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Predictive Value of Atrial Electromechanical Delay on Long-Term Cardiovascular Outcomes in Hemodialysis Patients

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Key Words
Left intra-atrial electromechanical delay time · Malnutrition · Combined CV events · Hemodialysis

Abstract

Background: Atrial electromechanical delay (AEMD) times were considered independent predictors of cardiovascular morbidity among the general population. We aimed at evaluating AEMD times and other risk factors associated with 2-year combined cardiovascular (CV) events in HD patients. ***Material and Methods:*** Sixty hemodialysis (HD) and 44 healthy individuals were enrolled in this prospective study. Echocardiography was performed before the mid-week dialysis session for HD patients. Data were expressed as mean ± SD. Spearman test was used to assess linear associations. Survival was examined with the Kaplan–Meier method. Multivariate Cox regression analysis was used to determine the predictors of combined CV events in this cohort. ***Results:*** At the beginning of the study, left intra-atrial-AEMD times were significantly longer in HD patients compared to the left intra-atrial-AEMD times in healthy individuals. After 24 months, 41 patients were still on HD treatment and 19 (31.6%) had died. Serum triglyceride, total cholesterol and albumin were found to be higher and C-reactive protein (CRP) levels, left intra-atrial EMD time (LIAT) and interatrial EMD times were found to be lower in survived HD patients. With the cut-off median values of 3.5 g/dl for albumin, 0.87 mg/dl for CRP, 157 mg/dl for total cholesterol and 151 mg/dl for triglyceride, the Kaplan–Meier curves demonstrated significant differences in terms of all-cause mortality. We also demonstrated the Kaplan–Meier survival curves of HD patients according to tertile values of LIAT. Cox regression analysis revealed that increased CRP and higher LIAT were found to be independent predictors of combined CV events. ***Conclusions:*** Increased LIAT and inflammation were found to be closely associated with 2 years combined CV events and all-cause mortality in HD patients.

Introduction

Despite intense medical treatment targeting cardiovascular (CV) diseases and developments in dialysis techniques, the risk of CV mortality is exceptionally high in

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patients with end-stage renal disease (ESRD) receiving hemodialysis (HD) compared to the age-, gender- and race-matched general population [1]. These heightened CV events cannot be explicable solely with Framingham risk factors. In this regard, both traditional factors, such as coronary artery disease, left ventricular hypertrophy, diastolic dysfunction, atrial and ventricular arrhythmia and sudden cardiac death, and novel kidney disease-related risk factors, such as malnutrition, inflammation, vascular calcification, anemia and various uremic toxins and cytokines, were found to be responsible for high CV morbidity and mortality in this population [2].

In recent years, the active and passive emptying volume of the left atrium (LA) and electromechanical functions have been demonstrated as potential indicators of cardiac arrhythmias in the general population [3]. The delay of atrial electromechanical conduction time may result in AF in the general population [4]. Atrial electromechanical delay (AEMD) times, including inter-atrial and left intra-atrial conduction delay (LIAT), were also found to be closely associated with high risk of mortality in the general population [5]. However, to our knowledge, there has been no data about whether delay in atrial conduction is a predictor of combined CV events in this population. Hence, the primary aim of this study was to determine the associated factors of AEMD times in HD patients. We also sought to explore the traditional and non-traditional factors of 2-year combined CV events in this population.

Study Population and Methods

The study protocol was approved by the Medical Ethics Committee of Erzincan University, Erzincan, Turkey. Written informed consent was obtained from all subjects included in the study.

This was a prospective study involving 60 ESRD patients receiving HD for ≥6 months in the Dialysis Unit of Erzincan University between December 2012 and December 2014. Patients aged 18–70 years who were willing to participate in the study were screened. A review of medical records (including information on age, sex, weight, duration of renal replacement treatment, medications, primary disease of ESRD) was undertaken. Exclusion criteria were (1) patients with active infection (clinically manifested as fever, cough, nausea, vomiting, diarrhea, etc.); (2) autoimmune disease; (3) severe secondary hyperparathyroidism; (4) congestive heart failure; (5) hypo/hyperthyroidism; (6) moderate-advanced mitral annular calcification; and (7) mitral valve regurgitation. Ninety-three patients were evaluated and 33 patients were excluded from the study. These 33 patients were excluded because of the following reasons: 17 refused to participate in the study, 9 had active infection, 5 had congestive heart failure (New York Heart Association classes III–IV); and 2 had autoimmune disease (including systemic lupus erythematosus and microscopic polyangitis). None of the patients included in the study had nephrotic-range proteinuria and mitral annular calcification and regurgitation. The remaining 60 HD patients fulfilled the criteria mentioned earlier and were enrolled in the study.

Forty-four age- and sex-matched healthy individuals referred from outpatient clinics of the Internal Medicine Department of Erzincan University were also enrolled as control subjects. They were subject to the same inclusion and exclusion criteria as the patients.

