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ORIGINAL PAPER

New perspective on fatigue in hemodialysis patients with preserved ejection fraction: diastolic dysfunction

Fatigue and diastolic dysfunction

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Abstract
The relationship between diastolic dysfunction and fatigue in hemodialysis patients with preserved ejection fraction is unknown. In this context, the objective of this study is to assess fatigue using the relevant scales and to demonstrate its relationship with diastolic dysfunction. The patients who underwent hemodialysis were evaluated prospectively. Patients' fatigue was assessed using the Visual Analogue Scale to Evaluate Fatigue Severity (VAS-F). The echocardiographic works were performed as recommended in the American Society of Echocardiography guidelines. A total of 94 patients [mean age 64.7 ± 13.5 years, 54 males (57.4%)] were included in the study. The median VAS-F score of these patients was 68.5 (33.25–91.25), and they were divided into two groups according to this value. Peak myocardial velocities during early diastole (e′) and tricuspid annular plane systolic excursion (TAPSE) values were found to be significantly lower in the group with high VAS-F scores, whereas the early diastolic flow velocities (E)/e′ ratio and pulmonary artery peak systolic pressures (PAP) were found to be significantly higher ($p < 0.05$, for all). E/e′ ratio (r 0.311, p 0.002) and PAP (r 0.281, p 0.006) values were found to be positively correlated with the VAS-F score, as opposed to the TAPSE (r − 0.257, p 0.012) and e′ (r − 0.303, p 0.003) values, which were found to be negatively correlated with the VAS-F score. High fatigue scores in hemodialysis patients may be associated with diastolic dysfunction. In addition, in our study, we determined the correlation of VAS-F score with E/e′ ratio, PAP and TAPSE.

Keywords Fatigue · Hemodialysis · Echocardiography · Diastolic dysfunction

Introduction

Fatigue is an unpleasant and subjective complaint frequently observed in hemodialysis (HD) patients. It is associated with impaired quality of life and depression [1]. In addition to chronic diseases such as inflammatory and autoimmune diseases and cancer, psychological factors are also involved in the etiology of fatigue [2–4]. In parallel, in HD patients, physiological, psychological and sociocultural factors have an effect on fatigue and are observed with a frequency of up to 80% [5]. The fatigue that develops in the first hours after dialysis is called post-dialysis fatigue (PDF) [5]. Many scoring systems are being used in the assessment and interpretation of subjective concepts such as fatigue, quality of life and PDF [5].

The relationship between fatigue and cardiovascular events in HD patients has been demonstrated independently of the nutritional status of the patients and any co-existing inflammatory process [6]. Impaired exercise tolerance and fatigue are common in cases of chronic heart failure as are in cases of end-stage renal disease [7, 8]. Arrhythmias and coronary artery disease are among the other common causes of fatigue in addition to congensive heart failure [7–9].

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The combination of diastolic function indicators and right ventricular systolic pressure is important in the diagnostic assessment of heart failure patients with preserved ejection fraction (HFpEF). Impairment of diastolic functions is associated with increased filling pressures, resulting in dyspnea and decreased effort capacity [10, 11]. Impairment of right heart functions on the other hand results in a decrease in preload, and symptoms develop in association with the said decrease [12]. Nevertheless, to the best of knowledge of the authors of this study, there is no study available in the literature that addressed the relationship between diastolic dysfunction and fatigue in HD patients. In this context, it is aimed with this study to assess the relationship between fatigue and left and right heart functions in HD patients with normal systolic functions.

Materials and methods

Study population

In this study, patients who underwent HD in the Dialysis Unit of Baskent University Alanya Hospital were evaluated prospectively. Patients who were over the age of 18 and have been receiving HD treatment for the last 3 months were included in the study with the exception of patients with an ejection fraction (LVEF) below 50%, moderate and/or severe heart valve disease, angina pectoris or known untreated severe coronary stenosis, cardiac rhythm other than sinus rhythm, uncontrolled hypertension (HT), malignancy, chronic liver disease, and sepsis or active serious infection, and of patients who were diagnosed with depression or have been using anti-depressant drugs, who have been delaying their dialysis treatment or whose dry weight could not be achieved and were unstable, who were pregnant, who were immobile and who were hypotensive in the HD session.

This study was conducted as a single-center study. Written consents were obtained from all patients after they were provided with detailed information on volunteering for the study. The study was approved by the Baskent University Institutional Review Board and Ethics Committee with the approval number KA21/380, and was supported by Baskent University Research Fund.

On a day when they did not undergo dialysis, patients had physical and electrocardiographic (ECG) examinations, and were administered transthoracic echocardiography [13]. Demographic characteristics and cardiovascular risk factors of the patients were obtained from the hospital database. The body mass index (BMI) values of the patients were obtained by dividing their weights in kilograms by the square of their heights in meters. Glomerular filtration rates (GFR) were calculated using the Chronic Kidney Disease Epidemiology Collaboration Formula [14]. All blood samples were taken before the start of the HD session.

