Prognostic Implications of Left Ventricular Global Longitudinal Strain in Predialysis and Dialysis Patients

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Chronic kidney disease (CKD) is a worldwide growing epidemic associated with an increased risk of cardiovascular morbidity and mortality. Left ventricular (LV) global longitudinal strain (GLS) is a measure of LV systolic function associated with prognosis in the general population. However, little is known about the association between LV GLS and survival in patients with CKD. The aim of the present study was to investigate the prognostic implications of LV GLS in predialysis and dialysis patients specifically. LV GLS was measured in a retrospective cohort of predialysis and dialysis patients (CKD stage 3b to 5) who underwent clinically indicated echocardiography between 2004 and 2015. Patients were divided into 4 groups according to quartiles of LV GLS: first quartile (LV GLS ≤10.6%, worst function), second quartile (LV GLS 10.7% to 15.1%), third quartile (LV GLS 15.2% to 17.8%), and fourth quartile (LV GLS ≥17.9%, best function). The primary end point was all-cause mortality. Of 304 patients (62 ± 14 years, 66% male), 65% were in predialysis and 35% in dialysis. During a median follow-up of 29 months (interquartile range 16 to 58 months), 34% of patients underwent renal transplantation and 36% died. Patients with LV GLS ≤10.6% showed significantly worse prognosis compared with the other groups (log-rank test, p <0.001). LV GLS ≤10.6% was significantly associated with increased risk of all-cause mortality (hazard ratio 2.18, 95% CI 1.17 to 4.06, p = 0.014) after correcting for age, gender, albumin levels, atrial fibrillation, and renal transplantation. In conclusion, in predialysis and dialysis patients, severely impaired LV GLS is independently associated with an increased risk of mortality. **(Am J Cardiol 2017;120:500−504)**

Chronic kidney disease (CKD) is a worldwide growing epidemic associated with an increased risk of cardiovascular morbidity and mortality.[1−4] Heart failure is particularly frequent in patients with CKD.[2] Pressure and volume overload and nonhemodynamic factors associated with CKD induce left ventricular (LV) hypertrophy, reduce capillary density, and increase myocardial fibrosis that lead to LV diastolic and systolic dysfunction.[5] These processes have been proposed as important determinants of increased mortality in this population.[5] LV global longitudinal strain (GLS) assessed with 2-dimensional speckle-tracking echocardiography is a marker of LV systolic function and has been shown to correlate with the extent of myocardial fibrosis.[6,7] The incremental prognostic value of LV GLS over conventional echocardiographic parameters of LV systolic function such as LV ejection fraction has been demonstrated in patients with various cardiovascular diseases (ischemic heart disease, valvular heart disease, and heart failure).[8] However, little is known about the association between LV GLS and prognosis in patients with CKD. Accordingly, the aim of the present study was to investigate the prognostic implications of LV GLS in predialysis and dialysis patients specifically.

Methods

From a departmental database of predialysis and dialysis patients, those who were clinically referred for transthoracic echocardiography at the Leiden University Medical Center between 2004 and 2015 were identified and included in this retrospective study. Patients were diagnosed with CKD stage 3b to 5 according to the classification of the Kidney Disease: Improving Global Outcomes 2012 Clinical Practice Guideline for the Evaluation and Management of CKD.[9] Patients younger than 18 years, with limited echocardiographic examination or with inadequate image quality for off-line analysis, were excluded. Clinical data were collected through review of the electronic medical records (HiX; ChipSoft, Amsterdam, the Netherlands) and the departmental cardiology information system (EPD-vision; Leiden University Medical Center, Leiden, the Netherlands) and retrospectively analyzed. Patients were followed up for the occurrence of all-cause mortality through case record review and the national death registry. The occurrence of renal transplantation during follow-up was registered through case record review. The institutional review board approved this retrospective analysis of clinically acquired data.