HD patients were receiving thrice-weekly dialysis for a 4-hour period with a standard bicarbonate-containing dialysate bath using a biocompatible HD membrane (Polysulfone, FX-80 series, Fresenius, Germany). Dialysate flow rates were 500 ml/min and blood-flow rates were 250–300 ml/min. The systolic blood pressure (SBP) and diastolic blood pressure (DBP) of patients and healthy subjects were measured in the upright sitting position after ≥5 min of rest using an Erka sphygmomanometer (PMS Instruments Limited, Berkshire, UK) with an appropriate cuff size. Two readings were recorded for each individual. The mean value of two readings was defined as the blood pressure. Patients with SBP and DBP >140 and 90 mm Hg, respectively, or who were already on antihypertensive treatment were assumed to be hypertensive. Twenty-two patients were taking antihypertensive drugs (7 of them on angiotensin-converting enzyme inhibitors; 5 receiving angiotensin-II receptor blockers; and 10 receiving a calcium-channel blocker). Nineteen patients were taking calcium-containing phosphate binders. None of our HD patients and healthy individuals was a smoker.

Biochemical Analyses

Venous blood samples for biochemical analyses were drawn after an overnight fast and before the midweek session in patients receiving HD and at the time of admission in all healthy individuals. All biochemical analyses including those for total cholesterol and plasma triglyceride concentrations were undertaken using an oxidase-based technique by the Roche/Hitachi Modular System (Mannheim, Germany) in the Central Biochemistry Laboratory of Erzincan University Mengucek Gazi Training and Research Hospital.

Definition of Neutrophil-to-Lymphocyte Ratio

Complete blood counts with automated differential counts, which included total white blood cells, neutrophils, and lymphocytes, were obtained at the time of admission. Neutrophil-to-lymphocyte ratio (NLR) was calculated as the ratio of the neutrophils to lymphocytes with both being obtained from the same automated blood sample obtained at the time of admission to the study.

Standard Echocardiographic Measurements

Echocardiographic examinations were performed with a machine equipped with a 2–4 MHz phased array transducer (Vivid S5, GE, Horten, Norway) by a cardiologist who was blinded to the clinical characteristics of ESRD patients and healthy individuals. Left ventricle (LV) end-systolic and end-diastolic dimensions, diastolic LV posterior wall thickness, diastolic ventricular septal thickness, and LA dimension were measured in the parasternal long-axis view. Apical four-and two-chamber views were obtained. Continuous single-lead ECG was obtained from all subjects during echocardiography.

Table 1. Demographic, clinic, and laboratory features of healthy individuals and HD patients

Parameters	Healthy individuals (n = 44)	HD patients (n = 60)	p value[#]
Age, years	52.3±8.38	54.2±11.9	0.362
Male/female	26/18	31/29	0.291
BMI, kg/m^2	26.3±4.95	24.02±1.98	0.002
SBP, mm Hg	124.86±15.25	125.67±19.97	0.824
DBP, mm Hg	74.93±13.49	77.17±10.55	0.345
Glucose, mg/dl	94.98±9.55	112.48±45.86	0.014
Urea, mg/dl	26.53±7.49	157.12±38.89	<0.0001
Creatinine, mg/dl	0.74±0.14	9.06±2.74	<0.0001
Calcium, mg/dl	8.91±0.6	8.16±0.94	<0.0001
Phosphorus, mg/dl	2.9±0.29	5.41±1.65	<0.0001
Albumin, g/dl	4.35±0.18	3.53±0.4	<0.0001
Uric acid, mg/dl	3.92±0.68	6.24±1.31	<0.0001
Total cholesterol, mg/dl	164.25±29.78 (162)	164.93±41.76 (157.5)	0.926
LDL-cholesterol, mg/dl	109.89±23.78 (111)	86.17±30.19 (83)	<0.0001
HDL-cholesterol, mg/dl	31.77±6.8 (133)	38.05±13.41 (36.5)	0.005
Triglyceride, mg/dl	120.27±67.19 (109)	199.33±130.79 (151)	<0.0001
NLR	1.22±0.31 (1.2)	2.64±1.57 (1.8)	<0.0001

Mean ± SD (median). [#] p values between 2 groups.

The mitral inflow early (E)-wave was obtained from the apical four-chamber view by pulsed wave Doppler. The mitral septal early (e') wave velocity was obtained from the apical four-chambers by pulsed wave tissue Doppler. E/e' ratio was calculated for estimating end-diastolic LV pressure. M-mode, conventional Doppler, and tissue Doppler measurements were carried out in accordance with the guidelines of the American Society of Echocardiography [6].

The LA function parameters were calculated as follows:
- LA passive emptying volume = $V_{max} - V_p$,
- LA passive emptying fraction (%) = $((V_{max} - V_p)/V_{max}) \times 100$,
- LA active emptying volume = $V_p - V_{min}$,
- LA active emptying fraction (%) = $((V_p - V_{min})/V_p) \times 100$ [7].