Hemodialysis technique

Blood pressure (BP) and pulse measurements of the patients were taken hourly during HD. HD was performed using Japanese Nikkiso DDB-06/09 HD machine, German Allmed Polypure dialyzer with a surface area of 1.8 to 2 m^2 depending on the body surface area, at a dialysate flow rate of 500–800 ml/min. HD was performed in HD dialysis unit conditions through arteriovenous fistula or dialysis catheter using ultrafiltration volume controlled Nipro machine and polysulfone hemodialyser (with a surface area of 1.6 to 2 m^2 depending on the body surface area) filters, with a dialysate sodium concentration of 135–145 milliequivalents per litre (mEq/l), and at a dialysate temperature of 36 to 36.7 °C depending on the patient's body temperature and BP. Urea reduction ratios (URR) and Kt/V ratios (K: dialyzer clearance of urea, t: dialysis time, and V: the volume of distribution of urea) of patients were calculated to demonstrate the dialysis efficiency, based on the laboratory tests carried out for control purposes at the end of dialysis.

Transthoracic echocardiography

Echocardiographic evaluation was performed using a GE Vivid E (3.5-MHz transducer, Horten, Norway) device. Two-dimensional, M-mode, pulse-wave (PW) and color Doppler imaging was performed from the parasternal long and short axis views, the apical four and five chamber views, and the subcostal view. M-mode and conventional echocardiographic works were carried out as recommended in the American Society of Echocardiography guidelines [15]. Additionally, left ventricular diameters and wall thickness were measured. LVEF was calculated using the Teichholz method. Left ventricular mass (LVM) was calculated using the Devereux equation [15]. Left ventricular mass index (LVMI) was calculated by dividing LVM by body surface area. Early (E) and late (A) diastolic flow velocities were determined using PW Doppler.

Tricuspid annular plane systolic excursion (TAPSE) was measured from the apical 4-chamber view by 2D echocardiography-guided M-mode recordings with the cursor placed on the free wall of the tricuspid annulus [16]. Pulmonary artery peak systolic pressure (PAP) was estimated in mmHg from the peak tricuspid underflow velocity using a modified Bernoulli equation (Fig. 1). This pressure value was revised upwards based on the evaluation of the right atrium and inferior vena cava (VCI) [17]. An image of the VCI was obtained from the subcostal view. VCI diameter was measured both at end-expiration (maximal diameter) and at end-inspiration (minimal diameter) [18]. A change

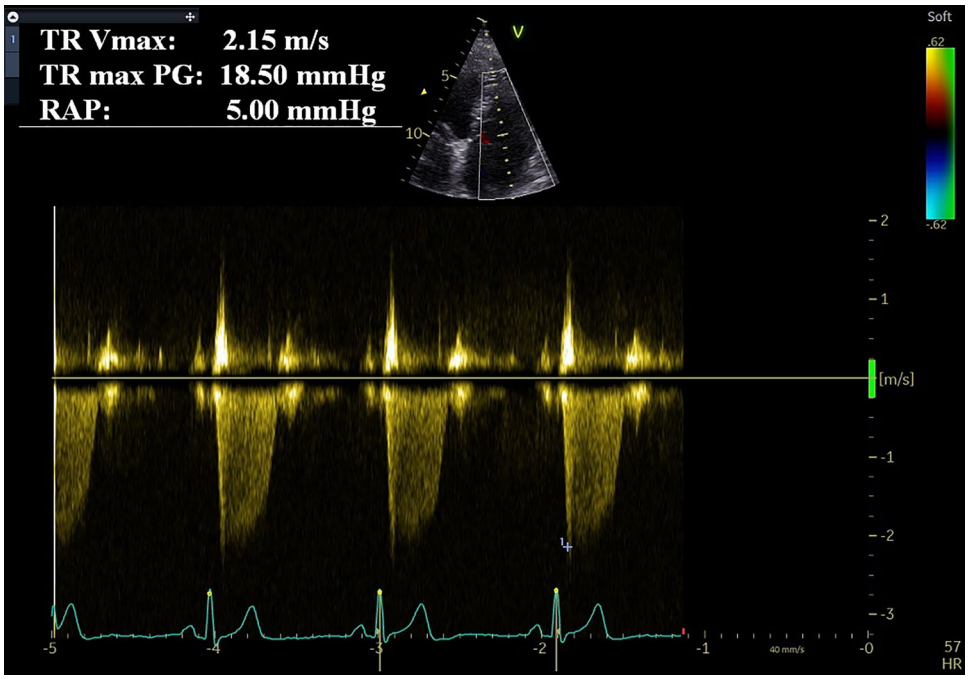

Fig. 1 Assessment of pulmonary artery pressure by echocardiography

of more than 50% was deemed as normal. Right ventricule (RV) diameter was measured from the basal segment of the right ventricular end-diastolic area and through the apical 4-chamber view [18].

Tissue Doppler imaging (TDI)

TDI measurements were performed at a high frame rate (> 150 fps), using minimal optimal gain, with transducer frequency between 3.5 and 4.0 MHz, and setting the Nyquist limit to 15–20 cm/s. The monitor sweep rate was set to 50 to 100 mm/s to optimize spectral analysis of myocardial velocities. A 5 mm PW-Doppler sample volume was placed in the basal segment of the apical four-chamber medial and lateral wall of the left ventricle in accordance with guidelines [19]. Early diastolic myocardial velocity (e′) was calculated from the septal and lateral wall using TDI, and the values obtained were averaged (Fig. 2).