Baseline clinical variables included demographic parameters, cardiovascular risk factors, medication use, and

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laboratory results. Estimated glomerular filtration rate was calculated by the CKD Epidemiology Collaboration (CKD-EPI) equation.[9] Residual renal function was calculated by the creatinine clearance using the concentration of creatinine in a 24-hour urine specimen and the predialysis plasma creatinine concentration.[10]

Patients were imaged in the left lateral decubitus position using commercially available systems (Vivid 7 or E9; General Electric Vingmed, Milwaukee, Wisconsin) equipped with 3.5-MHz or M5S transducers. The echocardiographic data were digitally stored in cine loop format for off-line analysis (EchoPac 112.0.1; GE Medical Systems, Horten, Norway). Linear dimensions of the left ventricle were measured on M-mode recordings from the parasternal long-axis view.[11] From the apical 4- and 2-chamber views, the LV end-diastolic and end-systolic volumes were measured according to the biplane Simpson's method, and LV ejection fraction was derived.[11] Left atrial volume was measured in the apical 4-chamber view using the disk summation technique and was indexed for body surface area. Right ventricular function was assessed by measuring the tricuspid annular plane systolic excursion on the focused apical 4-chamber view of the right ventricle applying anatomical M-mode.[11] Mitral regurgitation severity was graded semi-quantitatively by measuring the width of the vena contracta from color Doppler data.[12] Pulsed wave Doppler recordings of the mitral inflow were used to measure peak E (early diastolic) and A (late diastolic) wave velocities. LV relaxation was assessed with color-coded tissue Doppler imaging measuring the lateral E′ wave velocity of the mitral annulus in the apical 4-chamber view, and the E/E′ ratio was derived as a measure of LV filling pressures.[13] LV GLS was measured using 2-dimensional speckle-tracking echocardiography on standard routine grayscale images of apical 4-, 2-chamber and long-axis views.[14] Conventionally, LV GLS is presented as negative values because it indicates the shortening of the myocardium relative to the original length.[14] However, the magnitude (absolute value) of LV GLS is presented in this analysis.

Categorical variables were presented as numbers and percentages. Continuous variables with a normal distribution were presented as the mean ± SD and those without a normal distribution were presented as the median and interquartile range. Univariate Cox proportional hazard analysis was performed to identify the demographic, clinical, and echocardiographic variables associated with all-cause mortality. Multivariate survival analysis using Cox proportional hazard model was used to determine the independent association between LV GLS and all-cause mortality. LV GLS and LV ejection fraction were not included in the same model to avoid multicollinearity. The occurrence of renal transplantation during follow-up was introduced as a time-dependent covariate. Patients were divided into 4 groups according to quartiles of LV GLS. Cumulative event-free survival rates from the time of echocardiography were calculated using the Kaplan-Meier method and compared across the quartiles of LV GLS. All statistical tests were 2 sided and a p-value of <0.05 was considered statistically significant. Statistical analyses were performed using the SPSS software, version 20.0 (IBM Corp, Armonk, New York).

Table 1
Characteristics of predialysis and dialysis patients

Variable	N=304
Clinical characteristics:	
Age (years)	62 ± 14
Men	200 (66%)
Chronic kidney disease	
Pre-dialysis	197 (65%)
Dialysis	107 (35%)
Dialysis type (haemodialysis)*	82 (77%)
Dialysis vintage (days)*	157 (53-357)
Renal transplantation future	104 (34%)
Heart rate (beats per minute)	73 ± 15
Systolic blood pressure (mmHg)	136 ± 22
Diastolic blood pressure (mmHg)	77 ± 12
Body mass index (kg/m^2)	25 ± 5
NYHA class III-IV	29 (10%)
Smoker	184 (63%)
Diabetes mellitus	90 (30%)
Hypertension	252 (83%)
Hypercholesterolemia	120 (39%)
Previous myocardial infarction	71 (23%)
Previous CABG/PCI	76 (25%)
Peripheral artery disease	52 (17%)
Atrial fibrillation	63 (21%)
Medications:	
Diuretics	198 (67%)
ACE inhibitor/ARB	184 (62%)
Beta-blocker	182 (61%)
Calcium antagonist	119 (40%)
Statin	181 (61%)
Antiplatelet	99 (33%)
Oral anticoagulation	83 (28%)
Nitrates	34 (11%)
Laboratory results:	
Residual renal function (ml/min)*	5.3 (2.2-8.9)
eGFR CKD-EPI (mL/min/1.73m^2)†	18 ± 7
Creatinine (umol/L)†	312 ± 116
Urea (mmol/L)	22 ± 7
Corrected calcium (mmol/L)	2.2 ± 0.1
Phosphate (mmol/L)	1.4 ± 0.4
Parathyroid hormone (pmol/L)	16 (8-25)
Albumin (g/L)	41 ± 6
Glucose (mmol/L)	6 ± 3
LDL-cholesterol (mmol/L)	2.4 ± 1.1
Hemoglobin (mmol/L)	7.2 ± 1.0

