Kidney & Blood Pressure Research

Kidney Blood Press Res 2017;42:165-176
DOI: 10.1159/000473868
Published online: April 10, 2017
Accepted: February 07, 2017

Original Paper

Heart Failure with Preserved and Reduced Ejection Fraction in Hemodialysis Patients: Prevalence, Disease Prediction and Prognosis

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Key Words
Heart failure • Hemodialysis • Ejection fraction

Abstract
Background/Aims: Heart failure (HF) is a main cause of mortality of hemodialysis (HD) patients. While HF with reduced ejection fraction (HFrEF) is known to only affect a minority of patients, little is known about the prevalence, associations with clinical characteristics and prognosis of HF with preserved ejection fraction (HFpEF). ***Methods:*** We included 105 maintenance HD patients from the Medical University of Vienna into this prospective single-center cohort study and determined the prevalence of HFpEF (per the 2013 criteria of the European Society of Cardiology) and HFrEF (EF <45%), using standardized post-HD transthoracic echocardiography. We also assessed clinical, laboratory and volume status parameters (by bioimpedance spectroscopy). These parameters served to calculate prediction models for both disease entities, while clinical outcomes (frequency of cardiovascular hospitalizations and/or cardiac death) were assessed prospectively over 27±4 months of follow-up. ***Results:*** All but 4 patients (96%) had evidence of diastolic dysfunction. 70% of the entire cohort fulfilled HF criteria (81% HFpEF, 19% HFrEF). Age, female sex, body mass index, blood pressure and dialysis vintage were predictive of HFpEF (sensitivity 86%, specificity 63%; AUC 0.87), while age, female sex, NT pro-BNP, history of coronary artery disease and atrial fibrillation were

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Kidney Blood Press Res 2017;42:165-176
DOI: 10.1159/000473868
Published online: April 10, 2017

predictive of HFrEF (sensitivity 85%, specificity 90%; AUC 0.95). Compared to patients without HF, those with HFpEF and HFrEF had a higher risk of hospitalization for cardiovascular reason and/or cardiac death (adjusted HR 4.31, 95% CI 0.46-40.03; adjusted HR 3.24, 95% CI 1.08-9.75, respectively). ***Conclusion:*** Diastolic dysfunction and HFpEF are highly prevalent in HD patients while HFrEF only affects a minority. Distinct patient-specific characteristics predict diagnosis of either entity with good accuracy.

Introduction

Heart failure (HF) is a leading cause of mortality in chronic kidney disease (CKD) and especially end-stage renal disease patients [1-4]. To date, HF research in CKD patients has largely focused on systolic heart failure with reduced ejection fraction (HFrEF), which is widely generalized as heart failure *per se* and has been described in the context of cardiorenal syndromes [5, 6]. This has led to a neglect of diastolic heart failure, which clinically presents as heart failure with preserved ejection fraction (HFpEF). In non-CKD patients, this disease has been shown to associate with morbidity and mortality equal to HFrEF [7]. It frequently leads to atrial fibrillation, pulmonary hypertension and - ultimately - right heart failure and death [8-13]. Recently, new therapeutic avenues have become available with promising results regarding hemodynamics and renal function [14-16].

In CKD patients, most of the established HFpEF risk factors, such as age, long-standing arterial hypertension, fluid overload, anemia, atrial fibrillation and chronic inflammation are common, with a peak prevalence in maintenance hemodialysis (HD) patients. It must therefore be suspected that HFpEF is highly prevalent in HD patients. Yet, although it has recently been shown that diastolic dysfunction is predictive of cardiovascular events in incident HD patients [17], its true prevalence, associated factors and clinical outcomes are still unknown. In the light of future therapeutic options it is essential that these patients are identified easily, categorized correctly and characterized thoroughly in order to enable optimal care.

In the present study, we aimed at determining the prevalence of HFrEF and HFpEF in a cohort of HD patients, at defining factors predictive for the respective diagnosis and at assessing long-term outcomes.

Materials and Methods

Patients

The eligible study population consisted of 138 maintenance HD patients treated at the Medical University of Vienna. Approval of the local Ethics committee was obtained (EC-No. 1036/2013) and patients were included if they provided written informed consent. Exclusion criteria were defined as dialysis treatment <3 months, prior heart or lung transplantation, inability to provide informed consent, known significant *and* unrepaired coronary artery or valvular disease, congenital heart disease, COPD Gold IV, participation in another clinical study. Each patient was physically examined and questioned for signs and/or symptoms of heart failure including edema of the lower extremities, (exertional) dyspnea graded by the New York Heart Association criteria (NYHA I-IV) and paroxysmal nocturnal dyspnea/orthopnea. Fluid status was determined in an objective manner by bioimpedance measurement (see below). Concomitantly, information on the patients' medical history, smoking status, medication, residual urinary output and dialysis-associated parameters was collected by interview and review of the electronic medical record. History of coronary artery disease was defined as prior revascularization (through angioplasty or coronary artery bypass).