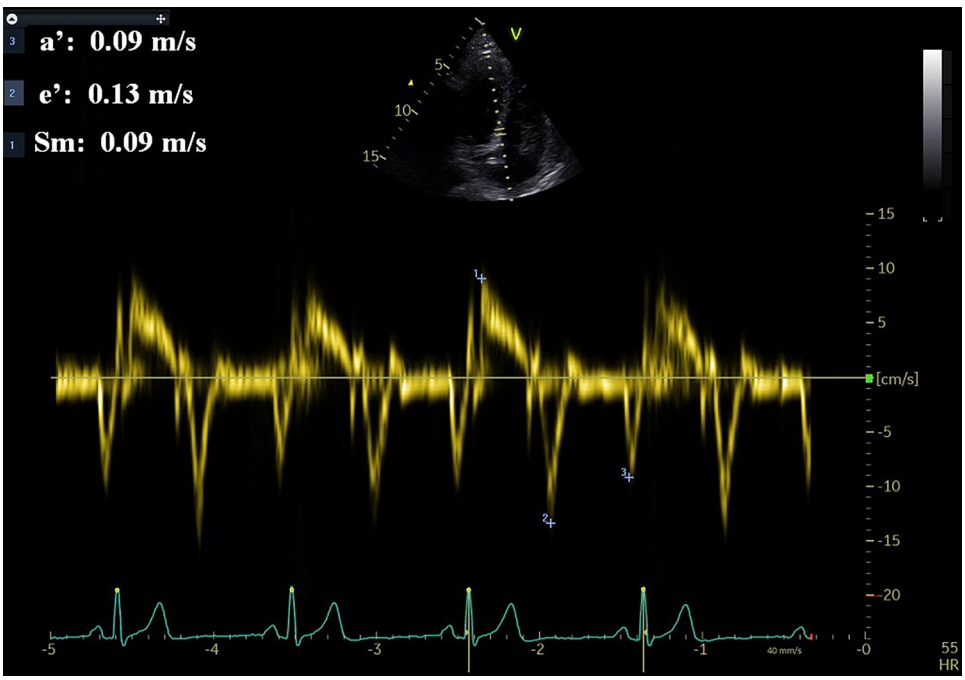

Fig. 2 Evaluation of Tissue Doppler images obtained from the basal part of the left ventricular septum of the patients. *Sm* myocardial velocity during ejection phase, *e′* early diastolic myocardial velocity, *a′*; late diastolic myocardial velocity

A single lead ECG was recorded during all recordings and data were calculated by averaging five consecutive cycles. Two-dimensional and M-mode measurements were reported by taking the average of 3 different measurements. All echocardiographic studies were performed by the same physician who did not know the patients' fatigue score.

Assessment of Fatigue. Fatigue was assessed using Visual Analogue Scale to Evaluate Fatigue Severity (VAS-F).

VAS-F was developed by Lee et al. to assess fatigue [20]. VAS-F consists of 18 items, each of which is scored out of 10. The 6th, 7th, 8th, 9th, and 10th items assess the energy level of the participant, whereas the other items assess fatigue [21]. Respectively "tired, sleepy, drowsy, fatigued, worn out, energetic, active, vigorous, efficient, lively, bushed, exhausted, keeping my eyes open, moving my body, concentrating, carrying on a conversation, desire to close my eyes, desire to lie down" statements were evaluated. In each item, participants are asked to place an "X" representing how they feel on a 10 cm straight line that extends between the most positive and the most negative statements. The items related to fatigue subscale are arranged to start from the most positive item to the most negative one, whereas the items related to energy are arranged the opposite. The higher the score obtained from the fatigue subscale and the lower the score obtained from the energy subscale, the higher the fatigue severity. Validity and reliability studies of the Turkish version of the VAS-F scale were carried out by Yurtsever et al. [22].