Measurements of Tissue Doppler Echocardiography

Pulsed wave tissue Doppler echocardiography (TDE) was obtained from an apical four-chamber window under continuous single lead ECG monitoring. Lead positions were modified for maximum P wave gain. Myocardial TDE velocities (peak systolic (S'), early diastolic (E') and late diastolic velocities (A')) were measured via spectral pulsed Doppler as of the LV-free wall from the apical four- and two-chamber view. The ultrasound beam was positioned as parallel as possible to the myocardial segment to acquire the optimal angle of imaging. Atrial electromechanical coupling (PA) is the time interval from the onset of P wave to the late diastolic wave on ECG. It was obtained from lateral mitral annulus, septal mitral annulus, and right ventricular tricuspid annulus and called PA lateral, PA septum, and PA tricuspid, respectively. The right atrial EMD time was defined as 'PA-tricuspid minus PA-septal', the left atrial EMD time as 'PA-lateral minus PA-septal', and inter-atrial EMD time as 'PA-lateral minus PA-tricuspid' [8]. An average measurement was achieved after obtaining these values three times. We performed the measurements from recordings by a second observer. The intra-observer and inter-observer variability for TDE were all <5%.

Statistical Analysis

Statistical analyses were carried out using the Statistical Package for Social Sciences for Windows version 15.0 (SPSS, Chicago, Ill., USA). Data are expressed as mean ± SD. Dichotomous variables were compared using the chi-square test. Statistical differences between parametric data of 2 groups were analyzed using the Student's t test. The Mann–Whitney U test was used to determine the differences between nonparametric data. Linear associations between continuous variables were assessed using the Spearman correlation test.

Significant determinants identified from univariate analysis and associated risk factors of combined CV events were studied in multivariate Cox regression analysis. The forward elimination method was preferred in Cox regression analysis. Linear logistic regression analysis was also used to determine the predictors of all-cause mortality. The backward elimination method was preferred in the stepwise regression analysis. $p > 0.1$ was used as a criterion for elimination in this model. $p < 0.05$ was considered significant for all tests.

Results

Baseline Characteristics of Study Population

The baseline characteristics of 60 HD patients and 44 healthy individuals are shown in table 1. Groups were similar in terms of age, gender, SBP, DBP, serum total and

Table 2. LA volumes, LA mechanical functions and AEMD times of healthy individuals and HD patients

Parameters	Healthy individuals (n = 44)	HD patients (n = 60)	p value#
Ejection fraction, %	67.3±6.09	59.57±7.41	<0.0001
LAV_{max}, ml/m^2	23.89±2.7 (24)	51.62±34.22 (51)	<0.0001
LAV_{min}, ml/m^2	9.5±1.5 (9)	26.92±19.89 (22)	<0.0001
LAV_p, ml/m^2	16.09±2.46 (16)	38.2±26.37 (34.5)	<0.0001
LA passive emptying volume, ml/m^2	7.8±2.54 (8)	13.43±11.82 (10.5)	0.002
LA passive emptying fraction, %	32.34±9.68 (32)	25.11±10.78 (25)	0.001
LA active emptying volume, ml/m^2	6.59±2.43 (6.5)	11.27±10.07 (10)	0.003
LA active emptying fraction, %	40±10.79 (40.5)	26.32±15.86 (28.2)	<0.0001
Left intra-atrial EMD time, ms	12.2±5.17 (11)	15.7±10.05 (12)	0.037
Right intra-atrial EMD time, ms	7.55±4.13 (7)	13.32±9.96 (11)	<0.0001
Inter-atrial EMD time, ms	19.57±7.99 (17.5)	28.15±13.39 (25)	<0.0001

Mean ± SD (median). LAV_{max} = Left atrium maximum volume; LAV_p = left atrium passive volume. # p values between 2 groups.

HDL-cholesterol; however, there were statistically significant differences regarding body mass index (BMI), serum urea, creatinine, calcium, phosphorus, albumin, uric acid, triglyceride and NLR.

The etiology of ESRD patients was diabetic nephropathy (n = 14, 23.3%), chronic glomerulonephritis (n = 9, 15%), hypertensive nephropathy (n = 28, 46.7%), polycystic kidney disease (n = 1, 1.7%), nephrolithiasis (n = 4, 6.7%), chronic tubulointerstitial nephritis (n = 2, 3.3%), and unknown (n = 2, 3.3%).

AEMD Times and LA Mechanical Functions of HD Patients and Healthy Individuals

Table 2 shows the measurements of AEMD times of healthy individuals and HD patients. Left and right intra-atrial EMD and inter-atrial EMD times were significantly lower in healthy subjects compared to those in HD patients.

Left atrial mechanical functions of healthy individuals and HD patients are also shown in table 2. LA minimum and maximum volume, LAVp, LA active and passive emptying volumes were lower; however, EF, LA active and passive emptying fractions were significantly higher in healthy subjects compared to similar fractions in HD patients.

Patient Survival and Causes of Death

After 24 months, 41 patients were still on HD treatment and 19 (31.6%) had died while being treated. The main causes of death were CV disease in 13 patients (68.4%), cerebrovascular disease in 1 patient (5.2%), infection in 2 patients (10.5%) and respiratory failure in 3 patients (15.7%). Of the 60 HD patients, 10 had acute myocardial infarction and 7 had atrial fibrillation. We included HD patients who had atrial fibrillation, acute myocardial infarction and CV death, as HD patients had combined CV events during 2 years of follow-up.

Baseline Characteristics of Survived and Deceased HD Patients

There were no significant differences between survived and deceased HD patients in terms of age, gender, BMI, systolic and diastolic blood pressure, serum glucose, calcium, phosphorus, uric acid, HDL and LDL-cholesterol levels and NLR. However, serum triglyceride, total cholesterol, albumin, urea, and creatinine levels were found to be lower and C-reactive protein (CRP) levels were found to be higher in deceased HD patients compared to HD patients who survived (table 3).

