# Predictive Value of Several Echo Parameters for Cardiovascular Events in Hemodialysis Patients with Mid-range and Preserved Ejection Fraction Heart Failure

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*Patients with end stage renal disease (ESRD) on hemodialysis (HD) are predisposed to higher rates of major cardiovascular events, through several well-known pathophysiological mechanisms. The rates of all-cause mortality are 6 to 10fold greater for these patients compared with general population. Furthermore, diabetes mellitus, history of cardiovascular disease, dialysis duration, and residual diuresis are factors related to cardiovascular events in hemodialysis. Whilst structural and functional echocardiographic abnormalities in dialyzed patients have been the surrogate for several survival studies, the predictive value of these echo parameters, are not clearly established in this field .In dialysis patients, it is still unclear which echo parameter is the best in determining cardiovascular outcome. The purpose of our study was to investigate the role of Doppler Echocardiography and Tissue Doppler Imaging (TDI) abnormalities, in providing predictive parameters for this particular population. The survival rates were analyzed by Kaplan–Meier curves and cardiac events predictors by Cox's proportional-hazards model. We found correlations between several echo measurements and cardiovascular events, especially diastolic dysfunction and impaired left ventricular parameters. We strongly recommend the use of these echocardiographic parameters in early detection of patients at high risk in order to reduce morbidity and mortality.*

*Keywords: dialysis echo, dialysis survival, diastolic dysfunction, Tissue Doppler Imaging*

Cardiovascular events are the most frequent cause for mortality in dialyzed patients representing almost 30-40% of registered mortality cases [1]. Also, non-cardiovascular death is considered important because regular dialysis in patients still has a high mortality risk associated with this state [2-4]. Therefore, we conducted this study to establish the correlations between echocardiographic parameters with several cardiovascular and non-cardiovascular events in dialyzed patients. Doppler Echocardiography is just one of the modern techniques used to evaluate myocardial function quantitatively. Several echo parameters, such as ejection fraction(EF), LVH, LAE and left ventricular (LV) systolic dysfunction, have been shown to represent independent outcome predictors in dialyzed patients [5-7]. Diastolic dysfunction with high filling pressures in dialysis patients often exists without the presence of systolic heart failure, and it may be evaluated by Doppler echo, especially Tissue Doppler Imaging (TDI), a technique that proved its prognostic significance value for CV events in general population[8,9,10]. These new Tissue Doppler methods should be able to detect even the slightest subclinical abnormalities in cardiac function, therefore, considering this good accuracy, TDI parameters are proposed as reliable predictive markers for cardiac events [1-11].

## Experimental part

### *Materials and method*

**Table 1**

BASELINE CHARACTERISTICS OF THE POPULATION

| *VARIABLE* | TOTAL (N=61) |
|---|---|
| MALE GENDER, (%) | 50.81 |
| AGE, YEARS | 50,2±14.02 |
| ARTERIOVENOUS FYSTULA, (%) | 89.4 |
| *DIALYSIS DURATION, MONTHS* | 39±14.7 |
| *BODY MASS INDEX(BMI), KG/M²* | 22.3±4.1 |
| *BODY SURFACE AREA(BSA), M²* | 1.74±0.35 |
| *ARTERIAL HYPERTENSION,(%)* | 87.9 |
| *DYSLIPIDEMIA,(%)* | 38.4 |
| *SMOKING HISTORY,(%)* | 46.2 |
| *DIABETES MELLITUS,(%)* | 28.2 |
| *HISTORY OF CARDIOVASCULAR DISEASE,(%)* | 25.1 |
| *SISTOLIC BLOOD PRESSURE,(mmHg)* | 134.9±18.4 |
| *DIASTOLIC BLOOD PRESSURE,(mmHg)* | 82.1±9.6 |
| *DRUGS* | |
| *ACEI/ARB(%)* | 62.9 |
| *BETA BLOCKER(%)* | 58.1 |
| *CCB(%)* | 62.8 |
| *STATINS(%)* | 27.8 |
| *DIURETICS(%)* | 60.8 |
| *ANTIPLATLET AGENT(%)* | 64.9 |