Continuous data are presented as mean ± SD or median (interquartile range). Categorical data are presented as numbers and percentages.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CABG = coronary artery bypass graft; CKD-EPI = chronic kidney disease epidemiology collaboration; eGFR = estimated glomerular filtration rate; LDL = low-density lipoprotein; NYHA = New York Heart Association; PCI = percutaneous coronary intervention.

* Measured only in dialysis patients.

† Measured only in predialysis patients.

Results

A total of 304 patients (66% men, mean age 62 ± 14 years) were included. Tables 1 and 2 summarize the clinical and echocardiographic characteristics of the overall patient population. During a median follow-up duration of 29 months (interquartile range 16 to 58 months), 104 (34%) patients underwent renal transplantation and 108 (36%) patients died.

Table 2
Echocardiographic characteristics of predialysis and dialysis patients

Variable	N=304
Ventricular septum width (mm)	11 ± 2
Posterior wall width (mm)	10 ± 2
Left ventricular end-diastolic diameter (mm)	53 ± 9
Left ventricular end-systolic diameter (mm)	36 ± 11
Left ventricular end-diastolic volume (ml)	112 ± 53
Left ventricular mass index (gr/m^2)	114 ± 36
Left ventricular end-systolic volume (ml)	54 ± 45
Left ventricular ejection fraction (%)	56 ± 16
Left atrial volume index (mL/m^2)	29 ± 15
TAPSE (mm)	18 ± 5
Moderate/severe mitral regurgitation	45 (15%)
Peak E-wave velocity (cm/s)	78 ± 31
Peak A-wave velocity (cm/s)	80 ± 26
Lateral E′ (cm/s)	6 ± 3
Lateral E/E′	12 (8-19)
Left ventricular global longitudinal strain (%)	14 ± 5

Continuous data are presented as mean ± SD or median (interquartile range). Categorical data are presented as numbers and percentages.
TAPSE = tricuspid annular plane systolic excursion.

On univariate Cox proportional hazard analysis, LV GLS and LV ejection fraction were significantly associated with all-cause mortality together with age, male gender, albumin levels, atrial fibrillation, and renal transplantation. LV GLS (hazard ratio [HR] 0.96, 95% CI 0.92 to 0.998; p = 0.041) and LV ejection fraction (HR 0.99, 95% CI 0.97 to 0.997; p = 0.019) were independently associated with all-cause mortality after correcting for age, male gender, albumin levels, atrial fibrillation, and renal transplantation.

Patients were divided into 4 groups according to quartiles of LV GLS: first quartile (LV GLS ≤10.6%, worst function), second quartile (LV GLS 10.7% to 15.1%), third quartile (LV GLS 15.2% to 17.8%), and fourth quartile (LV GLS ≥17.9%, best function). Kaplan-Meier curves of the cumulative event-free survival for the different quartiles of LV GLS are presented in Figure 1. Patients with LV GLS ≤10.6% (most impaired LV systolic function) showed significantly worse prognosis compared with the other groups (log-rank chi-square = 31.17, p <0.001). Importantly, patients within the lowest LV GLS quartile (LV GLS ≤10.6%) were less frequently recipients of renal transplantation (8% compared with 32% in patients with LV GLS 10.7% to 15.1%, 49% in patients with LV GLS 15.2% to 17.8%, and 47% in patients within the highest LV GLS quartile ≥17.9%). On multivariate analysis, LV GLS ≤10.6% was independently associated with increased risk of all-cause mortality after correcting for age, gender, albumin levels, atrial fibrillation, and renal transplantation as time-dependent covariate (Table 3).