Transthoracic echocardiography

All standardized post-dialysis transthoracic echocardiography studies were performed by board-certified physicians from the echocardiographic laboratory of the Medical University of Vienna using high-end scanners, such as GE Vivid 5 and Vivid 7 (GE Healthcare, Wauwatosa, WI, USA). Left ventricular ejection fraction was measured using the biplanar method of discs (modified Simpson's rule) [18]. Mitral flow Doppler measures (transmitral Doppler early filling velocity [E] and early diastolic mitral annular velocity [e']) were recorded in the apical 4-chamber view; e' was assessed at the septal mitral ring and expressed as the mean. If applicable, an E/A ratio (early/late filling velocity) was calculated. The examining cardiologist was blinded to clinical details of the examined patients besides their age, height and weight. A second, independent senior cardiologist validated all loop recordings.

Definition of HFrEF and HFpEF

The 2013 criteria of the European Society of Cardiology were used to clinically diagnose HFpEF [19]. These included: signs and/or symptoms of heart failure, normal or mildly reduced left ventricular EF on transthoracic echocardiography and evidence of diastolic dysfunction (abnormal left ventricular relaxation, filling or diastolic stiffness).

For further grading purposes, diastolic dysfunction was sub-classified according to the criteria of the American Society of Echocardiography: normal, grade I (abnormal relaxation), grade II (pseudonormal filling pattern) and grade III (restrictive filling) with consideration of an irreversibly restrictive pattern labeled as stage IV [20]. If an EF <45 % was determined, the patient was regarded as having HFrEF.

Biochemical Analyses

Markers of anemia, impaired lipid metabolism, mineral bone disorder and diabetes were determined at the respective dialysis session. Additionally, NT pro-BNP, a biologically inert peptide associated with myocardial wall stretching, was determined (reference range 0–125 pg/mL). As NT pro-BNP is known to decrease through hemodialysis [21], we opted for collection before the dialyiss session concomitantly to fluid status assessment.

Assessment of fluid status

At the time of clinical examination, all patients were at their prescribed dry weight ± 0.5 kg. All study participants underwent pre-dialysis bioimpedance spectroscopy (BIS)-based fluid volume assessment to objectively determine and quantify their current volume status and body composition. For this purpose, the body composition monitor (BCM, Fresenius Medical Care, Germany) was used. Based on a fluid model using body compartment resistance, extracellular volume (ECV), intracellular volume and total body volume were calculated allowing for the determination as well as quantification of fluid overload [22, 23]. Ultrafiltration volume was included in the measurement, and enabled a documentation of pre- and post-dialysis absolute and relative fluid overload (in liters and % ECV, respectively). Further, adipose and lean tissue mass were determined.

Follow-up

Patients continued to receive HD treatment at our center and were seen by a physician three times a week. After a mean of 27±4 months following initial assessment, follow-up was conducted by review of the electronic medical record. The following events were documented: occurrence of hospitalization for cardiovascular reason and/or cardiac death, non-cardiac death and kidney transplantation (KTX).

Statistical analyses

We analyzed 19 variables that were either known as HF risk factors from the literature, or else showing apparent differences from the 'no HF' group in the descriptive analyses (Tables 1-3). Univariate analysis was conducted by examining the distribution of potential predictor variables in i) patients without HF, ii) patients with HFpEF and iii) patients with HFrEF. For categorical predictors we calculated cross-tables and Pearson chi-square tests and for continuous variables we calculated means and standard deviations as well as Analysis of Variance (ANOVA) models. In addition, we categorized continuous predictors in three categories defined by tertiles, to identify the type of association pattern (suppl. Table 1). For all supplemental

material see www.karger.com/doi/10.1159/000473868. If the pattern was approximately linear, we considered the variable a continuous predictor in multivariate analysis. For multivariate analysis, we fitted two different logistic regression models (i) HFpEF vs. no HF and ii) HFrEF vs. no HF) aiming to obtain adjusted ORs for each potential risk factor. We selected covariates for each model by using a stepwise approach beginning with a model including all univariate variables. Due to the small sample size of our study we used as thresholds p=0.1 for forward selection and p=0.15 for backward selection. The final prediction model was validated calculating classification tables showing the number of individuals that were correctly and incorrectly classified by the multivariate prediction rule assuming a 50% probability cut-off to classify an individual as an HF case. Based on the classification tables we calculated sensitivity and specificity and the total prediction accuracy. Furthermore, we calculated receiver-operating characteristic (ROC) curves aimed to visualize the relationship between sensitivity and specificity over the whole range of possible probability cut-offs. The area under the ROC curve and 95% confidence intervals were calculated as a measure of overall discrimination ability.

