplant.

The median age of the study sample was 54 (44, 63) years. Overall, 60% of patients were men; 35% were non-Hispanic black, and 50% Hispanic. The patients who experienced a CVD event or death had significantly higher BMI and more frequent history of coronary artery disease (CAD) compared with patients who did not develop events (Table 1A). Patients who experienced the composite endpoint also had larger E/e' and reduced GLS compared with their counterparts who did not (Table 1B). There was no significant difference between the two groups in age, history of heart failure, diabetes, hypertension, family history of premature CAD, hemodialysis, medications, pre-transplant dialysis treatment, left atrial volume index, LV mass index or LVEF.

Patients were followed for a mean of 3.8 ± 0.5 years. Seventeen CVD events (ACS = 14, HF = 3), and four deaths occurred (total 21 events). In an initial model adjusting for age, sex, and race-ethnicity, the hazards ratio for CVD events or death increased by 28% per 1% decrement in absolute value of GLS (Table 2). A subsequent model included factors potentially or demonstrably related to outcome in bivariate analysis, namely, age, BMI, history of CAD, and E/e'. Aspirin was not included in this model because it was associated with history of CAD. In this second multivariable model, the relationship of GLS with CVD or death was moderately attenuated, but remained significant, with each 1% decrement in absolute GLS associated with a 23% increased hazards ratio for this adverse outcome. Kaplan-Meier curves show that participants with $|\text{GLS}| < 20\%$ had a significant higher rate of events than those with $|\text{GLS}| \geq 20\%$. The adjusted association of GLS, modeled as a continuous variable, and CVD events or death is depicted in Fig. 2.

Sensitivity analyses were performed to further explore the findings in key subgroups using more limited adjustment. First, only those patients who underwent echocardiography pre-transplant were assessed in relation to the primary outcome. A model adjusting for age, sex, and race-ethnicity showed that the hazards ratio for CVD events or death was significantly increased by 37% per 1% decrement in absolute value of GLS ($N = 65$, HR 1.37 [1.07, 1.77], $p = 0.014$). Second, the analysis was restricted only to patients who underwent echocardiography within 100 days of the transplant. After adjustment for age, sex, and race-ethnicity, the relative hazard of suffering the primary outcome increased by 25% per 1% decrement in absolute value of GLS ($N = 87$, HR 1.25 [1.11, 1.39], $p < 0.001$) (Table 2).

4. Discussion

This study shows that among patients undergoing successful kidney transplantation in an inner-city health system of predominantly Hispanic and African-American race-ethnicity, reduced GLS documented in the 6 months preceding or following transplant was significantly associated with hospitalization for CVD and all-cause mortality. This association in a predominantly Hispanic and African American cohort was independent of major demographic and clinical variables, as well as traditional echocardiographic measures.

To our knowledge, the present study is the first to show an independent relationship of STE GLS with outcomes in renal transplant recipients. CKD is a known independent risk factor of cardiovascular events with high prevalence of calcified atherosclerosis [22]. Kidney disease has been linked to the full range of CVD, including ischemic heart disease, cerebrovascular disease, peripheral vascular disease, HF, and sudden cardiac death [23][24]. Recently, coronary microvascular dysfunction has been increasingly recognized as a possible cause of CVD events in various conditions including CKD [25][26]. Still, CKD has adverse effects not only upon the vasculature, but also directly upon the myocardium [27]. Indeed, non-dialyzable uremic toxins such as indoxyl sulfate have been shown to contribute to cardiac fibrosis in CKD patients [28]. Early reduction in GLS by STE has been shown to be useful parameter to detect changes in myocardial deformation occurring early in a variety of disorders that lead to clinical heart disease [9] [12][29]. The reduction in GLS shown in our study likely represents myocardial dysfunction caused by multiple factors related to kidney impairment.

Previous studies have investigated the value of echocardiography for predicting outcomes in CKD patients. Chen et al. [30] demonstrated that concentric left ventricular hypertrophy (LVH) was associated with progression to dialysis, and that increased left atrial (LA) diameter and decreased LVEF were associated with faster renal function decline. An independent association between serum uric acid concentration and LV mass index was demonstrated, and this result suggested that the combination of hyperuricemia with LVH to be an independent and powerful predictor for CVD [31]. Our study showed no significant difference in LVEF, LA volume index, LV mass index and E or e' while comparing the groups with and without events after kidney transplant. Although our modest sample size precludes definitive assessment of such differences, we did detect a significantly higher E/e' among those who experienced an event, suggesting higher LV filling pressure in this group. Regardless, the significant association observed for GLS with incident CVD or death was independent of E/e', supporting GLS as a potentially valuable measure of subclinical myocardial disease, and particularly subclinical systolic dysfunction, in this setting.