AEMD Times and LA Mechanical Functions of Survived and Deceased HD Patients

Left atrial mechanical functions were found to be similar between survived and deceased HD patients. In contrast, we found that left intra-atrial and inter-atrial EMD times were significantly longer in deceased HD patients compared to the left intra-atrial and interatrial EMD times in survived HD patients (table 4).

Correlations between Combined CV Events and Other Parameters in HD Patients

We found positive correlations between combined CV events and CRP, interatrial time and LIAT (r = 0.33, p =

Table 3. Demographic, clinic, and laboratory features of survived and deceased HD patients

Parameters	Survived HD patients (n = 41)	Deceased HD patients (n = 19)	p value[#]
Age, years	53.32±13.91	56.16±5.42	0.395
Male/female	23/18	8/11	0.232
BMI, kg/m^2	24±1.98	24.05±2.01	0.921
SBP, mm Hg	127.07±22.42	122.63±13.27	0.428
DBP, mm Hg	76.59±11.64	78.42±7.83	0.535
Glucose, mg/dl	108.34±44.8	121.42±48.07	0.308
Urea, mg/dl	165.46±35.2	139.11±41.26	0.013
Creatinine, mg/dl	9.94±2.48	7.17±2.32	<0.0001
Calcium, mg/dl	8.11±1.03	8.26±0.73	0.556
Phosphorus, mg/dl	5.69±1.6	4.81±1.64	0.055
Albumin, g/dl	3.64±0.31	3.29±0.49	0.002
Uric acid, mg/dl	6.39±1.33	5.92±1.23	0.192
Total cholesterol, mg/dl	172.85±42.43 (166)	147.84±35.56 (135)	0.030
HDL-cholesterol, mg/dl	37.76±12.98 (36)	38.68±14.63 (37)	0.805
LDL-cholesterol, mg/dl	88.95±28.78 (89)	80.16±33.03 (71)	0.298
Triglyceride, mg/dl	230.56±138.86 (221)	131.95±78.79 (115)	0.006
NLR	2.39±1.28 (1.95)	3.16±2.01 (2.7)	0.080
CRP	1.04±1.41 (0.66)	2.32±2.16 (1.4)	0.008

Mean ± SD (median). [#] p values between 2 groups.

Table 4. LA volumes, LA mechanical functions and AEMD times of survived and deceased HD patients

Parameters	Survived HD patients (n = 41)	Deceased HD patients (n = 19)	p value[#]
Ejection fraction, %	60.02±7.82	58.58±6.51	0.487
LAV_{max}, ml/m^2	50.22±35.42 (51)	54.65±32.17 (51)	0.645
LAV_{min}, ml/m^2	25.16±18.32 (22)	30.72±22.99 (24)	0.319
LAV_p, ml/m^2	36.7±26.11 (34)	41.43±27.36 (38)	0.522
LA passive emptying volume, ml/m^2	13.52±13.24 (9)	13.22±8.27 (13)	0.926
LA passive emptying fraction, %	24.95±11.38 (23.8)	25.45±9.63 (27.2)	0.869
LA active emptying volume, ml/m^2	11.53±11.08 (9)	10.72±7.7 (11)	0.773
LA active emptying fraction, %	27.16±15.58 (23.1)	24.51±16.75 (29.5)	0.552
Left intra-atrial time, ms	13.37±7.01 (11)	20.74±13.51 (16)	0.007
Right intra-atrial time, ms	13.56±11.02 (11)	12.79±7.41 (11)	0.783
Inter-atrial time, ms	25.8±10.79 (24)	33.21±17.02 (34)	0.045
E/e'	7.94±4.94 (6.6)	9.2±4.46 (8.2)	0.108

Mean ± SD (median). LAV_{max} = Left atrium maximum volume; LAV_p = left atrium passive volume. [#] p values between 2 groups.

0.008; r = 0.25, p = 0.045; r = 0.34, p = 0.007, respectively). There were negative correlations between combined CV events and serum albumin, potassium (prior to HD), triglyceride and total cholesterol levels (r = –0.39, p = 0.002; r = –0.29, p = 0.02; r = –0.35, p = 0.06; r = –0.28, p = 0.03, respectively).

Prognostic Indicator Stratification of All-Cause Mortality in HD Patients

With the cut-off median values of 3.5 g/dl for albumin, 0.87 mg/dl for CRP, 157 mg/dl for total cholesterol and 151 mg/dl for triglyceride, the Kaplan–Meier curves demonstrated significant differences in terms of all-cause mortality (fig. 1a and b and 3a and b, respectively). Since