Discussion

CKD is associated with structural and functional LV remodeling as a consequence of pressure and volume overload and nonhemodynamic factors.[5] Pressure overload is the result of chronic hypertension and vascular stiffness, whereas anemia, arteriovenous fistulas, and sodium and water retention lead to volume overload.[15] To keep LV wall stress close to normal, the left ventricle responds to pressure and volume overload with hypertrophy and dilatation.[15] As LV hypertrophy progresses, the interstitial space also increases with accumulation of collagen (interstitial or replacement fibrosis) potentially causing a reduction in contractility. In addition, LV hypertrophy increases the myocardial oxygen demand, which causes myocardial hypoperfusion, cardiomyocyte loss, and further interstitial fibrosis.[15,16] Furthermore, nonhemodynamic factors associated with CKD such as inappropriate renin-angiotensin-aldosterone system activation, oxidative stress, inflammation, and stimulation of prohypertrophic and profibrogenic factors also contribute to LV remodeling.[5,15] These structural changes cause impaired LV contractility, which can be detected with LV GLS. Several studies have demonstrated the correlation between LV GLS and the extent of myocardial fibrosis.[6,7] In a recent study, Kramann et al[7] showed that LV strain parameters were significantly associated with the grade of myocardial fibrosis in rat models with uremic cardiomyopathy. The larger the extent of myocardial fibrosis, the more impaired the value of LV GLS. In addition, it has been shown that LV GLS is a more sensitive marker of LV systolic dysfunction than LV ejection fraction.[17] Patients with LV hypertrophy and preserved LV ejection fraction may show impaired LV GLS in various clinical scenarios indicating that LV GLS better reflects the true damage of the LV myocardium compared with LV ejection fraction.[18] In the present study, the mean LV ejection fraction was >50% in most predialysis and dialysis patients. However, mean LV GLS was significantly reduced suggesting that the LV contractility is significantly reduced probably because of ongoing LV remodeling with increased fibrosis formation.

The prognostic value of LV GLS has been demonstrated in several clinical scenarios, including patients with preserved LV ejection fraction.[8,19,20] However, the evidence correlating LV GLS and prognosis in patients with CKD is limited.[7,21,22] In a recent study, including 171 dialysis patients, LV GLS was independently associated with all-cause mortality (HR 1.10, 95% CI 1.03 to 1.17; p <0.01).[7] In addition, in 447 patients with a wide range of estimated GFR, LV GLS was independently associated with all-cause mortality (HR 1.08, 95% CI 1.01 to 1.15; p = 0.03).[21] Similar results were observed in a study including 183 patients with stage 4 and 5 CKD, where LV GLS was independently associated with all-cause mortality (HR 1.09, 95% CI 1.02 to 1.16; p = 0.01).[22] The present study, with the largest cohort of predialysis and dialysis patients so far, demonstrates that patients within the lowest quartile of LV GLS showed worse prognosis compared with the other groups, and LV GLS ≤10.6% was associated with twofold increased risk of all-cause mortality after correcting for renal transplantation. This is clinically relevant because renal transplantation is considered as a life-saving treatment in these patients and proper selection of patients receiving a renal transplant is crucial to optimize the results of this therapy. Whether LV GLS improves after renal transplantation has not been evaluated.

Several limitations should be acknowledged. First, this was an observational, retrospective study. In addition, only predialysis and dialysis patients from the departmental database were included in the present study, after having a