*ACEI= angiotensin-converting-enzyme inhibitor; ARB=Angiotensin II receptor blockers; CCB=calcium channel blocker;*

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This is a retrospective study of echocardiographic exams of 61 patients on chronic HD with preserved and mid range ejection fractions and the respective collected data that were performed over a timeframe of several months (20.4±11.3), between January 2015 to December 2017. All dialyzed patients, were treated with HD three times a week for more than 3 months. We selected the patients with accurate echo and data record(biannual records) in sinus rhythm, without severe valvular disease, congestive heart failure (NYHA classes III and IV), pulmonary disease or significant pericardial disease.

LV diastolic function parameters were assessed both conventional and through TDI. Using pulse-wave Doppler(PW) at the tip of the mitral leaflets in the 4-chamber view,mitral E-wave velocity, E-wave deceleration time (EDT), and late diastolic wave (*A*) velocity were obtained [8-9]. Mitral inflow E/A ratio and DT are used to identify the filling patterns: normal, impaired relaxation (grade 1), pseudo-normal (grade 2), and restrictive filling(grade 3) [8,9].PW-TDI was performed in high frame rate from the apical four chamber view to assess myocardial velocities. Systolic (s') and early wave (e')/ late wave (a') diastolic velocities were recorded in annular LV segments (septal and lateral). *E*/*E*2 ratio was calculated, and significant LV diastolic dysfunction was defined as *E*/*E*2 ≥14, septal *E*2 velocity <7cm/s, lateral *E*2 velocity<10 cm/s,CW TR velocity> 2.8 m/s and LA volume index(LAVI)>34ml/m² [8,9].TR velocity was recorded from a routine right ventricular inflow view using CW Doppler. E/E' ratio < 8 is associated with normal LV filling pressures, while a ratio above 12is associated with high filling pressures (PCWP > 12mmHg) [10-12,].

The primary endpoint or cardiovascular outcome included fatal and nonfatal cardiovascular events and non-cardiovascular events (infection, bleeding, neoplasia). Cardiovascular events were defined by unstable angina, nonfatal AMI, myocardial revascularization procedure, nonfatal cerebrovascular disease, peripheral artery disease, congestive heart failure requiring hospitalization and death from cardiovascular causes. The secondary outcomes included all cause overall mortality.

| *Variable* | *Cardiovascular event* | | *P* |
|---|---|---|---|
| | Y(n=11) | N(n=50) | |
| MALE GENDER, (%) | 63.8 | 48.9 | 0.381 |
| AGE, YEARS | 53.9±12.6 | 48.1±14.1 | 0.161 |
| BMI, KG/M² | 21.8±4.6 | 21.9±4.1 | 0.523 |
| ARTERIAL HYPERTENSION,(%) | 89.9 | 86.7 | 0.762 |
| TOTAL CHOLESTEROL,mg/dl | 170.2±92.4 | 145.8±44.1 | 0.175 |
| SMOKING HISTORY,(%) | 60.2 | 44.6 | 0.351 |
| DIABETES MELLITUS,(%) | 45.4 | 15.2 | 0.021 |
| HISTORY OF CARDIOVASCULAR DISEASE,(%) | 53.9 | 18.6 | 0.014 |
| SYSTOLIC BLOOD PRESSURE,(mmHg) | 137±17.1 | 135.4±21.6 | 0.852 |
| DIASTOLIC BLOOD PRESSURE,(mmHg) | 82.2±11.5 | 80.4±9.3 | 0.989 |
| LVEDD , (mm) | 5.3±0.5 | 5.0±0.5 | 0.138 |
| LVESD , (mm) | 3.1±0.6 | 3.7±0.6 | 0.023 |
| LAE ,(%) | 63.5 | 46.7 | 0.292 |
| LAVI(mL/m²) | 36.9±19.4 | 33.4±18.1 | 0.469 |
| LV DILATATION, (%) | 35.9 | 16.5 | 0.139 |
| EF,(%) | 51.7±12.2 | 61.3±12.4 | 0.023 |
| LV SYSTOLIC DYSFUNCTION (by s'), % | 49.6 | 21.6 | 0.028 |
| FS, (%) | 27.5±7.1 | 34.1±8.7 | 0.022 |
| LVH, (%) | 81.9 | 84.8 | 0.745 |
| LVMI, (g/m²) | 180.0±77.9 | 157.8±54.2 | 0.296 |
| GRADE I DIASTOLIC DYSFUNCTION,(%) | 100 | 81 | 0.123 |
| GRADE II AND III DIASTOLIC DYSFUNCTION,(%) | 60 | 32.2 | 0.088 |
| E/A RATIO | 1.3±0.6 | 1.2±0.5 | 0.721 |
| E/e' RATIO | 15.5±5.3 | 11.6±4.9 | 0.046 |