For outcome analyses, Kaplan-Meier curves and adjusted hazard ratios by Cox regression analysis were calculated (adjusted for age, sex, BMI and HD vintage).

All statistical analyses were conducted using the software packages SPSS System for Mac version 22.0.0 (SPSS, Inc., 2010, Chicago, IL) and STATA (StataCorp. 2013. *Stata Statistical Software: Release 13*. College Station, TX: StataCorp LP).

Results

Patient characteristics

Of 138 assessed patients, 115 were eligible, and 105 were included into the study (Figure 1). Of 100 patients with sufficient echocardigraphic quality, we identified 70 who met HF definition criteria, of which 13 were verified to have EF <45%. 57% of all patients fulfilled the definition criteria of HFpEF. Of these, 10% had a mildly reduced EF between 45 and 50%, the other 90% had an EF above 50%.

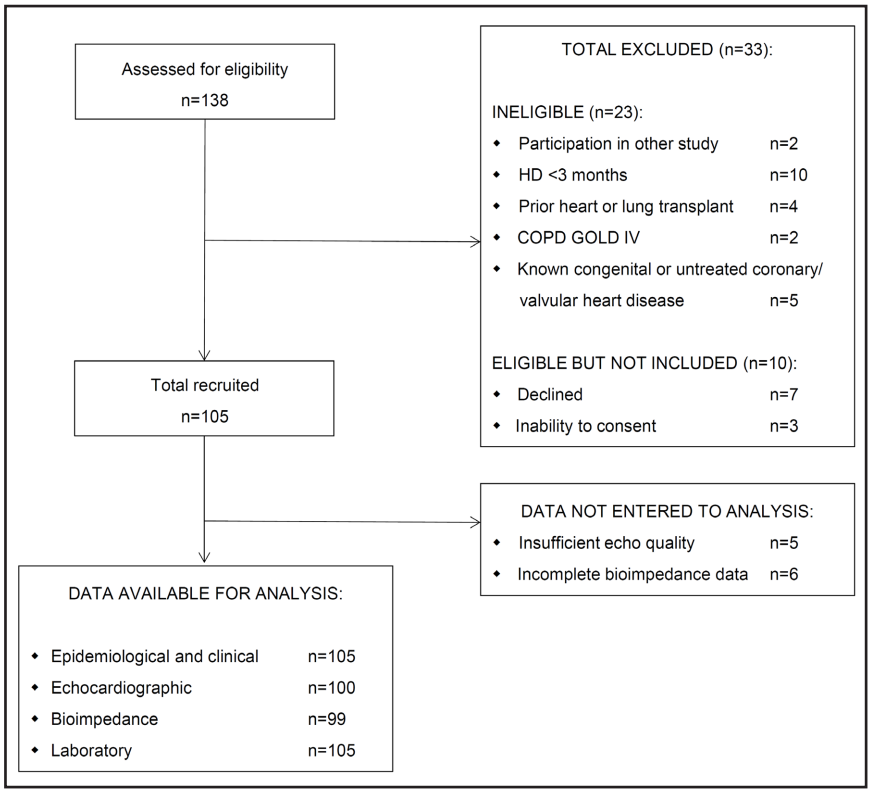


Fig. 1. Patient flow chart.

Overall, the patient groups were homogeneous regarding underlying renal disease and antihypertensive medication (Table 1). We observed a significant difference regarding patient age, which progressed from 45±15 years in patients without HF to 60±16 in those with HFpEF to 66±14 in those with HFrEF. Patients with HFrEF had more vascular comorbidities than HFpEF patients, who still had higher rates than patients without HF.

Table 1. Demographic, clinical and laboratory parameters stratified by clinical status of heart failure. Data presented as mean (SD). P–value of chi-square test (for categorical variables) or F-statistic of ANOVA (for continuous variables)

