Echocardiographic Parameters as Cardiovascular Event Predictors in Hemodialysis Patients

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Abstract

Background: Patients with chronic kidney disease (CKD) on hemodialysis have high rates of cardiovascular morbidity and mortality. Although structural and functional echocardiographic alterations in patients undergoing hemodialysis have been the subject of several survival analysis studies, the prognostic value of these alterations is not well established in literature.

Objective: To determine the prognostic value of echocardiographic parameters in patients with CKD on hemodialysis.

Methods: Sixty consecutive patients with CKD on hemodialysis were clinically evaluated and underwent Doppler echocardiography, being followed for 19 ± 6 months. The outcome measures were fatal and nonfatal cardiovascular events and overall mortality. The predictive value of echocardiographic variables was evaluated by Cox regression model and survival curves were constructed using the Kaplan-Meier method and log rank test to compare them.

Results: Rates of survival free of cardiovascular events, of cardiovascular and overall mortality in two years were 79.4%, 88.5% and 83% respectively. Diabetes, previous diagnosis of cardiovascular disease (CVD), ejection fraction, fractional shortening, left ventricular systolic diameter and E/e' ratio were predictors of cardiovascular outcome at univariate analysis. In the multivariate analysis, previous history of CVD (HR = 6.17, 95%CI: 1.7 - 22.2, p = 0.005) and moderate to severe diastolic dysfunction (HR = 3.76, 95%CI: 1.05 - 13.4, p = 0.042) were independent risk factors for cardiovascular events.

Conclusion: Moderate to severe diastolic dysfunction is an independent predictor of cardiovascular events in hemodialysis patients. (Arq Bras Cardiol 2012;99(2):714-723)

Keywords: Echocardiography, doppler; renal insufficiency, chronic; survival analysis; dialysis; prognosis.

Introduction

The annual mortality rates in patients with chronic kidney disease (CKD) undergoing dialysis are high. According to the dialysis census of the USA[1], the survival of hemodialysis patients in the country was 77.4% in one year and 34.2% in five years, from 1999 to 2003. In Brazil, the annual crude mortality was 17.1% in 2009[2].

Cardiovascular diseases (CVD) account for approximately 50% of all deaths in patients undergoing hemodialysis. Moreover, these patients are often hospitalized and CVD account for approximately one third of hospital admissions[3].

Structural and functional alterations detected by echocardiography, such as left ventricular (LV) hypertrophy and systolic and diastolic dysfunction, are very prevalent in the hemodialysis population. Doppler echocardiographic diagnosis of these abnormalities has been an important step for the characterization of individuals with higher cardiovascular risk[4,5].

Several studies have sought to determine the prognostic value of alterations such as LV hypertrophy and systolic dysfunction in patients undergoing hemodialysis[6-8]. However, studies evaluating the predictive value of diastolic dysfunction in this population are scarce. Thus, the objective of this study was to determine the prognostic value of echocardiographic parameters in patients with CKD undergoing hemodialysis.

Methods

Study design and population

This is an observational, analytical, prospective cohort study, carried out in the Dialysis Service of Centro de Nefrologia do Maranhão (CENEFRON). We evaluated 60 consecutive patients with CKD undergoing hemodialysis in this service. The hemodialysis sessions of all patients were performed three times a week, and lasted four hours, in volumetric machines

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(Baxter Tina®, USA; Fresenius 4008S® or Fresenius 4008B®, Germany). The dialysis filters used were Polysulfone, low-flow type (Hemoflow, Fresenius®, Germany), chosen according to the calculation of the patient's body surface.

Inclusion criteria were patients aged 18 years and older, undergoing hemodialysis for at least three months. Exclusion criteria were: recent history (less than six months) of acute myocardial infarction (AMI), percutaneous or surgical revascularization, unstable angina or cerebrovascular accident (CVA), decompensated congestive heart failure (CHF); severe valvular disease; pulmonary hypertension, blood pressure > 160/110 mmHg, uncontrolled atrial fibrillation or complex ventricular arrhythmia (nonsustained ventricular tachycardia, frequent and polymorphic extrasystoles, in pairs and salvoes), uncontrolled blood sugar levels, malignancies, active infection; irregular dialysis regimen; incapacity to obtain informed consent from the patient and inadequate echocardiographic window.

Patients were clinically evaluated and underwent a Doppler echocardiography during the period of February to September 2009, with an interval < 30 days between the two procedures. Subsequently, they were regularly followed until May 2011 or until the occurrence of outcome.

The project was approved by the CENEFRON Research and Ethics Committee in Research of Universidade Federal do Maranhão. We obtained a signed Free and Informed Consent Form (FICF) from all patients included in the study.

Doppler echocardiogram

The echocardiograms were performed on echocardiography equipment, model Vivid 3 Cardiovascular Ultrasound System (GE Healthcare, General Electric Company, USA) with a 3-7 mHz transducer and resources to obtain M-mode, two-dimensional and Doppler echocardiography (pulsed continuous, and tissue). The examinations were performed in the interdialytic period, within 24 hours after the dialysis session by a single medical professional, trained and skilled in echocardiography, with patients at rest and in left lateral decubitus position. Echocardiographic measurements followed the recommendations of the American Society of Echocardiography[9-12] and, for each variable, at least three cycles were analyzed.