**Table 2**
COMPARISON OF CHARACTERISTICS ACCORDING TO THE PRESENCE OF CARDIOVASCULAR EVENTS

*EF=Ejection traction, FS=Fractional shortening, E=Early diastolic flow velocity,*
*A=Late diastolic flow velocity, EDT=Mitral E-velocity deceleration time,*
*LAVI=left atrial volume index, LAE=left atrial enlargement,*
*e´=Average of the lateral and septal values, s'= mitral annular systolic velocity;*
*LVMI=left ventricular mass index; LVH=left ventricular hypertrophy;*

Conventional 2D echocardiography and TDI were performed using a commercial ultrasound machine (Siemens Acuson P300), in a non-dialysis day, so that cardiac hemodynamics would not be influenced by ultrafiltration parameters and process. The echo report was recorded at baseline and further after in similar conditions. Most of the patients benefited from cardiovascular protective medications which has already proven to reduce mortality [13-14]. Smoking, dyslipidemia and hypertension are risk factors involved in high CV risk associated with CKD and also with progression of kidney failure [15]. Furthermore, numerous trials have proven the importance of microRNAs for monitoring and for the prognosis of acute kidney injury(AKI) in this field[16,17]. Two-dimensional echo measurements, including left ventricular end diastolic and end systolic dimensions (LVEDD and LVESD), end-diastolic and systolic wall thickness of interventricular septum (IVSD and IVSS) and left ventricular posterior wall (PWTD and PWTS) were determined with the M-mode (Mm) technique[18]. Ejection fraction (EF) was determined using M mode, Simpson method and complemented by eyeballing. LV mass was calculated by Devereux's formula using the M-mode of the parasternal long axis view, and indexed to body surface area. LV hypertrophy was defined as LVMI >115 g/m² in men and >95 g/m² in women [8,9]. Left atrium diameter (LAD) was measured as anteroposterior diameter in M mode from parasternal long axis view and also as left atrial volume (LAVI-indexed to BSA) using biplane Simpsons method.

*Statistical analysis*

Statistical analysis was performed using Graph Pad Software, Inc. 3.1. To calculate the statistical significance, we performed comparisons betweengroups using the Student's t test and Chi-Square test.The hazard ratios (HR) and 95% confidence intervals (CI) for morbi-mortality rates were calculated using the Cox proportional hazard models for several clinical outcomes.Survival curves were designed using the Kaplan-Meier method and log rank test was used to compare survival curves in univariate analysis. Statistical significance was considered if p was $<0.05$.