	No HF (n=30)	HFPEF (n=57)	HFREF (n=13)	P-Value
DEMOGRAPHIC DATA				
Age (yrs)	44.7 (14.5)	59.5 (16.2)	66.0 (14.4)	**<0.001**
Dialysis vintage (yrs)	4.2 (4.2)	4.0 (5.6)	3.1 (2.7)	0.817
BMI (kg/m^2)	24.6 (6.0)	27.1 (5.1)	25.3 (3.9)	0.100
Sex (% male)	77	61	62	0.337
Residual urinary output (%)*	38	44	23	0.388
Smoking (%)	27	19	8	0.353
In employment (%)	30	11	15	0.070
Ethnicity (% Caucasian)	87	93	92	0.610
Renal disease (%)**	10/33/10/3/13/30	14/12/7/4/14/49	31/23/8/15/0/23	0.124
COMORBIDITIES				
Hypertension (%)	77	88	70	0.194
Atrial fibrillation (%)	7	12	16	**<0.001**
CAD (%)	10	30	54	**<0.001**
Diabetes mellitus (%)	13	26	8	0.175
COPD (%)	3	19	15	0.123
MEDICATION				
Beta blocker (%)	47	68	69	0.118
Alpha blocker (%)	27	26	31	0.947
RAS blocker (%)	53	53	54	0.996
Calcium antagonist (%)	53	70	23	**0.006**
Diuretic (%)	30	40	31	0.579
Other antihypertensive (%)	37	14	15	**0.042**
Amiodarone (%)	7	4	8	0.726
Platelet inhibitor (%)	10	49	77	**<0.001**
Oral anticoagulation (%)	7	25	54	**0.003**
Phosphate binder (%)	87	75	77	0.465
Vitamin D (%)	87	84	69	0.351
Immunosuppressive therapy (%)	23	23	31	0.828
ESA (%)	87	88	100	0.393
Iron (%)	87	75	85	0.417
LABORATORY PARAMETERS				
Na (mmol/l)	137 (3)	138 (3)	138 (3)	0.971
K (mmol/l)	5.0 (0.5)	5.0 (0.6)	5.4 (0.6)	0.087
PTH (pg/ml)	539 (508)	436 (341)	531 (537)	0.503
25-OH Vit D (nmol/l)	47 (30)	47 (27)	40 (20)	0.248
1,25-OH Vit D (pg/ml)	20 (12)	18 (10)	17 (10)	0.519
Hemoglobin (g/dl)	10.7 (1.2)	10.3 (1.3)	10.1 (1.4)	0.225
Ferritin (µg/l)	354 (346)	357 (494)	331 (425)	0.981
Transferrin saturation (%)	21.2 (7.8)	20.3 (14.4)	17.2 (6.4)	0.599
Triglycerides (mg/dl)	152 (67)	160 (107)	137 (57)	0.716
Total cholesterol (mg/dl)	166 (34)	163 (42)	158 (55)	0.823
LDL (mg/dl)	86 (27)	92 (34)	93 (45)	0.716
HDL (mg/dl)	49 (22)	40 (14)	37 (9)	**0.027**
HbA_1c (%)	5.2 (1.1)	5.3 (1.1)	4.9 (0.5)	0.599
NT pro-BNP (pg/ml)	2,851 [10,894]	7,027 [17,599]	30,478 [28,308]	**0.012**

BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; RAS, renin-angiotensin-system; ESA, erythropoiesis-stimulating agent; Na, sodium; K, potassium; LDL, low-density lipoprotein; HDL, high-density lipoprotein; BNP, brain natriuretic peptide. *Residual urinary output *≥500 ml/d (%); **(vascular/glomerular/polycystic/tubulo-interstitial/diabetic/other)

NT pro-BNP was markedly higher in HFrEF patients than in those without HF, while no statistical significance was attained between HFpEF and no HF patients. NT pro-BNP correlated well with NYHA stage (r=0.380, p<0.001) and diastolic dysfunction grading (r=0.376, p<0.001).

Bioimpedance spectroscopy measurements did not reveal differences regarding absolute and relative fluid overload among the patient groups. However, it showed significant differences regarding the patients' body composition, with HF patients exhibiting higher

Table 2. Dialysis-associated parameters stratified by clinical status of heart failure. Data presented as mean (SD). P–value of chi-square test (for categorical variables) or F-statistic of ANOVA (for continuous variables)

DIALYSIS-RELATED FACTORS	No HF (n=30)	HFPEF (n=57)	HFREF (n=13)	P-Value
Access (% AVF)	83	77	54	0.109
Prior KTX (% yes)	40	46	39	0.828
Dialysis duration (h)	4.0 (0.4)	4.0 (0.3)	3.9 (0.4)	0.206
Blood flow (ml/min)	296 (25)	282 (43)	270 (32)	0.091
Ultrafiltration (l)	2.0 (1.4)	2.2 (1.2)	2.3 (1.2)	0.778
RRsys Start (mmHg)	137 (21)	143 (23)	132 (23)	0.173
RRsys End (mmHg)	133 (18)	137 (27)	122 (32)	0.143
RRdiast Start (mmHg)	76 (11)	76 (15)	69 (21)	0.352
RR diast End (mmHg)	74 (10)	72 (14)	63 (23)	0.087
BODY COMPOSITION MONITOR DATA				
OH (l)	2.6±2.1	2.4±2.2	2.7±1.2	0.825
OH (% ECW)	11.9 (7.6)	12.3 (10.8)	14.6 (5.4)	0.676
OHpost (l)	0.3 (1.8)	0.2 (2.6)	0.5 (2.1)	0.922
OHpost (% ECW)	1.4 (10.8)	1.1 (13.4)	1.7 (11.7)	0.983
TBW (l)	40.0 (7.3)	38.9 (7.9)	36.4 (5.8)	0.441
ECW (l)	18.2 (3.3)	18.9 (3.4)	18.2 (3.2)	0.605
LTM (kg)	46.4 (11.6)	40.6 (12.6)	36.9 (7.2)	**0.037**
ATM (kg)	22.7 (13.6)	34.2 (15.7)	31.6 (13.9)	**0.008**