The assessment of LV geometry was obtained by two-dimensional image, with the following variables: end-diastolic septal thickness (EDS), end diastolic posterior wall (EDPW), left ventricular end-diastolic diameter of (LVEDD) and left ventricular end-systolic diameter (LVESD).

The assessment of LV geometry was obtained by the two-dimensional image, with the following variables: end-diastolic septal thickness (EDST), end-diastolic posterior wall thickness (PWT), left ventricular end-diastolic diameter (LVEDD) and left ventricular end-systolic diameter (LVESD).

The left ventricular mass (LVM) was calculated using the formula proposed by Devereux et al.[13] and then indexed to body surface area (BSA), to obtain the left ventricular mass index (LVMI = LVM / BSA) . The relative wall thickness (RWT) was obtained by the formula EDT + EDS/LVEDD. The left ventricular ejection fraction (LVEF) was calculated by the method described by Teichholz et al.[14] and the left ventricular systolic fractional shortening by the formula (LVEDD - LVESD)/ LVEDD. The left atrial volume (LAV) was determined from the two-dimensional planimetry using the biplane method of Simpson[15] and then indexed to the BSA to obtain the left atrial volume index (LAVi = LAV / BSA).

Mitral flow was measured in apical four-chamber view by pulsed Doppler. The sample was positioned between the distal ends of the mitral valve leaflets, and then the following variables were obtained: early (E) and late (A) transmitral diastolic velocities, E/A ratio and E-wave deceleration time (EDT). Tissue Doppler was performed in the apical four-chamber view to obtain the velocities of the mitral annulus. The sample was placed at the junction of the LV lateral wall with the mitral annulus[16], and then early (e') and late (a') diastolic velocities of the mitral annulus were identified, as well as the e'/ a' and E/e' ratios.

Left ventricular hypertrophy (LVH) was diagnosed when LVMI was > 115 g/m^2 for men and > 95 g/m^2 for women.

LV geometry was classified according to the values of RWT and LVMI as: concentric hypertrophy (presence of LVH and RWT > 0.42), eccentric hypertrophy (presence of LVH and RWT ≤ 0.42), concentric remodeling (absence of LVH and RWT > 0.42) and normal geometry (no LVH and RWT ≤ 0.42). We defined left atrial (LA) enlargement in the presence of LAVI > 28 mL/m^2, while LV dilatation was defined when the LVEDD was > 5.9 cm for men and > 5.3 cm for women[15].

Systolic dysfunction was considered when the EF was < 55%[15]. LV diastolic function was classified into four patterns: normal, abnormal relaxation (mild diastolic dysfunction), pseudonormal (moderate diastolic dysfunction) and restrictive (severe diastolic dysfunction). It was considered abnormal relaxation when E / A < 1; restrictive pattern when E/A > 2 and pseudonormal pattern when E/A was > 1 and < 2 in association with E/e' > 10[17].

Demographic, clinical and laboratory data

Demographic and clinical data, including age, sex, history of smoking, comorbidities and duration of dialysis were obtained from detailed analysis of medical records and interviews with the patient and the attending physician, when necessary. Previous cardiovascular event was defined as a history of typical angina or myocardial infarction, ischemic or hemorrhagic CVA and congestive heart failure with functional class > II.

Before performing each Doppler echocardiogram, blood pressure was measured and anthropometric data and ratios were obtained (weight, height, BSA, body mass index), which were measured according to standard procedures and using suitable materials. The body mass index (BMI) was calculated by dividing weight (kg) by squared height (m), considering malnutrition when < 18.5 kg/m^2. The BSA was obtained using the formula of Dubois and Dubois[18].

All biochemical measurements were performed by a single laboratory, located in CENEFRON, and data were collected from patients' charts.

Outcomes

The primary endpoint or cardiovascular outcome included fatal and nonfatal cardiovascular events. Cardiovascular events were defined by angina with coronary stenosis > 50% at coronary angiography, nonfatal AMI, myocardial revascularization procedure, nonfatal ischemic or hemorrhagic CVA, CHF requiring hospitalization and death from cardiovascular causes (including sudden death, AMI and CVA). The secondary outcomes included overall mortality.

Outcomes were obtained from monthly review of medical documentation, including medical records and death certificates, as well as communication with the physician and patient's relatives. Patients who underwent kidney transplant or who switched dialysis modality were censored in the study.

Statistical analysis

Statistical analyzes were performed using the Statistical Package for Social Sciences - SPSS ® 17.0 (SPSS Inc, USA). Quantitative variables were expressed as mean with standard deviation or median and categorical variables as percentages.

For comparison of proportions between groups with and without outcome, we used the Chi-square test and for comparison of quantitative variables, Student's *t* test for independent samples. To estimate the hazard ratios (HR), we performed univariate analysis using Cox proportional hazards model by and then, variables with $p < 0.10$ were included in the multivariate analysis using the same model. Survival curves were constructed using the Kaplan-Meier method and log rank test was used to compare survival curves in univariate analysis. The significance level was defined as $p < 0.05$.

Results

The study population consisted of 31 (51.7%) men and 29 (49.3%) women, with a mean age of 49.2 ± 13.7 years, ranging from 22 to 76 years. The demographic, clinical, biochemical and echocardiographic characteristics of the population are listed in Table 1.