## Results and discussions

Baseline characteristics of the population are listed in table 1 and group comparison according to CV outcome are shown in table 2. Group with CV outcome had an increased prevalence of diabetes, previous CV disease, higher LVESD and lower EF and FS with systolic and diastolic dysfunction.The most frequent echocardiographic diagnosewere: LV diastolic dysfunction (85.1%), LV systolic dysfunction (27.8%),LA enlargement (48.2%), LVH (84.9%) and LV dilatation (21%).Each echo parameter was included in the univariate hazard model as a continuous variable, whereas some were included as a categorical one. In table 3 and 4 are listed the predictors for cardiovascular event and the measured Echo parameters and their correlation with cardiovascular events using Cox regression model. The statistical significance was achieved for EF, FS, LVESD, LVESV WMA, s', e' and E/e' ratio.In the multivariate analysis

**Table 3**
ECHOCARDIOGRAPHIC PARAMETERS AND CORRELATION WITH CARDIOVASCULAR EVENTS USING COX REGRESSION MODEL(UNIVARIATE ANALYSIS)

| Parameter | Mean±SD | HR(95% CI) | P |
|---|---|---|---|
| EF (%) | 59.6±12.6 | 0.94 (0.91-0.98) | 0.030 |
| FS (%) | 33.6±8.7 | 0.94 (0.86-0.98) | 0.031 |
| E(cm/s) | 74.0±27.2 | 1.02 ( 1.01-1.10) | 0.049 |
| A (cm/s) | 90.8±25.6 | 1.02 ( 0.99-1.02) | 0.082 |
| E/A | 1.3±0.5 | 1.15 (0.61-2.59) | 0.748 |
| EDT (ms) | 211±73.1 | 1.01 (0.99-1.05) | 0.901 |
| LAVI(mL/m²) | 45.6±18.4 | 1.00 (0.98-1.02) | 0.790 |
| LAD (mm) | 41.0±6.98 | 0.98 (0.94-1.04) | 0.602 |
| CW TR velocity(m/s) | 2.4±0.5 | 1.17 (0.58-2.39) | 0.598 |
| LVMI(g/m²) | 134.1±38.7 | 1.01 (0.98-1.02) | 0.369 |
| LVEDD(mm) | 49.9±6.51 | 1.02 (0.99-1.08) | 0.181 |
| LVESD(mm) | 32.4±6.98 | 1.03 ( 1.01-1.08) | 0.046 |
| LVEDV(mL) | 95.1±32.5 | 1.02 (0.98-1.02) | 0.209 |
| LVESV(mL) | 42.8±22.6 | 1.01 (1.01-1.03) | 0.043 |
| IVSD(mm) | 11.9±2.12 | 0.92 (0.81-1.09) | 0.334 |
| IVSS(mm) | 15.1±2.72 | 0.98 (0.89-1.11) | 0.749 |
| PWTD(mm) | 11.4±1.91 | 0.94 (0.79-1.08) | 0.491 |
| PWTS(mm) | 17.1±2.61 | 0.97 (0.87-1.10) | 0.698 |
| WMA(vs none) | - | 3.72 ( 2.11-6.94) | < .001 |
| s'(cm/s) | 7.2±2.2 | 0.74(0.65-0.88) | < .001 |
| e'(cm/s) | 7.9±3.0 | 0.82 (0.71-0.95) | 0.009 |
| a'(cm/s) | 9.4±2.8 | 0.93 (0.82-1.04) | 0.169 |
| E/e' | 12.1±4.6 | 1.14 (0.99-1.21) | 0.004 |

*HR=hazard ratio; CI=confidence interval; EF=Ejection traction, FS=Fractional shortening, E=Early diastolic flow velocity, A=Late diastolic flow velocity, EDT=Mitral E-velocity deceleration time, LAVI=left atrial volume index, LAD=left atrial anteroposterior diameter, CW TR=continuous wave Doppler tricuspid regurgitation velocity, e´=Average of the lateral and septal values, IVSD=interventricular septum in diastole, IVSS= interventricular septum in systole, PWTD posterior wall in diastole, PWTS, posterior wall thickness in systole, WMA=wall motion abnormality, s'= mitral annular systolic velocity, a'=late diastolic mitral annular velocity; LVMI=left ventricular mass index*