AVF, arterio-venous fistula; KTX, kidney transplantation; RR, blood pressure; bpm, beats per minute; OH, overhydration; ECW, extracellular water; OHpost; postdialytic overhydration; TBW, total body water; LTM, lean tissue mass; ATM, adipose tissue mass.

adipose tissue mass and lower lean tissue mass irrespective of their classification (Table 2).

Several echocardiographic parameters distinguished the HFrEF group from that without HF, as these patients had larger left ventricular, left atrial and right atrial diameters, while in HFpEF, the respective values resembled those of no HF patients (Table 3).

Univariate association analysis

In the continuous logistic regression model we identified a strong association between HFpEF and higher age, BMI, adipose tissue mass, left atrial diameter, E/E' medial values and history of coronary artery disease (suppl. Table S2). The tertile model revealed an additional association between lower hemoglobin values, lower lean tissue mass and the hemodialysis vintage and HFpEF (suppl. Table S3).

Higher NT pro-BNP levels were not associated with HFpEF, standing in clear contrast to HFrEF. Additional factors associated with HFrEF in the univariate analysis were higher age, lower lean tissue mass, larger left atrial diameter, higher systolic pulmonary artery pressure, higher E/E' medial values as well as a prior documentation of atrial fibrillation and coronary artery disease (suppl. Tables S4 and S5).

Multivariate heart failure prediction models

On multivariate logistic regression, higher age, female sex, higher BMI, higher systolic blood pressure, dialysis vintage in the middle tertile and presence of coronary artery disease remained predictive for HFpEF diagnosis (overall p=0.002, Table 4). This prediction model was able to classify 78.2% of the patients correctly, leading to a sensitivity of 86.0% and a specificity of 63.3%. The area under the ROC curve was 0.87 (Figure 2A). For the HFrEF model, the parameters higher age, female sex, higher NT pro-BNP, history of coronary artery disease and atrial fibrillation were used for calculating the prediction model (overall p=0.026, Table 5). Here, 88.4% of the assessed patients were correctly classified, leading to a sensitivity of 84.6% and a specificity of 90.0% with an AUROC of 0.95 (Figure 2B).

Clinical outcomes

Sixty-two percent of HFrEF patients experienced hospitalization for cardiovascular reason and/or cardiac death, while only 14% of the HFpEF group and 3% of the no HF group did

Table 3. Echocardiographic parameters stratified by clinical status of heart failure. Data presented as mean (SD). P–value of chi-square test (for categorical variables) or F-statistic of ANOVA (for continuous variables)

	No HF (n=30)	HFPEF (n=57)	HFREF (n=13)	P-Value
TTE PARAMETERS				
LV (mm)	48 (6)	47 (6)	51 (6)	0.181
RV (mm)	30 (5)	32 (6)	37 (8)	**0.006**
LA (mm)	54 (7)	57 (7)	66 (13)	**<0.001**
RA (mm)	54 (7)	56 (7)	65 (14)	**<0.001**
AoAsc (mm)	33 (4)	34 (4)	34 (5)	0.351
IVS (mm)	14 (3)	15 (3)	15 (3)	0.651
AV V_{max} (mmHg)	1.8 (0.7)	2.0 (0.7)	1.9 (1.0)	0.505
AV PPG (mmHg)	14 (12)	18 (14)	17 (18)	0.502
TI V_{max} (mmHg)	2.7 (0.3)	2.8 (0.3)	3.1 (1.0)	0.259
sPAP (mmHg)	38 (10)	39 (8)	56 (13)	**<0.001**
Peak E (m/s)	0.8 (0.3)	1.0 (0.3)	1.3 (0.3)	**0.012**
Peak A (m/s)	0.7 (0.2)	0.9 (0.2)	0.9 (0)	**0.035**
E/A ratio	1.3 (0.4)	1.2 (0.5)	1.4 (0)	0.868
E' medial (m/s)	0.09 (0.03)	0.07 (0.02)	0.06 (0.02)	**0.031**
E/E' ratio	9.4 (3.9)	15.5 (8.0)	23.5 (8.4)	**0.002**
Diastolic dysfunction (%)				**<0.001**
None	13	0	0	
Grade I	67	67	9	
Grade II	20	23	0	
Grade III	0	3	9	
Grade IV	0	7	82	