Table 1 Demographic characteristics of patients and data on dialysis program

Variables	Total (n = 94)	Low VAS-F (n = 47)	High VAS-F (n = 47)	p-value
Age, (year)	64.7 ± 13.5	60.7 ± 13.1	68.7 ± 12.9	0.003
Male, n (%)	54 (57.4%)	33 (70.2%)	21 (44.7%)	0.012
Body mass index, (kg/m^2)	25.0 ± 4.1	24.8 ± 4.0	25.2 ± 4.4	0.592
Body surface area, (m^2)	1.88 ± 0.45	1.96 ± 0.50	1.79 ± 0.39	0.063
CAD, (n, %)	17 (18.1%)	6 (12.8%)	11 (23.4%)	0.180
Diabetes mellitus, n (%)	20 (21.3%)	7 (14.9%)	13 (27.7%)	0.131
Hypertension, n (%)	70 (74.5%)	29 (61.7%)	41 (87.2%)	0.005
Aspirin, n (%)	30 (31.9%)	12 (25.5%)	18 (38.3%)	0.184
Clopidogrel, n (%)	8 (8.5%)	3 (6.4%)	5 (10.6%)	0.714
Beta bloker, n (%)	42 (44.7%)	19 (40.4%)	23 (48.9%)	0.407
Calcium channel bloker, n (%)	52 (55.3%)	20 (42.6%)	32 (68.1%)	0.013
Statins, n (%)	13 (13.8%)	5 (10.6%)	8 (17.0%)	0.370
Alfa bloker, n (%)	26 (27.7%)	13 (27.7%)	13 (27.7%)	1.0
ACE-ARB, n (%)	9 (9.6%)	7 (14.9%)	2 (4.3%)	0.158
Serum albumin, (g/dL)	37.0 ± 3.2	37.7 ± 2.5	36.4 ± 3.7	0.054
Serum Sodium, (mmol/L)	138.4 ± 3.0	138.7 ± 3.0	138.0 ± 3.0	0.323
Serum potassium, (mmol/L)	4.89 ± 0.82	4.79 ± 0.74	4.99 ± 0.88	0.242
Calcium, (mg/dL)	8.80 ± 0.79	8.93 ± 0.79	8.66 ± 0.78	0.101
GFR, (mL/min/m2)	6.3 (4.8–8.2)	6.4 (4.9–8.6)	6.1 (4.7–8.0)	0.548
Hematocrit, (%)	36.0 ± 4.4	35.9 ± 4.1	36.0 ± 4.7	0.949
White blood cell count (× 10^9/l)	7.52 ± 2.20	7.45 ± 2.39	7.58 ± 2.01	0.777
Platelet count (× 109/l)	191 ± 68	183 ± 68	197 ± 69	0.340
Dialysis vintage, (months)	43 (22–84)	36 (16–72)	51 (26–86)	0.132
Session duration, (hour)	4.0 (3.5–4.0)	4.0 (3.5–4.0)	4.0 (3.5–4.0)	0.363
Fluid withdrawn by hemodialysis, (ml)	2790 ± 943	2809 ± 935	2772 ± 961	0.854
Weight reduction, (%)	3.7 ± 1.6	3.5 ± 1.3	3.8 ± 1.8	0.331
DeltaSBP, (mmHg)	16.9 ± 8.2	15.7 ± 7.6	18.1 ± 8.7	0.164
DeltaDBP, (mmHg)	16.4 ± 9.1	16.6 ± 8.8	16.2 ± 9.5	0.859
Kt/Vurea	1.59 ± 0.38	1.58 ± 0.38	1.60 ± 0.37	0.729
URR	73.0 ± 9.0	72.7 ± 8.4	73.4 ± 9.6	0.724

Data are presented as percentage, mean ± standard deviation or median (interquartile range)

CAD coronary artery disease, *ACE* angiotensin converting enzyme, *ARB* angiotensin receptor blockers, *GFR* glomerular filtration rate, *DeltaSBP* decrease in systolic blood pressure with hemodialysis, *DeltaDBP* decrease in diastolic blood pressure with hemodialysis, *URR* based on urea reduction ratio

Table 2 Comparison of echocardiographic parameters of hemodialysis patients

Variables	Total (N = 94)	Low VAS-F (n = 47)	High VAS-F (n = 47)	p-value
LVEDD, (mm)	47.2 ± 4.8	46.8 ± 4.3	47.6 ± 5.3	0.442
LVESD, (mm)	29.6 ± 3.7	29.6 ± 3.2	29.5 ± 4.2	0.870
LVMI, (gr/m^2)	121 ± 40	114 ± 38	128 ± 41	0.101
LVEF, (%)	62 ± 5	61 ± 4	63 ± 5	0.073
LA, (mm)	39.2 ± 5.1	38.8 ± 5.1	39.6 ± 5.0	0.408
E, (cm/sn)	73.6 ± 22.7	71.4 ± 20.0	75.7 ± 25.2	0.367
e′, (cm/sn)	7.6 ± 2.0	8.2 ± 2.1	7.0 ± 1.7	0.004
E/e′ ratio	10.1 ± 3.5	9.1 ± 3.1	11.1 ± 3.7	0.007
E/A ratio	0.90 ± 0.34	0.86 ± 0.30	0.93 ± 0.37	0.267
Right ventricle, mm	36.4 ± 4.2	36.0 ± 4.3	36.7 ± 4.0	0.375
TAPSE, (mm)	21.0 ± 3.0	21.9 ± 3.1	20.1 ± 2.7	0.004
PAP, (mmHg)	28.9 ± 8.7	26.4 ± 7.2	31.5 ± 9.3	0.004
Pericardial effusion, n (%)	19 (20.2%)	10 (21.3%)	9 (19.1%)	0.797
Vena cava inferior, (mm)	19.5 ± 4.1	19.8 ± 4.3	19.2 ± 4.0	0.487
Respiratory variation, n (%)	63 (67.0%)	36 (76.6%)	27 (57.4%)	0.048

Data are presented as percentage, mean ± standard deviation or median (interquartile range)