| Variable | Univariate HR(95% CI) | P | Multivariate HR(95% CI) | P |
|---|---|---|---|---|
| MALE GENDER | 0.58 (0.18-1.96) | 0.380 | | |
| AGE, YEARS | 1.02 (0.98-1.06) | 0.128 | | |
| BMI, KG/M² | 0.95 (0.81-1.11) | 0.450 | | |
| ARTERIAL HYPERTENSION | 1.22 (0.17-9.58) | 0.839 | | |
| TOTAL CHOLESTEROL, mg/dl | 1.01 (0.98-1.02) | 0.284 | | |
| SMOKING HISTORY | 1.80 ( 0.51-6.29) | 0.361 | | |
| DIABETES MELLITUS | 4.31 (1.29-13.9) | 0.019 | | |
| HISTORY OF CARDIOVASCULAR DISEASE | 4.45 (1.36-15.0) | 0.015 | 6.16 (1.69-21.9) | 0.005 |
| SYSTOLIC BLOOD PRESSURE, (mmHg) | 1.01 (0.98-1.01) | 0.960 | | |
| DIASTOLIC BLOOD PRESSURE, (mmHg) | 0.99 (0.94-1.06) | 0.843 | | |
| DIALYSIS VINTAGE | 0.98 (0.98-1.0) | 0.650 | | |
| ANTIPLATELETS | 1.89 (0.95-3.45) | 0.072 | | |
| ACEI/ARB | 0.64 (0.36-1.10) | 0.089 | | |
| CCB | 0.89 ( 0.49-1.54) | 0.646 | | |
| BETA BLOCKER | 1.15 (0.635-1.45) | 0.668 | | |
| DIURETICS | 0.82 (0.56-1.44) | 0.472 | | |
| STATINS | 0.80 (0.38-1.79) | 0.597 | | |
| GRADE I DIASTOLIC DYSFUNCTION | 25.89(0.03-3447) | 0.370 | | |
| GR II AND III DIASTOLIC DYSFUNCTION | 3.01 (0.85-10.69) | 0.089 | 3.75 (1.06-13.3) | 0.041 |
| E/e' RATIO | 1.14 (0.97-1.31) | 0.006 | | |
| LV SYSTOLIC DYSFUNCTION (BY S') | 0.64 (0.46-1.19) | 0.007 | | |

**Table 4**
CARDIOVASCULAR EVENTS PREDICTORS USING COX REGRESSION MODEL

were included: the history of cardiovascular disease, DM, EF, grade I and grade II/III diastolic dysfunction and E/e' ratio. LVESD, LVEDD, FS and s' were not added in the Cox regression model because they are correlated with the ejection fraction. In the final regression model, history of CVD and severe diastolic dysfunction showed to be independent predictors for fatal and non-fatal cardiovascular events.There were 9 deaths and 6 non-fatal cardiovascular events. 3 deaths were due to other causes (2 infections and 1 bleeding).Cardiovascular disease represented for 70.7% of all deaths (4 myocardial infarction and 3 cerebrovascular disease). The non-fatal cardiovascular events were: 1 CVD, 3 AHF events and 3 cases of ACS. The survival curves free of CV events and CV mortality, are shown in figure 1 and 2, respectively. Figure 3 highlights the survival curves free of CV outcome

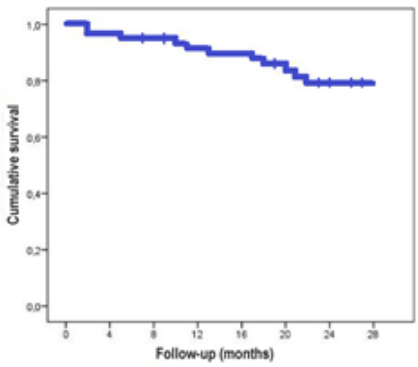

Fig. 1.