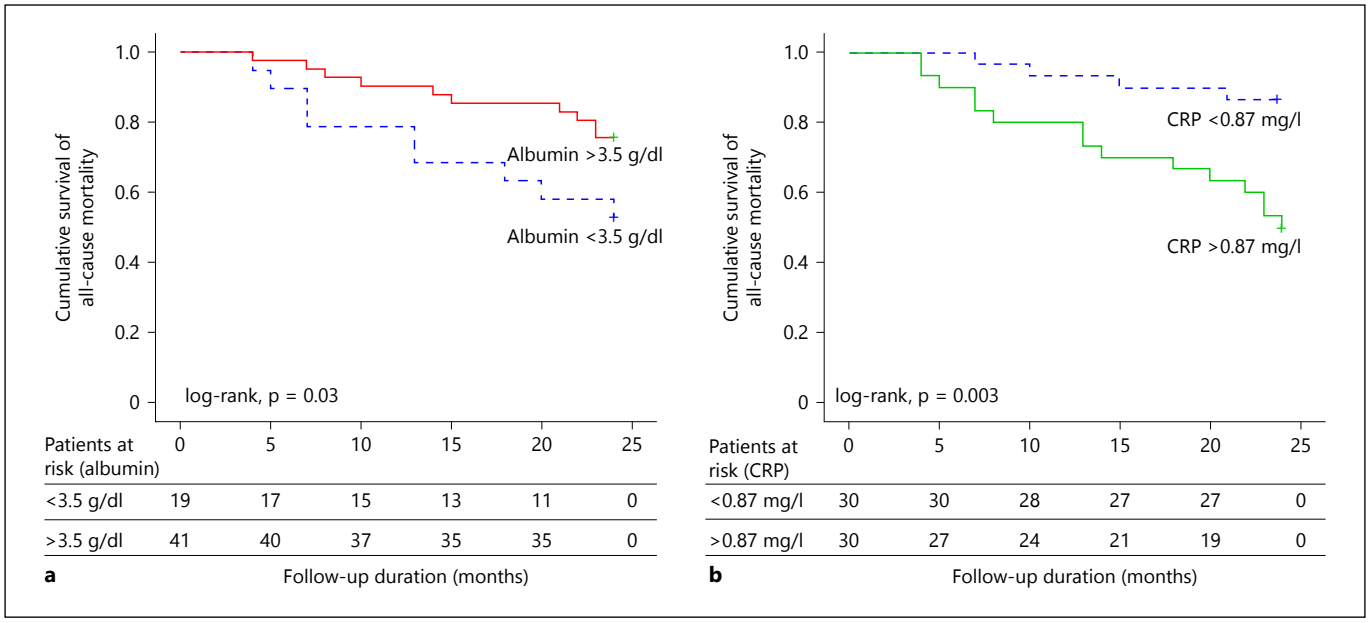

Fig. 1. **a**, **b** Kaplan–Meier survival analysis of HD patients according to the median values of serum albumin and CRP.

there has been no data regarding the cut-off value of atrial EMD times in HD patients, we preferred to demonstrate the Kaplan–Meier survival curve of HD patients based on tertile values of left intra-atrial delay time (HD patients with LIAT <10 ms, HD patients with LIAT ≥10 and <14 ms, and HD patients with LIAT ≥14 ms; fig. 2).

Cox Regression Analysis of Survival in HD Patients

Significant determinants identified from univariate analysis and combined CV events associated factors were studied in Cox regression analysis. Because the presence of coronary artery disease, CRP and diabetes mellitus were found to be closely associated with increased risk of mortality in HD patients [9–11], we included these two categorical covariates in the Cox regression model. We preferred to add independent variables, such as LIAT, left atrial volume, age, presence of diabetes mellitus, presence of coronary artery disease, serum albumin and CRP, one by one in each step to examine their effects on combined CV events. Therefore, model 1 is adjusted for LIAT, model 2 is adjusted for left atrial volume and LIAT, model 3 is adjusted for age and LIAT, model 4 is adjusted for presence of diabetes mellitus and LIAT, model 5 is adjusted for the presence of coronary artery disease and LIAT, model 6 is adjusted for serum albumin levels and LIAT, model 7 is adjusted for serum CRP levels and LIAT. According to the first and seventh models of multivariate Cox regression analysis, LIAT and CRP were found to be

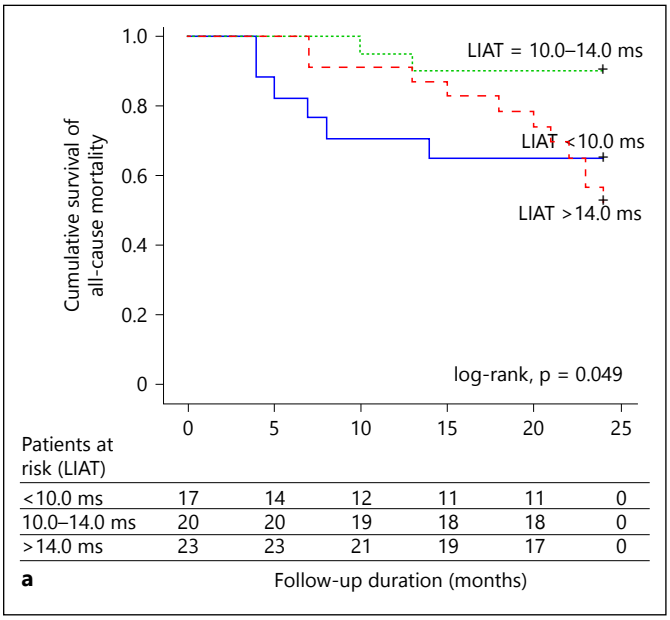

Fig. 2. Kaplan–Meier survival analysis of HD patients according to the tertiles of left intra-AEMD times.

related factors of combined CV events in HD patients (table 5).