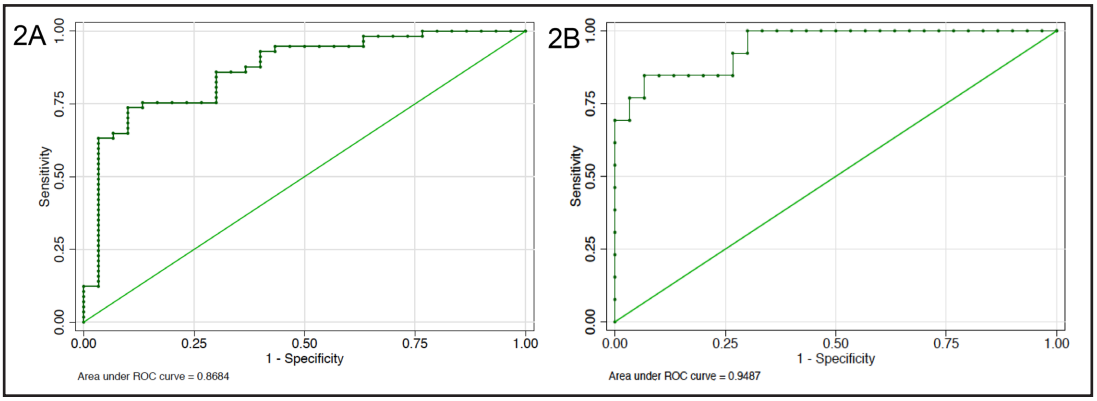
TTE, transthoracic echocardiography; LV, left ventricular diameter; RV, right ventricular diameter; LA, left atrial diameter; RA, right atrial diameter; AoAsc, diameter of the ascending aorta; IVS, interventricular septum; AV, aortic valve; PPG, peak pressure gradient; sPAP, systolic pulmonary artery pressure, E, early medial diastolic mitral velocity; A, late medial mitral velocity; E', early lateral diastolic mitral velocity.

Fig. 2. 2A. Multivariate receiver operating characteristics curve for HFpEF. The factors patient age, sex, body mass index, predialytic systolic blood pressure, dialysis vintage and history of coronary artery disease were entered into the model. AUROC = 0.87. 2B. Multivariate receiver operating characteristics curve for HFrEF. The factors patient age, sex, NT pro-BNP and history of coronary artery disease and atrial fibrillation were entered into the model. AUROC = 0.95.

Table 4. Multivariate prediction model for HFPEF vs. no HF

Variable	P-Value	OR	CI (95%)
Age	**0.020**	1.05	1.01-1.10
Female	0.056	3.96	0.97-16.21
BMI	**0.016**	1.25	1.04-1.49
RRsys Start	**0.024**	1.04	1.00-1.07
HD vintage			
Tertile 1 vs. 2	**0.029**	5.36	1.19-24.15
Tertile 3 vs. 2	0.215	2.35	0.61-9.07
CAD	0.101	4.37	0.75-25.45

BMI, body mass index; HD, hemodialysis; CAD, coronary artery disease.



(Figure 3). The majority of patients without HF (60%) received a kidney transplant during follow-up. Most HFpEF patients remained on HD without cardiac events (57%), while only 18% were kidney transplanted. In all three groups, non-cardiac deaths were comparable.

Kaplan-Meier curve analysis regarding the outcome of hospitalization for cardiovascular reason and/or cardiac death showed a significant difference between all analyzed groups (p (Log rank) <0.001; Figure 4). Multivariable Cox regression analysis (adjusted for age, sex, BMI and HD vintage) showed a higher risk in HFpEF patients compared to those without HF (adjusted HR 4.31; 95% CI 0.46-40.03, p=0.199). As expected, the HFrEF group had a profoundly increased risk of reaching this outcome (adjusted HR 3.24; 95% CI 1.08-9.75, p=0.037).

Table 5. Multivariate prediction model for HFREF vs. no HF

Variable	P-Value	OR	CI (95%)
Age	0.078	1.07	0.99-1.15
Female	0.099	12.93	0.62-271.71
NT pro-BNP	0.050	1.00	1.00-1.00
CAD	0.077	10.74	0.77-148.96
Atrial fibrillation	0.106	11.39	0.60-216.51

BNP, brain natriuretic peptide; CAD; coronary artery disease.