The present study relied on a single center experience to investigate the association of GLS with outcomes following renal transplantation. To achieve a sufficient sample size to explore this relationship, we included patients with echocardiograms performed within 6 months prior to, or after, renal transplantation. Standard practice at our center is to perform echocardiography in the pre-transplant evaluation, but post-transplant echocardiograms were done at physician discretion, and may have included clinical indications. Recognizing that inclusion of patients undergoing echocardiography post-, rather than pre-transplant could bias our results, we performed sensitivity analyses limited to patients with pre-transplant echocardiograms; these analyses showed that the relationship for GLS and risk of CVD or death was maintained as compared with the overall cohort after adjustment for demographic covariates. Moreover, a similar demographic-adjusted relationship was observed when the peri-transplant window was reduced to 100 days before or after transplant. These sensitivity analyses support the robust association of GLS with outcomes, and provide impetus for larger studies that specifically evaluate the incremental prognostic value of GLS obtained pre-transplant and risk of adverse events post-transplant.

Intervendor and inter-observer/intra-observer variabilities are known technical limitations in STE analysis. Intervendor variability has been improved since 2010 when the joint task force on strain standardization was established among the European Association of Cardiovascular Imaging and the American Society of Echocardiography and Industry. However, small but significant difference in GLS measurement still exists among vendors [32]. To avoid this intervender variability, Digital Imaging and Communications in Medicine (DICOM) data acquired from patients using echocardiography device of a single vendor was used in this study, and the data was processed using a software dedicated for speckle-tracking analysis of a single vendor. Another strength of the present study is that all the speckle-tracking analyses were performed by a single experienced echocardiographer (K.F.) within two weeks, thereby avoiding inter-observer variability and minimizing intra-observer variability.

There are several limitations in our study. First, this study was designed after the data were obtained, such that only data already collected were available for this study. Second, bias may have occurred in the process of patient selection, as only those patients who had echocardiography within 6 months of the kidney transplant were evaluated in this study. As noted above, however, the results held after narrowing the time interval between echocardiography and transplantation or restricting the analysis to patients who had echocardiography pre-transplant. Third, patients with poor image quality for STE analysis were excluded from this study, which is a general limitation in any echocardiography-based study. Fourth, we based our determination of GLS from two apical views, rather than three apical views now more common in clinical practice, because 8 patients in our cohort did not have apical-3-chamber views suitable for strain assessment, which would have further compromised our sample size. The two-view approach has been shown to yield useful prognostic information [13]. To the extent that the three-apical-view approach affords more extensive and accurate assessment of GLS, the association for three-apical-view GLS could be stronger than that documented here for two-chamber GLS. Fifth, our final model had a potential of overfitting from a statistical point of view given the limited number of events; however, the 95% confidence intervals did not meaningfully widen from the minimally to fully adjusted model, indicating that overfitting was not a problem in the present analyses. Sixth, our findings come from a predominantly Hispanic and black cohort, and the results are not necessarily generalizable to other ethnic groups. In this regard, it bears noting that the GLS cutpoint of -20 used for dichotomization in our Kaplan-Meier analysis comes from outside populations, and different vendors. Additional study is necessary to identify optimal vendor-specific cutpoints applicable to different populations. Last, as noted above, the sample size was modest, limiting the number of covariates that could be simultaneously adjusted for in our models. Hence, our findings will require replication in larger samples with more extensive adjustment for covariates.

5. Conclusion

GLS proved to be independently associated with CVD events and death. This study suggests that GLS determined by echocardiography may be an important screening tool for risk stratification of patients undergoing kidney transplant. Additional studies are required to determine the incremental value of speckle-tracking GLS in patients undergoing pre-renal-

transplant evaluation, and whether intensification of cardiovascular preventive strategies in those with reduced GLS could improve cardiovascular outcomes.

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Fig. 1. Strain analysis. (A) Tracing of endocardium for analysis, (B) strain calculation, (C) an example of segmental and average longitudinal strain curve.

Fig. 2. Kaplan-Meier curve. The patient group with impaired GLS (absolute value $<20\%$) showed significantly increased risk of CVD events or death compared to the group with preserved GLS (absolute value $\geq 20\%$).