LVEDD left ventricular end-diastolic diameter, *LVESD* left ventricular end-diastolic diameter, *LVMI* left ventricular mass index, *LVEF* left ventricular ejection fraction, *LA* left atrium, *E* early diastolic flow velocities, *e′* peak myocardial velocity during early diastole, *A* late diastolic flow velocities, *TAPSE* tricuspid annular plane systolic excursion, *PAP* pulmonary artery peak systolic pressure

Table 3 Correlation analysis with VAS-F score

Variables	r	p
Age	0.331	0.001
e′	−0.303	0.003
E/e′ ratio	0.311	0.002
TAPSE	−0.257	0.012
PAP	0.281	0.006

E early diastolic flow velocities, *e′* peak myocardial velocity during early diastole, *TAPSE* tricuspid annular plane systolic excursion, *PAP* pulmonary artery peak systolic pressure

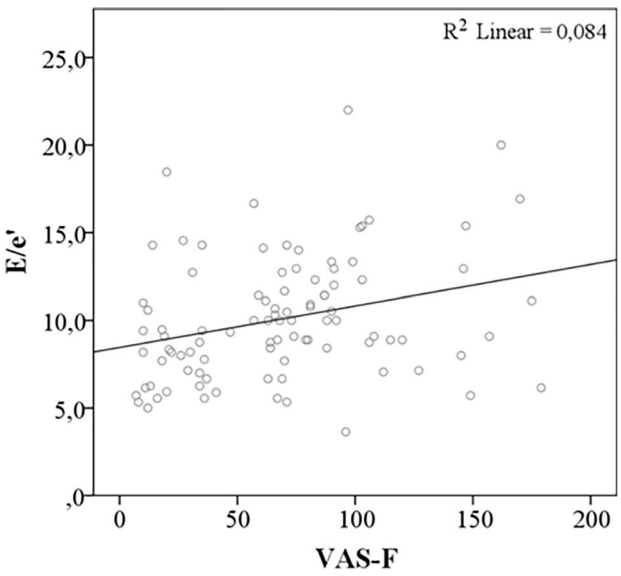

Fig. 3 Scatter plot of E/e′ ratio and VAS-F score. *E/e′* E/e′ ratio, *E* early diastolic flow velocities, *e′* peak myocardial velocity during early diastole

Calculation of sample size

The Cochran formula was used for calculating the sample size:

$$Sample\ size = \frac{Z^2 \times (P) \times (1 - p)}{d^2}$$

where Z = standard normal variate at 5% type 1 error ($p < 0.05$; 1.645 was used in the formula), p = expected proportion in a population based on previous studies or pilot studies, and d = absolute error or precision (which is to be decided by the researcher).

In the study by Gordon et al., with a precision/absolute error at 5% and type 1 error at 5%, approximately 86% of the dialysis patients were found to experience fatigue [23]. In view of the foregoing, the sample size has been calculated as follows:

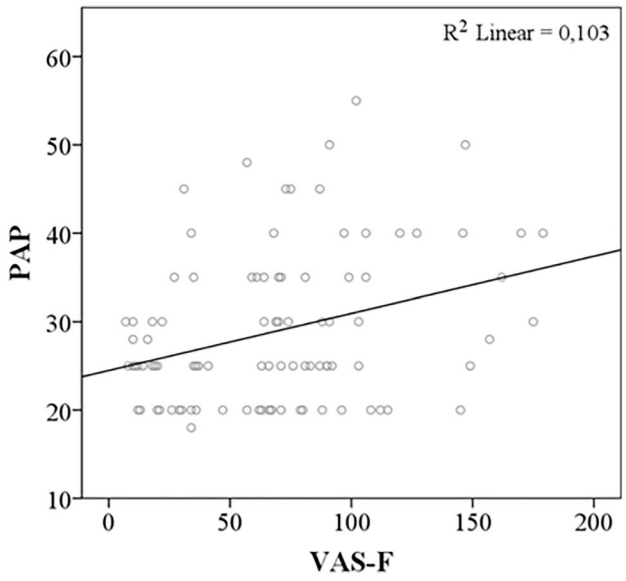

Fig. 4 Scatter plot of pulmonary artery peak systolic pressure and VAS-F score. *PAP* pulmonary artery peak systolic pressure

$$130 = \frac{1,645^2 \times (0,86) \times (1 - 0,86)}{0,05^2}$$

Statistical analysis

Statistical analyses of the research data were performed using the SPSS 24.0 (Statistical Package for Social Sciences version 24.0 software package, SPSS Inc., Chicago, Illinois, U.S.) software. The conformance of the variables to the normal distribution was assessed using visual (histograms, probability curves) and analytical (Kolmogorov–Smirnov's or Shapiro–Wilk) methods. Accordingly, the numerical variables that were found to conform to the normal distribution were expressed as mean ± standard deviation (SD), and the numerical and categorical variables that were found not to have conformed to the normal distribution were expressed as median (interquartile range) and percentage (%) values, respectively. Statistical analyses of the numerical and categorical variables between groups were performed using the student's t-test or Mann–Whitney U test, and the chi-squared test or Fisher's exact test, respectively. The correlation of the VAS-F score between other numerical variables was analyzed using Spearman's rank correlation coefficient. One-way logistic regression analysis was performed first to determine the independent predictors that indicate the presence of high VAS-F scores, and the parameters that were found to be significant as a result of this analysis were then further analyzed using multiple regression analysis. The receiver operating characteristic (ROC) curve and Youden index [max (Sensitivity + Selectivity − 1)] were used to determine the threshold values, and the areas under the ROC curve and the probability (p) values were deemed to be statistically significant if above 0.5 and below 0.05, respectively.