We also compared steepness of albumin according to the median LA volume value. There was no relationship between albumin and LIAT (data not shown).

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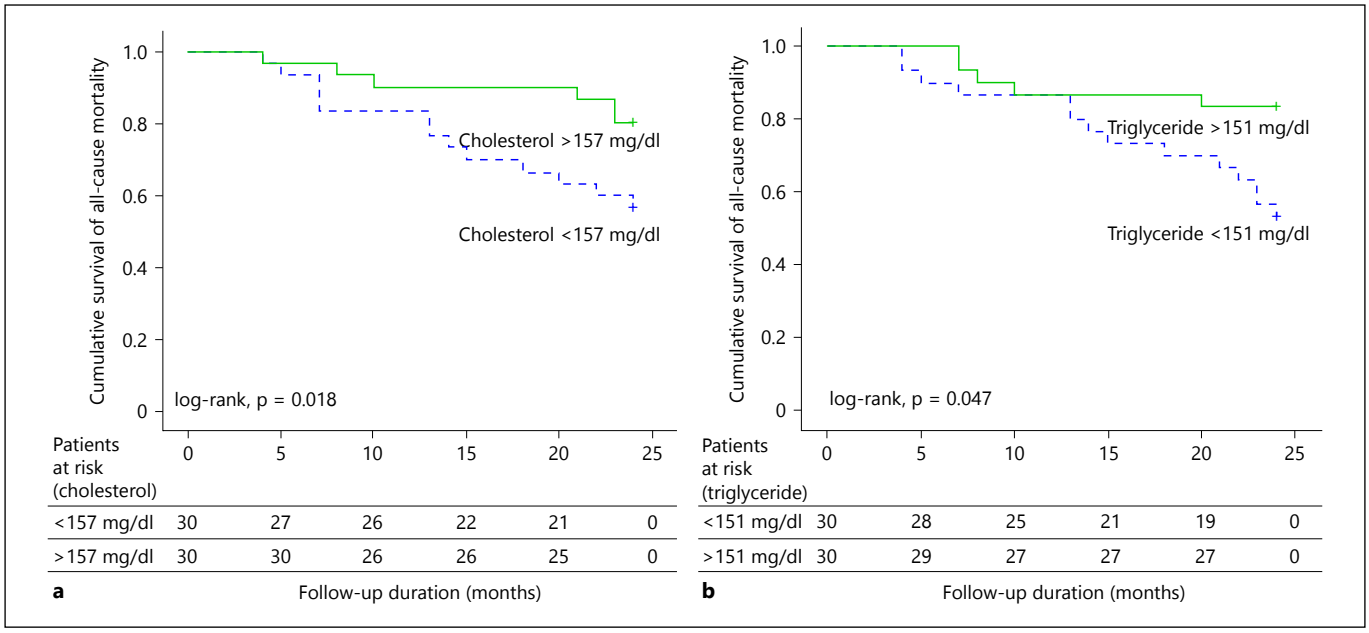

Fig. 3. a, **b** Kaplan–Meier survival analysis of HD patients according to the median values of serum total cholesterol and triglyceride.

Table 5. Multivariate Cox regression analysis for combined cardiovascular events in HD patients

Predictor	Potential confounder (adjusted for)	Hazard ratio for combined events (95% CI)	p value
Left intra-atrial EMD time, ms	Model 1	1.04 (1.01–1.08)	0.03
	Model 2, left atrial volume	1.01 (0.98–1.03)	0.84
	Model 3, age	1.00 (0.98–1.02)	0.94
	Model 4, diabetes mellitus	0.91 (0.42–1.96)	0.80
	Model 5, coronary heart disease	0.90 (0.37–2.17)	0.81
	Model 6, albumin, g/dl	1.15 (0.42–3.17)	0.78
	Model 7, CRP	1.23 (1.03–1.49)	0.03
	Model 8, E/e'	1.01 (0.92–1.10)	0.90

Model 1 is adjusted for left intra-atrial EMD time, model 2 is adjusted for left atrial volume and left intra-atrial EMD time, model 3 is adjusted for age and left intra-atrial EMD time, model 4 is adjusted for presence of diabetes mellitus and left intra-atrial EMD time, model 5 is adjusted for presence of coronary artery disease and left intra-atrial EMD time, model 6 is adjusted for serum albumin levels and left intra-atrial EMD time, model 7 is adjusted for serum CRP levels and left intra-atrial EMD time and model 8 is adjusted for E/e' levels and left intra-atrial EMD time.

Predictors of All-Cause Mortality in HD Patients

Age, presence of diabetes, albumin, CRP, LIAT, presence of CAD and E/e' were entered into the regression model as independent variables, and all-cause mortality was entered as a dependent variable. At the end of the sixth step, two variables including CRP and LIAT remained statistically significant in the model. Hence, the multivariate linear regression analysis revealed that LIAT, as well as CRP, were independent predictors of all-cause mortality in HD patients (standardized $\beta = 0.374$, $p = 0.002$, 95% CI 0.007–0.028 for LIAT and standardized $\beta = 0.294$, $p = 0.014$, 95% CI 0.017–0.139 for CRP).