The cause of CKD was attributed to hypertensive nephrosclerosis in 30% of cases, to chronic glomerulonephritis in 30%, to diabetic nephropathy in 16.7%, to polycystic kidney disease in 5%, to chronic pyelonephritis in 1.7% and to other diseases in 16.7% of cases.

Among the individuals included in the study, 25% had a previous diagnosis of CVD: three patients diagnosed with CHF, six with a history of typical angina or acute myocardial infarction and six with a history of CVA.

The main diagnosed echocardiographic alterations were: left atrial enlargement (49.2%), LV dilatation (20%), LVH (85%), systolic dysfunction (26.7%) and diastolic dysfunction (83.6%).

According to the degree of diastolic dysfunction, 16.4% of patients had restrictive flow; 20% had pseudonormal pattern and 47.3%, abnormal relaxation. Regarding LV geometry, 68.3% of patients had concentric hypertrophy; 16.7%, eccentric hypertrophy, 8.3% had concentric remodeling and 6.7% had normal geometry.

Table 1 – Demographic, clinical, biochemical and Doppler echocardiographic characteristics

Characteristics	Value (n=60)
Age (years)	49.2 ± 13.7
Male sex (%)	51.7
Duration of dialysis (months)	40 (4-278)
SAH (%)	88.3
DM (%)	20
Previous cardiovascular event (%)	25
History of smoking (%)	46.6
SBP (mmHg)	135.4 ± 18.6
DBP (mmHg)	81.8 ± 9.7
BMI (kg/m^2)	22.4 ± 3.9
Malnutrition (%)	13.3
Albumin (g/dL)	3.3 ± 0.5
Hemoglobin (g/dL)	10.7 ± 2.1
Total cholesterol (mg/dL)	150.9 ± 56.3
Calcium x phosphorus product (mg^2/dL^2)	50.3 ± 21.6
LVEDD (cm)	5.0 ± 0.6
EF (%)	59.8 ± 12.6
LVMI (g/m^2)	162.4 ± 58.8
LAVI (mL/m^2)	33.2 ± 17.9
EDS (cm)	1.2 ± 0.2
EDPW (cm)	1.2 ± 0.2
RWT	0.5 ± 0.1
e' (m/s)	0.08 ± 0.03
E/A	1.2 ± 0.6
E/e'	11.7 ± 4.4

The table data are expressed as mean ± standard deviation, median (range) or percentage. HBP: High blood pressure, DM: Diabetes mellitus, SBP: systolic blood pressure, DBP: diastolic blood pressure, BMI: body mass index, LVEDD: end-diastolic diameter of left ventricular EF: ejection fraction, LVMI: mass index left ventricle; LAVi: left atrial volume index, EDS: end-diastolic thickness of interventricular septum; EDPW: end-diastolic thickness of posterior wall of left ventricle; RWT: relative wall thickness, e '- early diastolic velocity of mitral annulus; E: early diastolic transmitral velocity; A: late diastolic transmitral velocity.

The mean follow-up was 19.6 ± 6 months and during this period, there were nine deaths and five non-fatal cardiovascular events. CVD accounted for 66.7% of all deaths (three AMI and three CVA), while the other three deaths were attributed to other causes (one due to hypovolemic shock and two due to septic shock). The non-fatal cardiovascular events were: a CVA, two hospitalizations for decompensated CHF and two episodes of angina with coronary stenosis > 50% at coronary angiography.

The event-free survival rates in one and two years were 91.5% and 79.4%, respectively, for cardiovascular events, 96.5% and 88.5% for cardiovascular mortality and 96.5 % and 83% for overall mortality.

Figures 1 and 2 show the survival curves free of cardiovascular mortality and fatal and nonfatal cardiovascular events, respectively.

Table 2 shows the comparison of demographic, clinical, biochemical and echocardiographic characteristics between groups with and without cardiovascular events. Patients with cardiovascular outcome had a higher prevalence of diabetes and previous cardiovascular event, higher LVSD and lower values of EF and systolic fractional shortening.

The univariate Cox model for cardiovascular events is shown in Table 3. At univariate analysis, diabetes mellitus, prior history of CVD, LVESD, EF and systolic fractional shortening were significantly associated with cardiovascular outcome. Multivariate analysis included variables: diabetes mellitus, previous cardiovascular event, EF, moderate to severe diastolic dysfunction and E/e' ratio. The variables LVESD and systolic fractional shortening were not included in the regression model because they are variables correlated with EF. In the final regression model, prior diagnosis of CVD and moderate to severe diastolic dysfunction showed to be independent risk factors for fatal and nonfatal cardiovascular events (Table 4).

Table 5 shows the univariate Cox model for cardiovascular mortality. Only a prior history of CVD was significantly associated with cardiovascular mortality in the univariate analysis. Multivariate analysis was not performed, because when using the variable selection criterion for the multivariate model ($p < 0.1$), only prior CVD and malnutrition would be entered in the final model.

The rate of survival free of cardiovascular events during follow-up was 87.2% and 55% in the groups with and without history of prior CVD, respectively ($p = 0.007$). While the rate of survival free of cardiovascular events was 66.4% in patients with moderate to severe diastolic dysfunction, in the group with abnormal relaxation or normal diastolic function it was 87.3% ($p = 0.075$). Figure 3 shows the survival curves free of cardiovascular outcome according with the presence or absence of moderate to severe diastolic dysfunction.