Results

This study was designed as a prospective study including 130 patients. 3 patients, who did not give their consent, 14 patients who were found to have moderate to severe valve disease, 10 patients who were found to have LVEF below 50%, and 9 patients who were found to meet other exclusion criteria, were excluded from the study. The mean age of the remaining 94 patients, of whom 54 (57.4%) were male, was calculated as 64.7 ± 13.5 years. The median value of the VAS-F score was calculated as 68.5 (33.25–91.25). The patients included in the study were divided into 2 groups, based on whether their VAS-F scores were below or above the median VAS-F score.

The group with high VAS-F scores ($VAS\text{-}F_H$) had a significantly higher ratio of females and patients with advanced age as compared to group with low VAS-F scores ($VAS\text{-}F_L$) ($p = 0.012$ and $p = 0.003$, respectively). Additionally, the $VAS\text{-}F_H$ group had also a higher ratio of patients with HT as well as the HT patients using calcium channel blockers in the treatment of HT as compared to the $VAS\text{-}F_L$ group (Table 1). The differences between the two groups in terms of other demographic data and data related to the dialysis session were not significant (Table 1).

Echocardiographic assessments revealed significantly lower TAPSE values whereas significantly higher PAP values in the $VAS\text{-}F_H$ group than in the $VAS\text{-}F_L$ group ($p = 0.004$ in both cases) (Table 2). The VCI diameter was not found to have differed significantly between the groups, whereas the respiratory variation observed in the VCI was observed less in the $VAS\text{-}F_H$ group ($p = 0.048$) (Table 2).

Correlation analysis revealed that age ($r = 0.331$, $p = 0.001$), E/e′ ratio (r 0.311, p 0.002) and PAP (r 0.281, p 0.006) values were positively correlated with the VAS-F scores, as opposed to the TAPSE (r − 0.257, p 0.012) and e′ (r − 0.303, p 0.003) values, which were found to be negatively correlated with the VAS-F scores (Table 3). Among the parameters of diastolic dysfunction and right ventricular function, the strongest correlation with VAS-F was E/e′ ratio and PAP. Scatter plots of these parameters were obtained with the VAS-F score (Figs. 3, 4).

Age, gender, PAP, TAPSE, E/e′ ratio and HT, which were found to have p values less than 0.05 in one-way logistic regression analysis, were deemed to be correlated with the VAS-F scores, and were further analyzed using the multiple regression analysis (Table 4). From among the variables deemed to be correlated with the VAS-F scores as a result of the one-way logistic regression analysis, only HT (OR

Table 4 Logistic regression analysis results for higher scores for fatigue

	Univariable analysis		Multivariable analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	1.050 (1.014–1.087)	0.006	1.033 (0.992–1.076)	0.117
Male	0.343 (0.147–0.801)	0.013	0.460 (0.166–1.274)	0.135
CAD	2.088 (0.701–6.215)	0.186		
Diabetes mellitus	2.185 (0.783–6.097)	0.136		
Hypertension	4.241 (1.500–11.989)	0.006	4.223 (1.335–13.361)	0.014
Serum albumin	0.870 (0.752–1.007)	0.062		
Serum sodium	0.932 (0.809–1.072)	0.324		
Serum potassium	1.356 (0.816–2.253)	0.240		
Calcium	0.639 (0.373–1.097)	0.104		
GFR	0.954 (0.864–1.054)	0.353		
Hematocrit	1.003 (0.915–1.100)	0.948		
White blood cell count	1.027 (0.854–1.236)	0.774		
Platelet count	1.003 (0.997–1.009)	0.338		
Body mass index	1.028 (0.931–1.134)	0.588		
LVMI	1.009 (0.998–1.020)	0.103		
LVEF	1.087 (0.991–1.191)	0.077		
Right ventricle	1.046 (0.947–1.155)	0.372		
TAPSE	0.812 (0.699–0.943)	0.006	0.862 (0.723–1.029)	0.101
PAP	1.077 (1.021–1.136)	0.007	1.018 (0.953–1.088)	0.593
Pericardial effusion	0.876 (0.320–2.401)	0.797		
Vena cava inferior	0.965 (0.874–1.066)	0.483		
Respiratory variation	0.413 (0.170–1.003)	0.051		
E/e′ ratio	1.191 (1.042–1.360)	0.010	1.085 (0.927–1.269)	0.309
Dialysis vintage	1.004 (0.997–1.010)	0.253		
Session duration	0.509 (0.107–2.415)	0.395		
Fluid withdrawn by hemodialysis	1.000 (1.000–1.000)	0.852		
Weight reduction	1.141 (0.875–1.488)	0.329		
DeltaSBP	1.037 (0.985–1.0	0.167		
DeltaDBP	0.996 (0.953–1.041)	0.858		
URR	1.008 (0.964–1.055)	0.721		
Kt/Vurea	1.214 (0.410–3.589)	0.726		