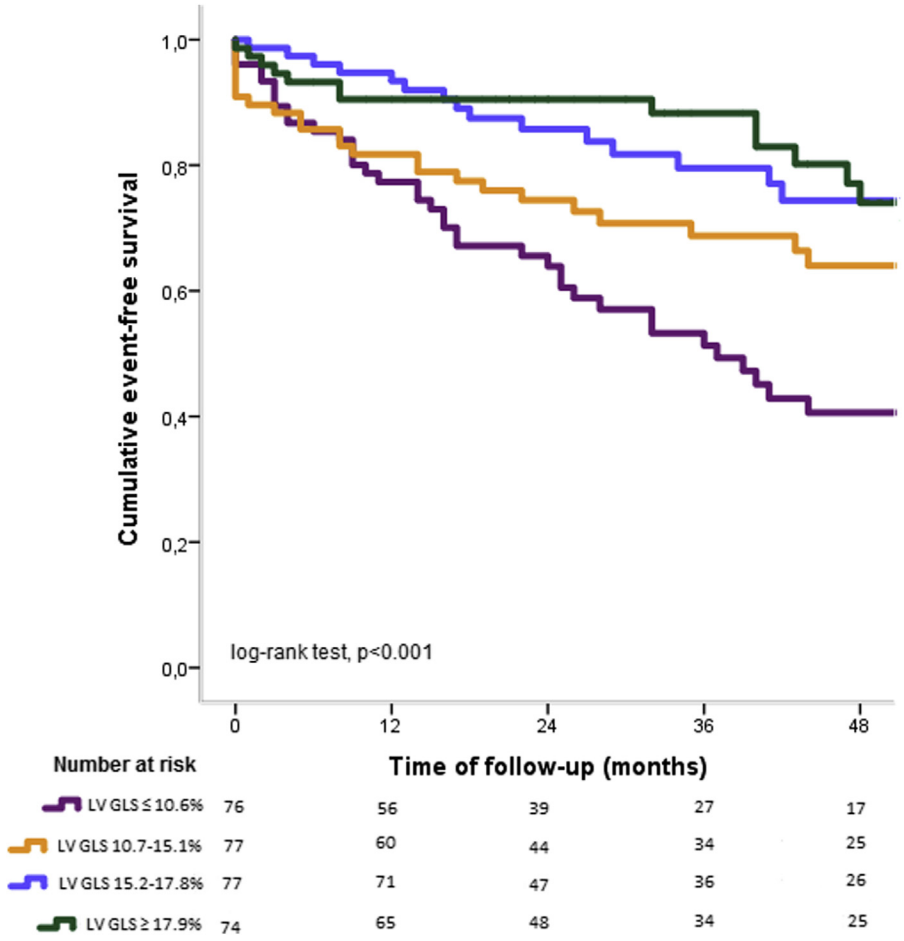

Figure 1. Kaplan-Meier curves of the cumulative event-free survival according to the LV GLS quartile. The cumulative survival rates were compared between the different quartiles of LV GLS.

Table 3
Association between LV GLS and all-cause mortality: Cox proportional hazard model

Variables	Univariate HR (95% CI)	P-value	Multivariate HR (95% CI)	P-value
Renal transplantation	0.08 (0.04-0.15)	<0.001	0.31 (0.15-0.66)	0.002
Age (years)	1.07 (1.05-1.09)	<0.001	1.05 (1.03-1.07)	<0.001
Men	1.26 (0.83-1.90)	0.279	1.02 (0.67-1.57)	0.917
Albumin (g/L)	0.90 (0.87-0.93)	<0.001	0.89 (0.86-0.92)	<0.001
Atrial fibrillation	2.06 (1.35-3.13)	0.001	1.15 (0.73-1.80)	0.542
LV GLS (versus ≥17.9%)				
15.2-17.8%	1.41 (0.71-2.79)	0.323	1.80 (0.91-3.59)	0.094
10.7-15.1%	2.12 (1.12-4.01)	0.021	1.38 (0.72-2.64)	0.328
≤10.6%	4.00 (2.19-7.31)	<0.001	2.18 (1.17-4.06)	0.014

CI = confidence interval; GLS = global longitudinal strain; HR = hazard ratio; LV = left ventricular.

clinically indicated echocardiography, introducing a potential selection bias. Furthermore, echocardiography was performed after dialysis therapy, where LV GLS may have been affected by changes in loading conditions.

In predialysis and dialysis patients, severely impaired LV GLS was independently associated with worse prognosis, even after correction for renal transplantation.

Disclosures

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