Discussion

This study showed free survival rates of overall mortality of 96.5% in one year and 83% in two years. These rates are comparable to those found by Silva et al.[19], who found survival rates of 91% and 84% in one and two years respectively, in a study carried out in Brazil. Data from dialysis censuses show survival rates of 88.6% in one year and 79.1% in two years in Europe[20] and 77.4% in one year and 63% in two years in the USA[1]. The characteristics of patients included in this study could explain the differences found. We studied patients with more controlled mean blood pressure, which is uncommon in this population. Furthermore, the average EF was preserved in the subjects studied, characterizing a population of more stable patients from the point of view of LV systolic function.

CVD accounted for 66.7% of all deaths during follow-up. The proportion found is similar to those reported in studies on cardiovascular and overall mortality in hemodialysis patients[6,21]. However, multicenter studies, such as the

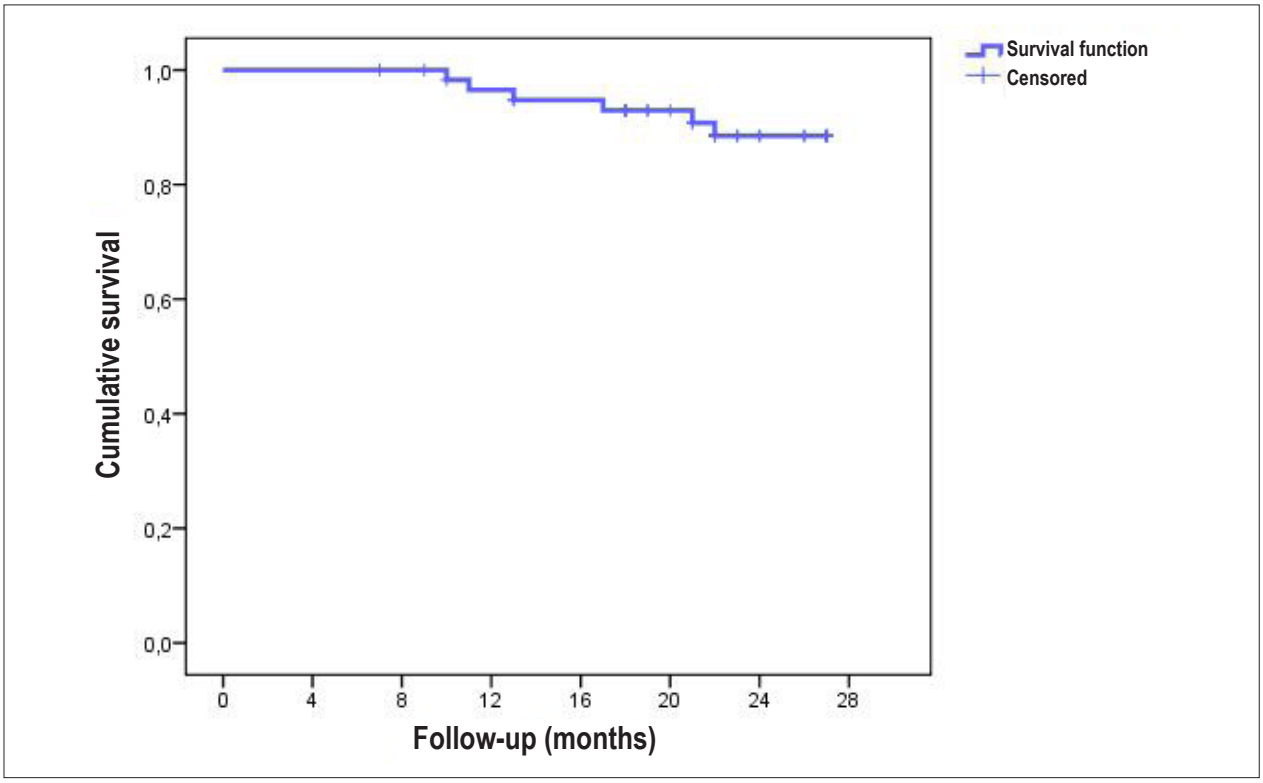

Figure 1 - *Curve of survival free of cardiovascular mortality*

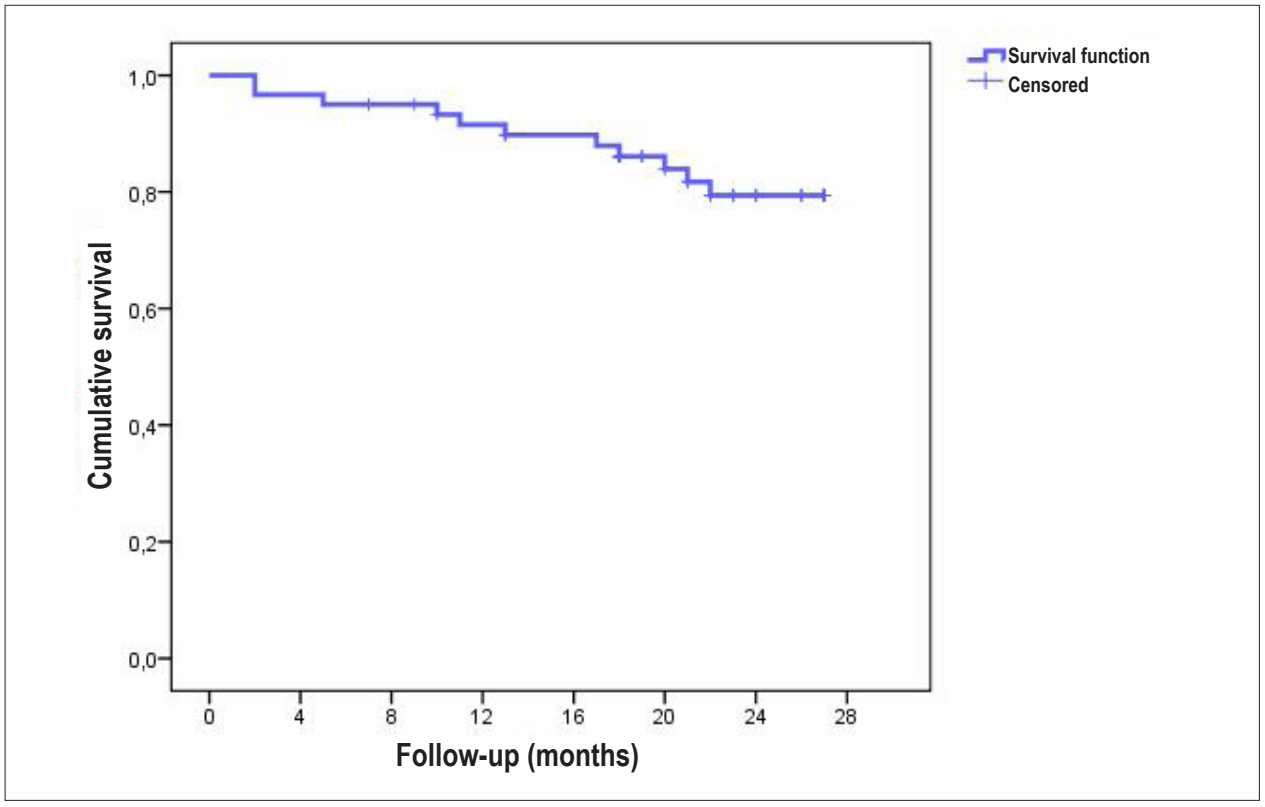

Figure 2 - *Curve of survival free of fatal and nonfatal cardiovascular events*

HEMO and AURORA studies, showed rates of less than 50% of mortality due to heart disease in the dialysis population[22,23]. These results confirm that CVD remain the leading cause of morbidity and mortality in hemodialysis patients. Hemodialysis patients have a 10-20-fold higher risk of cardiovascular mortality compared with the general population[24] and this is due to the fact that individuals are exposed to both traditional as well as non-traditional factors for cardiovascular complications[25].

Univariate analysis suggested that traditional risk factors such as diabetes and previous history of CVD are related to a higher risk of cardiovascular events. On the other hand, age, smoking, and hypercholesterolemia were not risk factors for the occurrence of cardiovascular outcome. Although some studies showed a higher prevalence of traditional risk factors in the population with CKD than in the general population[26], high rates of cardiovascular complications have not been