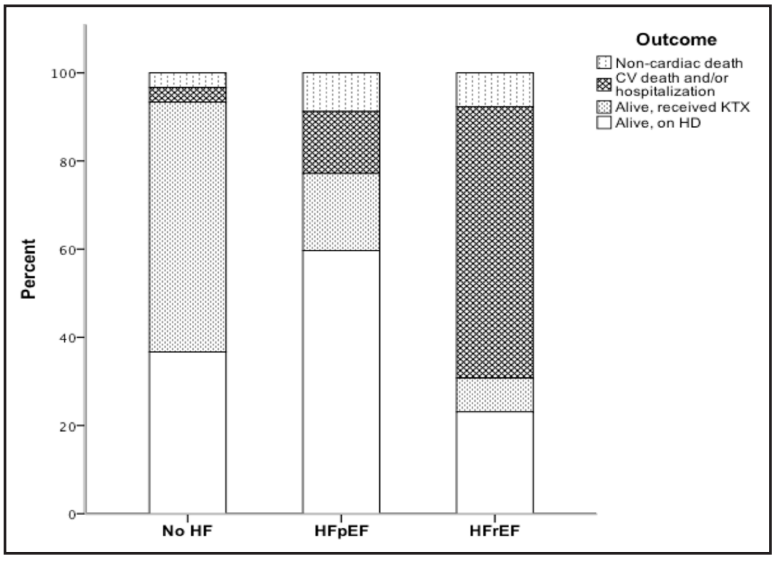


Fig. 3. Clinical outcomes according to heart failure diagnosis in percent. CV, cardiovascular; KTX, kidney transplantation; HD, hemodialysis.

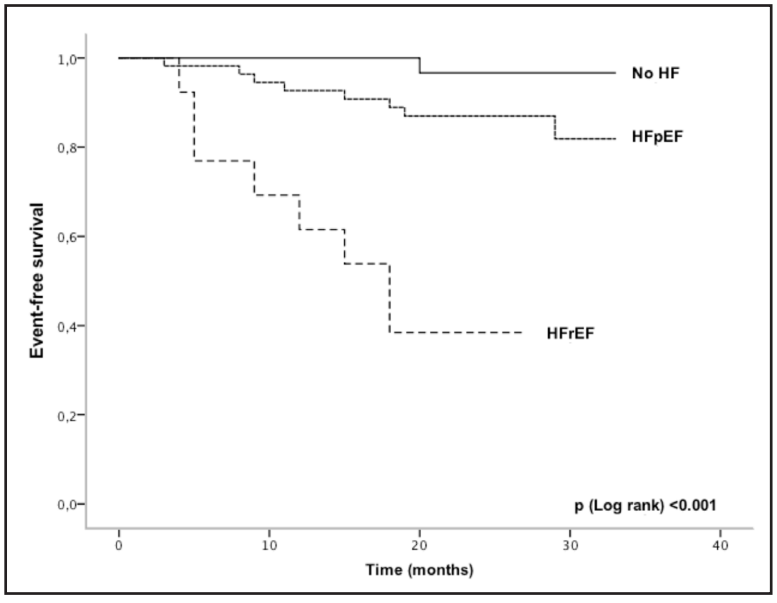


Fig. 4. Kaplan-Meier estimates of survival without hospitalization for cardiovascular reason and/or cardiac death. HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

Discussion

In the present study, more than 50% of all maintenance HD patients fulfilled the diagnostic criteria for HFpEF, while only 13% of patients were affected by HFrEF. Diastolic dysfunction was found to be an extremely prevalent pathology in HD patients, even in those who did not clinically suffer from heart failure symptoms. As diastolic dysfunction has been proven to be predictive for cardiovascular

events [17], our finding should foster careful cardiac follow-up of these patients. Similarly to HFpEF in patients without renal disease, higher age, female sex and higher BMI as well as higher blood pressure were good predictors of HFpEF diagnosis. Contrarily, several distinct comorbidities such as diabetes or left ventricular hypertrophy that are known to be associated with HFpEF in non-CKD patients were not associated with HFpEF in the present study on HD patients.

A critical factor regularly associated with HF is fluid overload [24]. The use of diuretics resulting in a reduction of fluid overload is usually intended to alleviate symptoms [25]. Recently, Koell et al. were able to detect in a large HFpEF cohort that fluid overload is indeed associated with a higher rate of hospitalization for cardiovascular reasons and/or death [26]. Importantly, a critical finding was that a well-controlled fluid status results in better outcomes irrespective of renal function. It should thus be regarded as highly important to correctly define a patient's dry weight and aim at maintaining it. In our cohort, there was no statistical significance between the three analyzed groups regarding fluid overload, yet with slightly higher values in HFrEF patients, which might reflect awareness of the HD staff concerning the maintenance of fluid status.

However, important differences in our patients' body composition were noted: while lean tissue mass reflecting muscle mass was lower in HFpEF and even more in HFrEF patients, adipose tissue mass was highest in the HFpEF group. This finding enables a more detailed understanding of these patient groups than body mass index analysis alone, and characterizes HFpEF patients as typically overweight and untrained.