OR odds ratio, *CI* confidence interval, *CAD* coronary artery disease, *GFR* glomerular filtration rate, *LVMI* left ventricular mass index, *LVEF* left ventricular ejection fraction, *TAPSE* tricuspid annular plane systolic excursion, *PAP* pulmonary artery peak systolic pressure, *E* early diastolic flow velocities, *e′* peak myocardial velocity during early diastole, *DeltaSBP* decrease in systolic blood pressure with hemodialysis, *DeltaDBP* decrease in diastolic blood pressure with hemodialysis, *URR* based on urea reduction ratio

4.223, 95% CI 1.335–13.361) was found to be correlated with the VAS-F scores as a result of the multiple regression analysis (Table 4).

In the correlation analysis, E/e′ ratio and PAP, which are the most significant parameters related to LV and RV function, were further analyzed using ROC curve analysis in terms of their predictive value to predict high VAS-F scores. Consequentially, ROC curve analysis revealed that the E/e′ ratio [Area Under the Curve (AUC) 0.673, 95% CI 0.563–0.782, p 0.004] and PAP (AUC: 0.663, 95% CI 0.554–0.773, p 0.006) were strongly predictive of high VAS-F scores (Fig. 5). E/e′ ratios above 8.8 were found to predict high VAS-F scores with a sensitivity of 76.6% and a specificity of 53.2%, whereas PAP values above 28.9 mmHg were found to predict high VAS-F scores with a sensitivity of 57.4% and specificity of 70.2% (Table 5).

Discussion

The findings of this study indicated that the fatigue observed in HD patients is associated with diastolic dysfunction and right ventricular functions. Additionally, PAP values and E/e′ ratios were found to be correlated with VAS-F scores. To the best of knowledge of the authors of

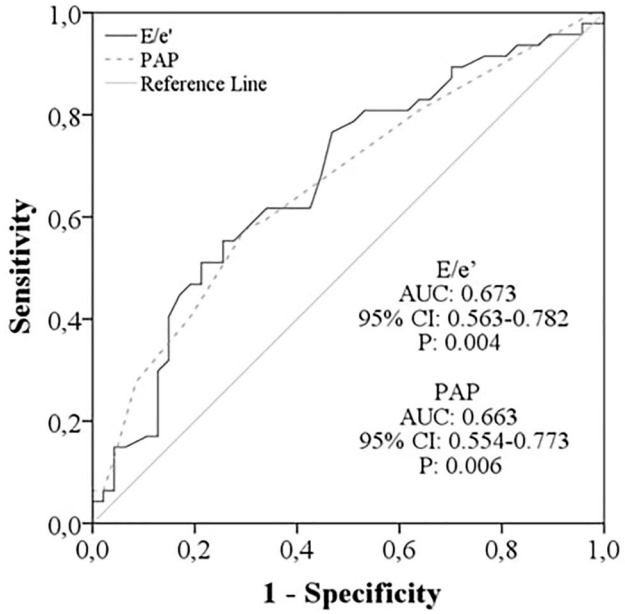

Fig. 5 ROC analyzes of pulmonary artery peak systolic pressure and E/e′ ratio to predict high VAS-F score. *AUC* area under curve, *CI* confidence interval, *E* early diastolic flow velocities, *e′* peak myocardial velocity during early diastole, *E/e′* E/e′ ratio, *PAP* pulmonary artery peak systolic pressure

this study, this is the first study, in which fatigue in HD patients was evaluated using echocardiography.

To date, VAS-F scale was used to assess fatigue in association with many diseases and conditions, including HD [2, 8]. In these studies, many factors such as biochemical and hematological factors, comorbidities and psychosocial condition were found to be associated with fatigue in HD patients [5]. The VAS-F score in this study was similar or even slightly higher than in previous studies [5]. This said difference in results was attributed firstly to the relatively older age of the population of this study, and secondly to the difference between the sociocultural statuses of HD patients in Turkey and developed countries.

Fatigue is an important symptom, even though it is less common in the general population as compared to other medical and psychological diseases such as cancer, depression, and anxiety. Fatigue is becoming increasingly more prevalent in the elderly population in parallel to the decrease in the physical activity and sleep quality. In the study of Christie et al., elderly patients were found to have high VAS-F scores, nevertheless, no statistically significant difference was found between the young and middle age groups in terms of VAS-F scores [24]. As a matter of fact, age has been found to be an important factor in fatigue that occur in relation to concomitant diseases such as chronic inflammatory disease and cancer [5]. Similarly, in this study, the mean age of the VAS-F_H group was higher. On the other hand, when it comes to gender, Ozberk et al. found as a result of their study, in which they assessed fatigue in HD patients using the VAS-F scale, that female patients had higher VAS-F scores prior to HD [25]. The effect of gender on fatigue varies in studies conducted so far [5]. Cultural factors are thought to affect the relationship between fatigue and gender [5]. In our study, VAS-F scores of female patients were found to be higher as compared to male patients.