fully explained by such risk factors[24,25]. Additionally, factors known to be non-traditional, such as anemia, malnutrition, inflammatory state, alterations in calcium-phosphorus product, among others, have been implicated as independent factors associated with cardiovascular complications in dialysis patients[27-30]. In the present study, however, these factors did not correlate with an increased risk of cardiovascular morbidity and mortality.

Evidence indicates that the LV systolic dysfunction parameters are independently associated with the occurrence of fatal and nonfatal cardiovascular events in patients on dialysis, with no difference in predictive power between the methods used to evaluate it[7]. In this study, we observed, at univariate analysis, that reductions in EF or systolic fractional shortening are related to increased risk of cardiovascular events.

LVH is a strong predictor of cardiovascular morbidity and mortality in hemodialysis patients[31]. LVH was present in 85% of patients in this study, a rate similar to the ones reported by other authors[6,32]. Zoccali et al.[31] showed that increased LVMI in hemodialysis patients was an independent predictor of cardiovascular events, regardless of basal LVM values. In this study, LVMI was not associated with cardiovascular morbidity and mortality. This result can be attributed to more stable characteristics of the patients included in the sample and the follow-up period of this study.

LAV is a potentially useful parameter to assess diastolic dysfunction and is related to the severity and duration of the dysfunction[5]. In a study of a population on renal replacement therapy, Barberato et al.[33] showed that LAVI was a predictor of mortality. In this study, although LAVI was mildly elevated in both groups, the variable was not an independent predictor of cardiovascular events and cardiovascular mortality. Possible explanations for the lack of association might be: in anemic patients, this index does not reflect diastolic dysfunction[34]; the evaluated patients were not part of a population with chronic kidney disease with significant LV systolic function impairment; and the number of patients was insufficient to find statistically significant differences.