Previously, Wang et al. found in a large cohort of peritoneal dialysis patients a comparably high rate of patients with heart failure, yet a significantly higher rate of HFrEF patients [27]. Similarly, we also found that HF patients tend to be older and exhibit a higher frequency of background cardiovascular morbidity as well as strongly differing NT pro-BNP values. As peritoneal dialysis is generally associated with lower hemodynamic strain during the treatment compared to HD and, most importantly, as HD is by far the more common treatment strategy for end-stage renal disease patients globally, we believe our data contribute much-needed information concerning HF in end-stage renal disease.

Opposing HFpEF-associated factors, HFrEF proved to be linked with different parameters: especially a history of cardiovascular morbidity (coronary artery disease and atrial fibrillation) should draw the clinician's attention towards a potential presence of systolic heart failure. Additionally, strongly elevated NT pro-BNP levels were not associated with HFpEF, but only with HFrEF diagnosis. This result stands in contrast with an analysis by Kamano et al., who used NT pro-BNP levels as a predictive marker for diastolic dysfunction and HFpEF in HD [28]. According to our results, NT pro-BNP should only be applied for the exclusion of HFrEF, but cannot help in distinguishing HFpEF patients from those without HF. The interpretation of NT pro-BNP in HD patients thus remains a complex issue not only due to its renal elimination but also due to a described increase in states of fluid overload [29]. Yet, it has previously been shown to be associated with higher mortality in HD patients [30] and has recently been successfully been implemented in the diagnostic process of HFrEF together with a lipid panel analysis and might therefore remain a practical tool for HF diagnosis in HD patients [31].

Importantly, factors associated with the respective diagnosis were different between HFpEF and HFrEF patients. This finding complies with the emerging hypothesis that HFpEF and HFrEF are two distinct disease entities and HFpEF is not a precursor state of HFrEF [32, 33]. Accordingly, the multivariate prediction models for the two diseases contained different parameters. Nonetheless, both models showed satisfactory sensitivity/specificity as well as overall prediction accuracy at 78% and 88%, respectively. However, these models should be applied with caution until further validation of the results in larger maintenance HD patient cohorts in order to establish a robust heart failure risk score in this unique population becomes available [34]. Such a prediction model might have considerable implications in rapid patient assessment before further cost and labor-intensive cardiac studies, such as right heart catheter examination, would have to be applied.

With regard to the cohort's clinical outcomes, patients with HFrEF exhibited an extremely elevated risk of experiencing hospitalization for cardiovascular reason and/or cardiac death compared to patients without HF. This finding is comparable to results from Derthoo et al., who analyzed a cohort of HD patients with HFrEF versus normal EF, where it was not further specified whether these patients qualified as having HFpEF [35]. Similarly, only about 50% of HFrEF patients were alive after 24 months. These patients will need to be followed very closely for signs of cardiac decompensation.

While HFpEF patients also exhibited an increased risk of reaching this clinical outcome, this finding did not formally meet statistical significance. Yet, it is very striking that while many patients without HF received a kidney transplant during the follow-up period of 27 months, most HFpEF patients simply remained on HD without experiencing cardiovascular complications necessitating hospitalization. It can now be speculated that – maybe due to their higher age and BMI or even due to their sex – they were either not evaluated or not listed for transplantation. It will be important to prospectively follow both patients without HF as well as those with HFpEF after transplantation with regard to clinical and organ outcome in order to make an informed decision as to whether HFpEF patients should or might even need to be pro-actively evaluated for transplantation.

Some limitations need to be discussed: as it appears likely that some patients who are initiated on maintenance HD already have diastolic dysfunction and HFpEF, it is not possible to assess the developmental processes that might occur during earlier CKD stages in our cohort. Further, our study's sample size necessitates additional validation. The multivariate models were primarily fitted to estimate the multivariate adjusted association measures for each factor. Thus, we did not calculate any resampling validation statistics such as split-sample validation or bootstrapping. Additionally, we did not perform invasive hemodynamic testing in our cohort, which might have led to an underdiagnosis of the disease. Due to the current unavailability of therapeutic options for HFpEF, the associated risks were felt to outweigh the benefits. However, the comprehensive description of the cohort leading to a prediction model for both types of HF can be regarded as a distinctive strength of this analysis.

Conclusion

In summary, diastolic dysfunction and HFpEF are highly prevalent in maintenance HD patients compared to HFrEF. As therapeutic options are currently becoming available for these patients, early, quick and correct identification is important. Distinct patient-specific characteristics described in our study enable diagnosis prediction of either entity with good accuracy. Prospective studies are now required to validate these results, determine the disease course and define its impact on overall patient morbidity and mortality and – ideally – its reversibility with medical treatment and/or kidney transplantation.

Disclosure Statement

The Austrian Science Fund (FWF) supported this study (KLI 246). All authors have reported that they have no relationship relevant to the contents of this paper to disclose.

Acknowledgments

The authors thank the nursing staff of the hemodialysis units for their support with bioimpedance measurements and data collection.

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