Table 1

A) Patient characteristics and B) echocardiographic parameters in patients with or without CVD event or death after kidney transplant.

Entiresample (n = 111)		No event (n = 90)		CVD event or death (N = 21)		p-value
	Median (25th percentile, 75th percentile)		Median (25th percentile, 75th percentile)		Median (25th percentile, 75th percentile)	
A						
Age, year old	54 (44, 63)		53 (42, 62)		59 (52, 64)	0.053
Male, n (%)	60 (54.1)		48 (53.3)		12 (57.1)	0.752
Race-ethnicity						0.769
Non-Hispanic White	10 (9.0)		7 (7.8)		3 (14.3)	
Non-Hispanic Black	35 (31.5)		29 (32.2)		6 (28.6)	
Hispanic	50 (45.1)		41 (45.6)		9 (42.9)	
Others	16 (14.4)		13 (14.4)		3 (14.3)	
Clinical variables	n (%)		n (%)		n (%)	p-value
Diabetes	45 (40.5)		35 (38.9)		10 (47.6)	0.463
Hypertension	99 (89.2)		80 (88.9)		19 (90.5)	1.000
Smoking	6 (5.4)		5 (5.6)		1 (4.8)	1.000
Hemodialysis	82 (73.9)		80 (88.9)		19 (90.5)	1.000
BMI, kg/m ²	28.1 (23.0,31.8)		27.3 (22.8,31.1)		30.5 (28.3, 33.4)	0.032
Systolic blood pressure, mmHg	135 (120,152)		135(118,151)		135 (124,156)	0.522
Family history of premature CAD	6 (5.4)		4 (4.4)		2 (9.5)	0.317
CAD	20 (18.0)		12 (13.3)		8 (38.1)	0.023
Heart failure	4 (3.6)		2 (2.2)		2 (9.5)	0.161
Treatment	n (%)		n (%)		n (%)	p-value
ACE/ARB	25 (23.8)		21 (25.0)		4 (19.1)	0.567
beta blocker	55 (52.4)		44 (52.4)		11 (52.4)	1.000
Statin	34 (32.4)		24 (28.6)		10 (47.6)	0.095
Aspirin	35 (33.3)		23 (27.4)		12 (57.1)	0.009
Hemodialysis	95 (87.2)		76 (86.4)		19 (90.5)	1.000
Peritoneal dialysis	2 (1.8)		2 (2.3)		0 (0.0)	1.000
B						
LVEF, %	62 (57, 65)		62 (58, 65)		60 (51, 70)	0.687

	Entiresample (n = 111) Median (25th percentile, 75th percentile)	No event (n = 90) Median (25th percentile, 75th percentile)	CVD event or death (N = 21) Median (25th percentile, 75th percentile)	p-value
L/A volume index, ml/m ²	34.5 (27.3, 43.8)	33.9 (27.3, 42.6)	35.8 (28.1, 44.6)	0.629
Relative wall thickness	0.42 (0.37, 0.50)	0.41 (0.37, 0.50)	0.44 (0.40, 0.51)	0.296
LV mass index, g/m ²	97.7 (73.7, 119.9)	95.2 (71.9, 121.9)	103.5 (86.9, 113.9)	0.610
E, cm/s	90.3 (75.0, 111.2)	86.9 (75.0, 106.9)	108.3 (80.2, 136.6)	0.059
e', cm/s	8.1 (6.4, 11.2)	8.3 (6.8, 11.7)	7.0 (6.1, 9.6)	0.124
E/e'	11.2 (8.0, 16.0)	10.6 (7.7, 15.2)	13.1 (11.8, 16.8)	0.032
GLS, %	-20.3 (-22.8, -17.0)	-20.7 (-22.9, -17.8)	-16.3 (-19.6, -13.8)	<0.001

Table 2

Multivariable models and sensitivity analysis to assess the hazards ratio for CVD events or death per 1% decrement in absolute value of GLS.

	N	HR [95% CI]	p-value
<i>Entire sample</i>			
Model 1	111	1.28 [1.13,1.44]	<0.001
Model 2	105	1.23 [1.07,1.42]	0.003
<i>Echo pre-transplant</i>			
Model 1	65	1.37 [1.07,1.77]	0.014
<i>Echo within 100 days of transplant</i>			
Model 1	87	1.25 [1.11,1.39]	<i>p</i> < 0.001

(A) Adjusted for age, sex, race-ethnicity.

(B) Adjusted for age, sex, race-ethnicity, HTN, DM, CAD, HF, E/E'.