Table 2 – Comparison of demographic, clinical, biochemical and echocardiographic characteristics according to the presence of cardiovascular outcome

Characteristics	Cardiovascular Outcome		p value
	No (n = 49)	Yes (n = 11)	
Age (years)	47.9 ± 13.8	54.5 ± 12.4	0.153
Male sex (%)	49	63.6	0.379
SAH (%)	87.8	90.9	0.768
DM (%)	14.3	45.5	0.020
Previous cardiovascular event (%)	18.4	54.5	0.012
History of smoking (%)	43.8	60	0.349
SBP (mmHg)	135.1 ± 19.1	136.3 ± 16.9	0.843
DBP (mmHg)	81.8 ± 10	81.82 ± 8.7	0.990
BMI (kg/m^2)	22.5 ± 3.8	21.6 ± 4.5	0.501
Malnutrition (%)	12.2	18.2	0.601
Albumin (g/dL)	3.3 ± 0.5	3.2 ± 0.5	0.741
Hemoglobin (g/dL)	10.6 ± 2.1	11.1 ± 2.3	0.504
Total cholesterol (mg/dL)	146.2 ± 43.5	172.13 ± 95.2	0.170
Calcium x phosphorus product (mg^2/dL^2)	50.3 ± 21	50.2 ± 25.1	0.986
LA enlargement (%)	45.8	63.6	0.287
LVEDD (cm)	4.9 ± 0.6	5.2 ± 0.6	0.136
LVESD (cm)	3.2 ± 0.7	3.8 ± 0.7	0.021
LV dilatation (%)	16.3	36.4	0.133
EF (%)	61.5 ± 12.2	51.9 ± 11.6	0.021
Systolic dysfunction (%)	22.4	45.5	0.119
SFS (%)	33.9 ± 8.5	27.4 ± 6.9	0.021
LVMI (g/m^2)	158.5 ± 53.8	179.3 ± 78	0.294
LVH (%)	85.7	81.8	0.744
Diastolic dysfunction (%)	80	100	0.122
Moderate to severe diastolic dysfunction (%)	31.1	60	0.086
LAVI (mL/m^2)	32.4 ± 17.6	36.8 ± 19.5	0.474
EDS (cm)	1.2 ± 0.2	1.2 ± 0.2	0.749
EDPW (cm)	1.2 ± 0.2	1.2 ± 0.2	0.581
RWT	0.4 ± 0.1	0.4 ± 0.06	0.469
e'(m/s)	0.09 ± 0.03	0.07 ± 0.01	0.097
E/A	1.2 ± 0.6	1.3 ± 0.6	0.720
E/e'	11.2 ± 4.1	13.8 ± 5.1	0.094

The table data are expressed as mean ± standard deviation, median (range) or percentage. Percentages were compared by chi-square test and means were compared by Student's t test. SAH: systemic arterial hypertension, DM: Diabetes mellitus, CVD: Cardiovascular Disease, SBP: systolic blood pressure, DBP: diastolic blood pressure, BMI: body mass index; LA: left atrium, LV: left ventricle; LVEDD: LV end-diastolic diameter; LVESD: LV end-systolic diameter; EF: ejection fraction; SFS: systolic fractional shortening, LVMI: left ventricular mass index, LVH: left ventricular hypertrophy; LAVI: left atrial volume index, EDS: end-diastolic thickness of interventricular septum; EDPW: end-diastolic thickness of posterior wall of left ventricle; RWT: relative wall thickness, e '- early diastolic velocity of mitral annulus ; E: early diastolic transmitral velocity; A: late diastolic transmitral velocity.

Table 3 – Predictors of cardiovascular events by univariate analysis using the Cox regression model

Characteristics	HR	95%CI	p value
Age (yrs.)	1.03	0.99 - 1.08	0.127
Male sex	0.57	0.17 - 1.95	0.371
SAH	1.23	0.16 - 9.60	0.845
DM	4.30	1.3 - 14.2	0.017
Previous cardiovascular event	4.44	1.35 - 14.6	0.014
History of smoking	1.79	0.5 – 6.37	0.364
Duration of dialysis (months)	0.99	0.98 - 1.01	0.651
SBP (mmHg)	1.00	0.97 – 1.0	0.955
DBP (mmHg)	0.99	0.93 – 1.06	0.841
BMI (kg/m2)	0.94	0.80 - 1.10	0.449
Malnutrition	1.67	0.36 - 7.81	0.514
Albumin (g/dL)	0.78	0.25 – 2.41	0.670
Hemoglobin (g/dL)	1.12	0.83 – 1.49	0.455
Total Cholesterol (mg/dL)	1.00	0.99 – 1.01	0.282
Calcium x phosphorus product (mg2/dL2)	1.00	0.97 - 1.03	0.940
LA enlargement	1.71	0.5 – 5.85	0.390
LVEDD (cm)	1.80	0.77 - 4.23	0.175
LVESD (cm)	1.95	1.06 - 3.56	0.030
LV dilatation	2.6	0.77 - 9.02	0.122
EF (%)	0.95	0.91 - 0.99	0.029
Systolic dysfunction	2.55	0.78 - 8.38	0.122
SFS (%)	0.93	0.87 - 0.99	0.030
LVMI (g/m2)	1.00	0.99 - 1.01	0.386
LVH	0.62	0.13 - 2.90	0.548
Diastolic dysfunction	26.72	0.02 – 34575	0.369
Moderate to severe diastolic dysfunction	2.99	0.84 – 10.61	0.090
LAVI (mL/m2)	1.01	0.98 - 1.04	0.505
EDS (cm)	1.2	0.09 - 15.05	0.889
EDPW (cm)	1.67	0.12 - 22.45	0.699
RWT	0.08	0.00 - 49.97	0.450
E/A	1.14	0.5 – 2.58	0.759
E/e'	1.13	0.98 – 1.29	0.087