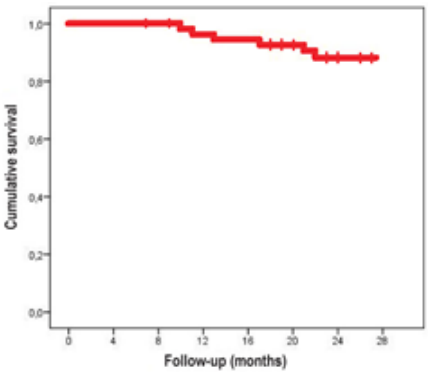

Fig. 2.

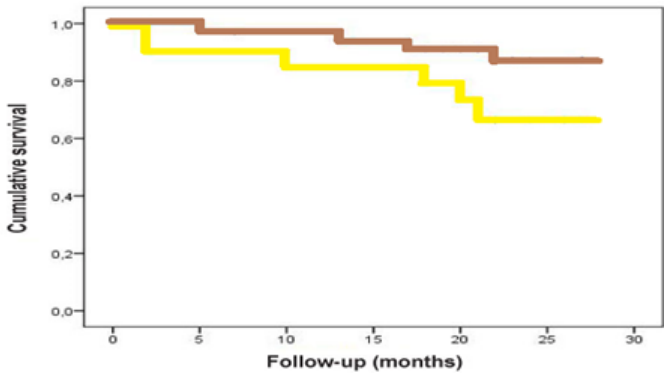

Fig.3.

between grade I diastolic dysfunction and grade II/III diastolic dysfunction (yellow line).

Only diastolic dysfunction, E/e' ratio and prior history of CVD were parameters that achieved statistical significance associated with cardiovascular mortality in the univariate analysis.Increased E/e' ratio was correlated with high risk of cardiovascular event.The E/e' ratio, representative of LV diastolic function, was the strongest predictor of all cardiovascular events.

This study has its limitations, represented by the relative small number of studied patients that could influence the power of some variables. Also the timeframe duration was less than 2.5 years, influencing the lack of association between some echo parameters and cardiovascular mortality. Hemodialysis patients are exposed to a higher risk of ischemic and arrhythmic events [19,20]. High blood pressure precipitates LVH which also represent a predictor for sudden cardiac death due to arrhythmic and ischaemic events [21,22]. In ESRD, GFR alone proved to be a reliable follow-up parameter, as a marker for cardiovascular events [23]. This special population in order to establish its risk profile needs further studies in order to better quantify the risk which in true may be even greater, depending on the cardiovascular profile. This study included patients which most of them had a mid range ejection fraction and preserved ejection fraction[24-26]. It remains to be established to which degree in this population the ejection fraction contributes to the overall risk and survival rate and dialysis duration. The new Tissue Doppler and Speckle tracking techniques can add more prognostic value for us in order to understand and treat the dialyzed patient involved in the pathophysiological continuum between kidney and heart [8-12,24-26,27]. Also, in some studies, arterial stiffness assessed by carotid femural pulse wave velocity [28], late potentials related arrhythmias [19], low EF or low RR variability[19], were associated with higher mortality risk and are useful marker because they are correlated with overall cardiovascular mortality[29,30], used even in hemodialysis patients. The LV dysfunction is evident in almost half of ESRD patients starting dialysis and can be induced by hemodialysis itself [6,29,31,32]. Furthermore, we underline the need for more, dynamic, complex, experimental large, randomized protocols, which may have general and cardiovascular implications [33-41].

## Conclusions

This study underlines that significantly diastolic dysfunction and E/e' ratio are the most predictive parameters for cardiovascular events and all-cause mortality. Diastolic dysfunction (grade II and III), evaluated through Echo Doppler and Tissue Doppler was an independent predictor for cardiovascular events, and should be added in the standard evaluation of dialyzed patients. Therefore, enabling the early detection of these high-risk patients, we can take measures to reduce morbi-mortality.The present study may help us for better guidance and surveillance in dialyzed patients with abnormal echo parameters.

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