Calcium channel blockers (CCBs) are commonly used in antihypertensive, antiarrhythmic and antianginal treatments [26]. Fatigue can be observed as a side effect in these treatments. The most commonly used anti-hypertensive agent in our study was CCB. The groups were not found to have differed in terms of other treatment agents and chronic diseases. On the other hand, there were significantly more patients with HT and who have been using CCB in the VAS-F_H group, which might be the reason for increased fatigue in these patients. The variables which were found to be independent risk factors for high VAS-F as a result of the one-way analysis were ruled out as a result of the multiple regression analysis, with the exception of HT. Nevertheless, the fact that HT is commonly present in the HD patients will limit its use as a parameter in the assessment of fatigue.

In contrast to PW-Doppler and TDI parameters, the size of the heart chambers changes in TTE after HD [27]. It has also been shown that diastolic functions can also be altered by HD [28]. In order to minimize these changes, patients were evaluated on a day without HD session. An increase in LVMI and deterioration in diastolic functions are frequently observed in HD patients [29, 30]. The E/e′ ratio is associated with LV filling pressure and diastolic dysfunction [13]. It has been shown that increasing E/e′ ratio is associated with survival in HD patients in addition to increased left atrial pressure [31]. Increased left atrial pressures and diastolic dysfunction may be associated with decreased effort

Table 5 Above the threshold value, the data of pulmonary artery peak systolic pressure and E/e′ ratio predicting high VAS-F score

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
E/e′ratio > 8.8	76.6	53.2	62.1	69.4	64.9
PAP > 28.9 mmHg	57.4	70.2	65.9	62.3	63.8

PPV positive predictive value, *NPV* negative predictive value, *E* early diastolic flow velocities, *e′* peak myocardial velocity during early diastole, *PAP* pulmonary artery peak systolic pressure

capacity and fatigue, similar to diastolic heart failure [12]. Additionally, HT, as is HD, has been reported to be associated with increased LVMI and diastolic dysfunction [32]. Given the effects of volume load, arterial stiffness and erythropoietin on the development of HT, the presence of HT as a comorbidity in HD patients is not surprising [33]. In support of this, 3 out of every 4 people in the study population of this study were found to have HT. Impaired diastolic functions have diagnostic value in HFpEF [10, 11]. Diastolic functions can be both a consequence and a cause of diseases. Nevertheless, the relationship between the diastolic functions and fatigue in HD patients has not been evaluated before until this study. In this study, in accordance with the hypothesis set forth, e′ value, a diastolic function parameter, was found to be lower, whereas the E/e′ ratio, another diastolic function parameter, was found to be higher in the VAS-F_H group.

TAPSE is one of the parameters showing right ventricular function and is measured with M-mode from the lateral tricuspid annulus during systole and diastole. Values less than 17 mm indicate right ventricular dysfunction [34]. The decrease in TAPSE is associated with mortality in those with heart failure and pulmonary hypertension [35]. Up to 45% of patients with HFpEF have right ventricular dysfunction [36]. PAP has an important role in the evaluation of right heart functions in TTE. Left heart pathologies and primary lung diseases account for the majority of the increase in PAP. Increased PAP and right heart failure are associated with mortality [35]. In addition, an increase in PAP and a decrease in e′ velocity in patients with HFpEF have been demonstrated at rest and during exercise by invasive and non-invasive methods [11]. In HFpEF, one of the common symptoms besides dyspnea is fatigue [10]. In hemodialysis patients, deterioration in diastolic functions and right ventricular functions, similar to HFpEF, may be one of the factors leading to fatigue. Our study also supported this information. TAPSE was lower and PAP was higher in patients with high VAS-F score, and there were correlations with VAS-F score. LVMI values were found to be higher as expected in HD patients or in patients with HT, albeit not in association with fatigue [37].

E/e′ ratios above 8.8 and PAP values above 28.9 mmHg were found to be strong predictors of fatigue in HD patients. In addition, a weakly positive correlation was found between the E/e′ ratios and the PAP values. In view of the findings of this study, diastolic heart failure treatment and better control of volume load may be recommended to reduce complaints of fatigue and improve quality of life in HD patients with diastolic dysfunction and impaired right ventricular functions. As this has been the first echocardiographic study to assess fatigue in HD patients, large-scale studies are needed to corroborate the findings of this study.

Apart from its strengths, there were also some limitations to this study. First and the most obvious limitation was that the study was conducted as a single-center study and with a relatively low number of patients. Secondly, echocardiographic parameters were not compared using invasive measurements. In our study, the effects of medical treatment and changes in hemodialysis session on fatigue were not evaluated in patients with diastolic dysfunction.

Conclusion

Based on the findings of this study, it was concluded that the increases in the E/e′ ratios and PAP values were correlated with the VAS-F scores, and therefore were associated with fatigue in HD patients. In addition, HT was found to be an independent risk factor for fatigue in these patients.

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Declarations

Conflict of interest The authors declare that there is no conflict of interest.

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