HR: Hazard ratio; HR: Hazard ratio; 95% CI: confidence interval 95%, SAH: Systemic Arterial Hypertension; DM: Diabetes mellitus; CVD: Cardiovascular Disease; SBP: systolic blood pressure, DBP: diastolic blood pressure; BMI: body mass index; LA: left atrium; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; LV: left ventricle, EF: ejection fraction; SFS: systolic fractional shortening, LVMI: left ventricular mass index; LVH: left ventricular hypertrophy; LAVI: left atrial volume index, EDS: interventricular septum end-diastolic thickness; EDPW: end-diastolic thickness of posterior wall of left ventricle; RWT: relative wall thickness, e '- early diastolic velocity of mitral annulus; E: early diastolic transmitral velocity; A: late diastolic transmitral velocity.

Table 4 – Predictors of cardiovascular events by the multivariate analysis of Cox regression model

Characteristics	HR	95%CI	p value
Previous cardiovascular event	6.17	1.7 – 22.2	0.005
Moderate to severe diastolic dysfunction	3.76	1.05 – 13.4	0.042

HR: Hazard ratio; 95%CI: 95% Confidence Interval

In the multivariate analysis, previous diagnosis of CVD remained a risk factor for fatal and nonfatal cardiovascular events. Zoccali et al.[7] in a study of 254 hemodialysis patients, Rakhit et al.[35] in a study that included 176 patients with CKD stages 4 and 5 on conservative treatment or dialysis, and Cheung et al.[22] in the HEMO multicenter study, described a similar result in the final model of Cox multivariate analysis.

The present study demonstrated a high prevalence of diastolic dysfunction in patients with CKD on hemodialysis, corresponding to 83.6%, with 36.4% of patients having moderate to severe diastolic dysfunction. Studies carried out in hemodialysis patients showed that the prevalence of diastolic dysfunction in this population can vary from 63.5% to 87%, depending on the criteria used for definition and patients included in the sample[36-38].

Diastolic dysfunction is characterized by alterations in ventricular relaxation and compliance[5] and its high prevalence can be explained by the fact that the CKD expose the heart to pressure and volume overload and associated hemodynamic factors that cause myocardial alterations[39]. Myocardial fibrosis resulting from these processes is a major determinant of LV stiffness and elevated filling pressures, predisposing to the development of diastolic dysfunction[39].

The presence of moderate to severe diastolic dysfunction was the only independent echocardiographic predictor of cardiovascular events. A study that employed only parameters derived from mitral inflow and pulmonary venous flow for the categorization of diastolic function showed that diastolic dysfunction is an independent predictor of mortality in patients on renal replacement therapy by hemodialysis[40].

In a recently published study, which evaluated 129 hemodialysis patients and the used conventional Doppler and tissue Doppler criteria to classify diastolic dysfunction, Barberato et al.[37] showed that overall mortality was significantly higher in patients with diastolic dysfunction with pseudonormal pattern and restrictive flow, when compared to the group with diastolic dysfunction and abnormal relaxation or normal diastolic function. In this study, advanced diastolic dysfunction was showed to be an independent predictor of cardiovascular events.

The present study has limitations: the number of patients studied could influence the power of some variables, such as LAVI; duration of follow-up < two years, may have influenced the lack of association between left ventricular function parameters and cardiovascular mortality. The strengths are: the study is prospective and longitudinal; feasible techniques were used for the noninvasive analysis of diastolic function, allowing periodic analysis in patients who have high rates of cardiovascular events.

Table 5 – Predictors of cardiovascular mortality by univariate analysis of Cox regression model

Characteristics	HR	95%CI	p value
Age (years)	1.04	0.98 – 1.11	0.186
Male sex	0.52	0.09 – 2.83	0.449
SAH	0.52	0.06 – 4.51	0.557
DM	2.08	0.38 – 11.38	0.397
Previous cardiovascular event	6.59	1.20 – 36.14	0.030
History of smoking	0.72	0.12 – 4.29	0.715
Dialysis duration (months)	0.99	0.98 – 1.01	0.697
SBP (mmHg)	1.01	0.97 – 1.05	0.617
DBP (mmHg)	1.00	0.93 – 1.09	0.822
BMI (kg/m2)	0.87	0.69 – 1.09	0.235
Malnutrition	4.33	0.77 – 24.47	0.097
Albumin (g/dL)	0.36	0.07 – 1.72	0.202
Hemoglobin (g/dL)	1.03	0.69 – 1.54	0.863
Total cholesterol (mg/dL)	1.00	0.99 – 1.01	0.115
Calcium x phosphorus product (mg2/dL2)	0.99	0.95 – 1.03	0.663
LA hypertrophy	1.93	0.35 – 10.57	0.445
LVEDD (cm)	1.77	0.56 - 5.61	0.332
LVESD (cm)	1.70	0.73 - 3.96	0.217
LV Dilatation	2.12	0.39 – 11.56	0.386
EF (%)	0.97	0.91 - 1.02	0.259
Systolic dysfunction	3.0	0.60 - 14.86	0.179
SFS (%)	0.95	0.87 - 1.03	0.234
LVMI (g/m2)	1.00	0.99 - 1.02	0.513
LVH	1.41	0.16 - 12.11	0.753
Diastolic dysfunction	25.92	0.01 - 1034696	0.547
Moderate to severe diastolic dysfunction	1.18	0.20 – 7.09	0.852
LAVI (mL/m2)	1.02	0.98 - 1.05	0.362
EDS (cm)	0.47	0.01 - 15.77	0.673
EDPW (cm)	2.46	0.07 - 81.13	0.614
RWT	0.21	0.00 - 1059.50	0.718
E/A	0.72	0.19 - 2.76	0.636
E/e'	1.02	0.84 - 1.24	0.847