Table 6. Demographic, clinic, biochemical features of groups according to LIAT

Parameters	Group 1 (LIAT <10 ms)	Group 2 (LIAT ≥10, <14 ms)	Group 3 (LIAT ≥14 ms)	p*	p#	p¥
Age, years	55±11	48±14	58±7	0.06	0.7	0.01
Male/female	7/10	11/9	13/10	0.59	0.58	0.35
BMI, kg/m^2	24±1.9	24±2.0	23±1.9	0.84	0.4	0.4
SBP, mm Hg	122±22	124±19	128±19	0.4	0.2	0.5
DBP, mm Hg	75±12	76±11	73±7	0.8	0.2	0.2
Albumin, g/dl	3.4±0.28	3.7±0.33	3.5±0.34	0.004	0.1	0.1
Uric acid, mg/dl	6.5±1.3	6.1±1.3	6.0±1.2	0.42	0.3	0.9
Total cholesterol, mg/dl	168±35	165±42	161±46	0.89	0.26	0.4
LDL-cholesterol, mg/dl	94±28	80±32	85±29	0.09	0.17	0.6
Triglyceride, mg/dl	196±99	222±134	181±149	0.55	0.31	0.17
NLR	2.2±1.0	2.0±0.9	3.48±1.9	0.44	0.017	0.04
CRP, mg/dl	1.5±1.7	0.5±0.3	2.1±2.1	<0.001	0.8	0.001

Mean ± SD. * p = Group 1 vs. 2, # p = group 1 vs. 3, ¥ p = group 2 vs. 3.

Demographic, Clinic, Biochemical Features of Groups According LIAT

We demonstrated the demographic, clinic and biochemical characteristics of HD patients according to LIAT <10 ms as group 1, LIAT ≥10 and <14 ms as group 2 and LIAT ≥14 ms as group 3 in table 6. When we compared groups 1 and 2 on the basis of serum albumin and CRP levels, we found that HD patient with LIAT <10 ms had higher serum CRP levels and lower serum albumin levels ($p < 0.05$, for both).

Discussion

There were five main findings of this study. First, AEMD times were significantly prolonged in HD patients compared to the AEMD times in healthy subjects. Second, LIAT and interatrial EMD times were significantly longer in deceased HD patients compared to LIAT and interatrial EMD times in survived HD patients. Third, serum albumin, total cholesterol and triglyceride levels (as markers of malnutrition) were found to be lower; however, serum CRP and NLR levels (as markers of inflammation) were found to be higher in deceased HD patients compared to serum CRP and NLR levels in survived HD patients. Fourth, in the bivariate correlation analysis, combined CV events were positively associated with CRP, inter-atrial time and LIAT, whereas it was negatively correlated with serum albumin, potassium (prior to HD session), triglyceride, and total cholesterol levels. Fifth, LIAT and CRP were found to be related factors of combined CV events in HD patients in the Cox regression model.

To our knowledge, this is the first study that investigated the parameters including AEMD times regarding long-term CV outcomes in HD patients.

Atrial electromechanical conduction time is a measure of atrial conduction characteristics, which represent electrical and functional continuity of atrial myocytes [12]. AEMD times including inter-atrial and left and right intra-atrial conduction delay times might be responsible for the initiation and continuation of AF, which is the most commonly seen arrthythmia in ESRD patients [12, 13]. Recently, Karavelioğlu et al. [14] demonstrated that the atrial EMD times including inter-atrial time and LIAT were significantly longer in HD compared to the atrial EMD times in healthy individuals. In addition, Tekce et al. [15] investigated the effect of single dialysis on inter-atrial and left-right intra-atrial EMD times. They showed that AEMD times were longer in HD patients compared to healthy individuals and were reduced after a single dialysis session.

Our results were in accordance with those of previous studies. In this study, we found that AEMD times were significantly prolonged in HD patients compared to AEMD times in healthy individuals. We also demonstrated that deceased HD patients had longer LIAT and interatrial EMD times compared to survived HD patients. There were positive correlations between combined CV events and LIAT, inter-atrial EMD times and serum CRP levels.

The attributable risk factors related to prolonged LIAT might include increased malnutrition and chronic low-

grade inflammation and decreased potassium levels, which are commonly seen in HD patients [16, 17]. In the general population, the most important clinical implications of LIAT include the increased risk of atrial fibrillation and more importantly the increased risk for CV mortality including sudden cardiac death (SCD) [5]. The risk factors of SCD in ESRD comprise both traditional and novel risk factors including inflammation and malnutrition [18]. In this regard, Parekh et al. [19] demonstrated that decreased albumin as a measure of malnutrition elevated hsCRP and IL-6 levels, as measures of chronic inflammation were associated with an increased risk of SCD, independent of traditional CV risk factors. In this study, we found that increased CRP levels as a measure of chronic low-grade inflammation and LIAT were found to be independent predictors of combined CV outcomes. Our results were in accordance with those of the previous studies [20–22]. Hence, it is wise to consider that the increased CV morbidity and mortality might be secondary to increased inflammation via atrial EMD delay time prolongation in ESRD patients.

Diabetes mellitus has been a well-known risk factor for increased mortality in general and in HD population [23, 24]. However, after adjusting for risk factors including diabetes and coronary artery disease, we could not demonstrate a relation between these parameters and combined CV events in our cohort.

Besides other factors, AEMD was found to be closely associated with atrial fibrosis [25, 26]. Thus, it is plausible to think that increased inflammation via increased atrial fibrosis might be a risk factor for prolonged LIAT in ESRD patients.

In contrast to a previous study [15] that showed an association between volume removal during HD and atrial electromechanical conduction intervals, we could not demonstrate any correlation between removed ultrafiltration volume and AEMD times in HD patients. Our HD patients were relatively old, had longer dialysis vintage and some of them had diabetes and hypertension. However, HD patients who were enrolled in the study conducted by Tekce et al. [15] were non-diabetic, non-hypertensive, younger and clinically well patients whose HD duration was relatively shorter when compared to that of our patients. Advanced age and diabetes, hypertension and dialysis duration are well-known risk factors for impaired left atrial mechanical functions and AEMD times [27–29].

In this study, there were only 19 patients who had reached the primary outcome. Hence, many covariates in the multivariate Cox model might result in an unstable estimate. To strengthen our results, we included atrial fibrillation, acute myocardial infarction and CV death as combined CV events. In this regard, we showed that if the LIAT increases by 1 ms, the risk of combined CV events independently increased 1.04-fold and if the model is adjusted for CRP, the risk of combined CV events independently increased 1.04-fold on multivariate Cox regression analysis in HD patients. We could not demonstrate the effects of advanced age, presence of diabetes and coronary artery disease and left atrial volume and serum albumin levels on combined CV events.

According to our study results, an increase in CRP and LIAT were found to be predictors of all-cause mortality in HD patients. In the literature, it has been established that increased CRP, as a marker of chronic inflammation, is closely associated with all-cause mortality in HD patients [11]. However, in the present study, for the first time, our group demonstrated that delay in left atrial EMD time is also a predictor of increased mortality in this population.

When we evaluate Kaplan–Meier analyses of our HD patients, we found that increased CRP and decreased triglyceride, total cholesterol and albumin levels were significantly associated with survival (fig. 1, 3). These are markers of nutritional status and increased inflammation that are components of malnutrition-inflammation-athesclerosis syndrome in HD patients [16] and these parameters have been also demonstrated to be associated with increased mortality in HD patients [30, 31].

Since, there has been no data regarding the cut-off value of atrial EMD times in HD patients, we preferred to demonstrate the Kaplan–Meier survival curve of HD patients according to tertile values of left intra-atrial delay time (HD patients with LIAT <10 ms, HD patients with LIAT ≥10 and <14 ms, and HD patients with LIAT ≥14 ms; fig. 2). We realized that HD patients with LIAT <10 ms died early (in the first 8 months) in the follow-up period when compared to HD patients with LIAT ≥10 and <14 ms. When we compared these two groups in terms of serum albumin and CRP levels, we found that HD patient with LIAT <10 ms had higher serum CRP levels and lower serum albumin levels; this means that these patients had higher inflammation and malnutrition.

In patients with heart failure, routine assessment of left ventricular functions has been recommended. Zoccali et al. [32] revealed that reduced left ventricular ejection fraction was significantly correlated with increased adverse events in 254 a symptomatic HD patients. Therefore, evaluating HD patients in terms of cardiac function is critical. Hence, the assessment of LIAT and inflamma-

tion parameter, such as CRP, might be a useful adjunct in predicting CV events when using echocardiography for evaluating other cardiac parameters in HD patients.

LA mechanical functions including LAV_{max}, LAV_{min}, LAV_p, LA active and passive emptying volumes, left intra-atrial and interatrial EMD times were found to be higher in HD patients compared to similar functions in healthy subjects. These latter 2 parameters were also found to be higher in deceased HD patients compared to survived HD patients. Since, patients with prolonged LIAT have a large and poorly contractile LA with reduced and delayed left ventricular filling, one of the main reasons of LIAT might be associated with impaired LA mechanical functions in ESRD patients. We could not find any correlation between left atrial mechanical functions and combined CV events in this study.

Our study has several limitations. First, this study had a single-center design and the sample size was relatively small. Second, all of the HD patients and healthy individuals enrolled in the study were Turkish. One should consider that our results cannot be applied to all HD patients because of the differences between them in terms of their nationalities. Third, follow-up period was also relatively short to evaluate the effects of variables including AEMD times on mortality and other CV events in our study cohort. Finally, therapeutic interventions and medical treatment were not evaluated in this study.

In conclusion, according to the results of our study, HD patients had prolonged AEMD times and increased LA active and passive emptying volumes compared to healthy individuals. Besides traditional risk factors, novel risk factors including low-grade chronic inflammation and malnutrition might be responsible for delayed atrial electromechanical time and LA mechanical dysfunction in this population. Further well-designed, randomized, and controlled trials are needed to support our results.

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Disclosure Statement

None of the authors declare conflict of interest.

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