HR: Hazard ratio; HR: Hazard ratio; 95% CI: confidence interval 95%, SAH: Systemic Arterial Hypertension; DM: Diabetes mellitus; CVD: Cardiovascular Disease; SBP: systolic blood pressure, DBP: diastolic blood pressure; BMI: body mass index; LA: left atrium; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; LV: left ventricle, EF: ejection fraction; SFS: systolic fractional shortening, LVMI: left ventricular mass index; LVH: left ventricular hypertrophy; LAVI: left atrial volume index, EDS: interventricular septum end-diastolic thickness; EDPW: end-diastolic thickness of posterior wall of left ventricle; RWT: relative wall thickness, e '- early diastolic velocity of mitral annulus ; E: early diastolic transmitral velocity; A: late diastolic transmitral velocity.

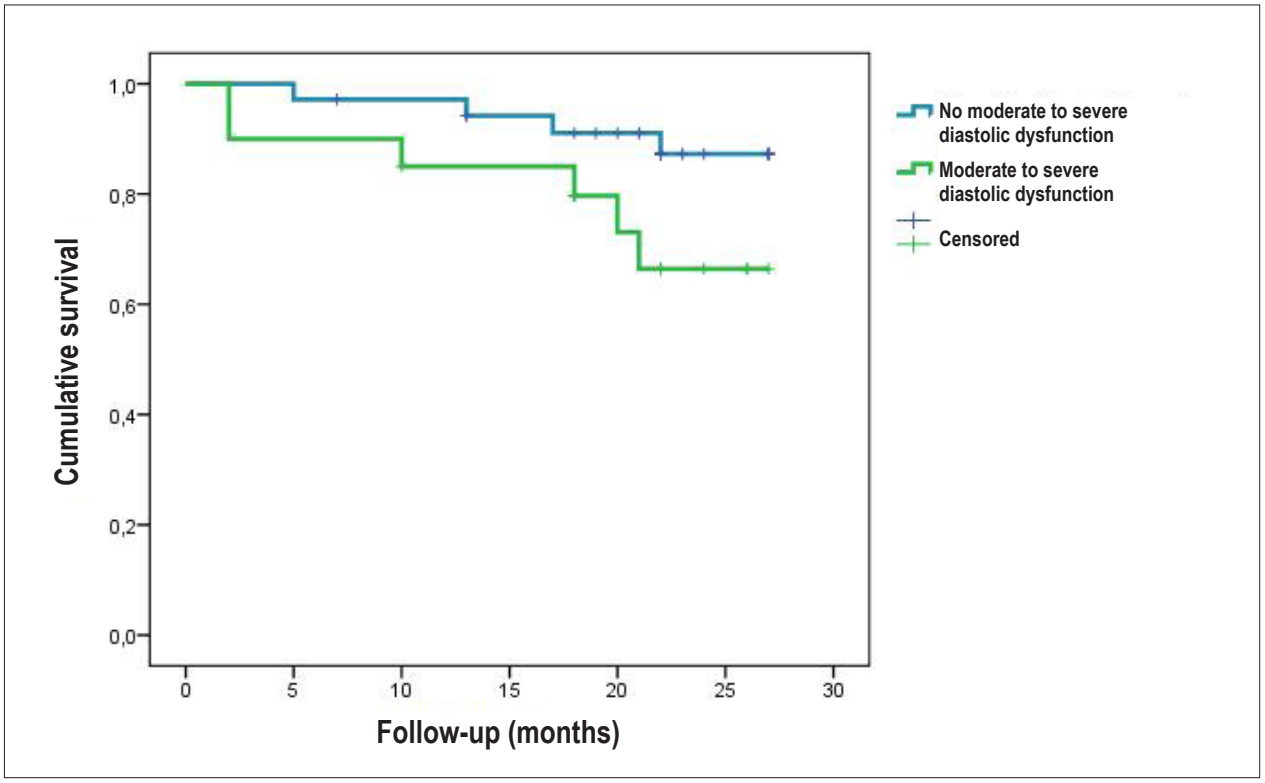

Figure 3 - *Curves of survival free of cardiovascular events according to the presence of moderate to severe diastolic dysfunction*

Conclusions

Hemodialysis patients have high rates of cardiovascular morbidity and mortality. The presence of diabetes, previous history of CVD and a lower EF are factors potentially related to cardiovascular events. Moderate to severe diastolic dysfunction was an independent risk factor for cardiovascular events, and although further studies are necessary to validate this finding, it is recommended that diastolic function evaluation, made through pulsed Doppler and tissue Doppler parameters, be included in the evaluation of patients undergoing hemodialysis. This measure will enable the early detection of individuals at risk in order to reduce morbidity and mortality.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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