Prevalence and Risk Factors of Heart Failure with Preserved Ejection Fraction in Middle-Aged Maintenance Haemodialysis Patients on a Twice-Weekly Schedule: Experience from a Single Indian Centre

Editoriale

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ABSTRACT

Background. Data on the prevalence of cardiac failure with preserved ejection in the haemodialysis population, which impacts treatment strategy, mortality, and morbidity, are scarce.

Aims and Objectives.

- Estimate the prevalence of heart failure with preserved ejection fraction (HFpEF) in haemodialysis patients
- Classify cardiac failure and ascertain the risk factors influencing HFpEF in haemodialysis patients.

Methods. All consenting individuals on haemodialysis over 18 years of age were included. Lung ultrasound was performed as per the LUST study protocol, and the labs were documented. Echocardiographic parameters were measured using two-dimensional (2D ECHO).

Results. A total of 102 patients consented to participate in the study, which included 63 males (61.8%) and 39 females (38.2%). The mean patient age was 53 ± 13.1 years. The dialysis vintage of the participants was 38.92 ± 6.947 months. 47 (46.1%) patients had diabetes and 88 (80.4%) had hypertension. ECG findings included sinus rhythm (51/102, 50%), sinus tachycardia (22/102, 21.6%), ST-T wave abnormalities (18/102, 17.6%), and atrial fibrillation (11/102, 10.8%). Heart failure with preserved ejection fraction (HFpEF) was present in 44/102 (43.14%), heart failure with mid-range EF in 14/102 (13.72%), and heart failure with reduced EF in 13/102 (12.7%) patients. The ejection fraction was positively associated with haemoglobin ($r = 0.23$; $p = 0.044$), and calcium levels ($r = 0.25$; $p = 0.03$). E/lateral e' ratio was positively correlated with NT pro-BNP ($r = 0.63$; $p < 0.001$), systolic blood pressure ($r = 0.44$; $p = 0.003$) and age ($r = 0.353$; $p = 0.003$) and negatively correlated with transferrin saturation ($r = -0.353$; $p = 0.027$) and diastolic blood pressure ($r = -0.31$; $p = 0.040$). Binary logistic regression analysis revealed that the odds of diastolic dysfunction increased by 2.3 times with each unit increase of creatinine, and diabetics have 7.66 times higher risk for diastolic dysfunction. Binary logistic regression involving ejection fraction (EF) and all laboratory and clinical parameters revealed odds of HFpEF increased by 1.93 times with each unit increase in age, odds of HFpEF increases by 1.53 times with each unit increase in phosphorous and odds of HFpEF increased by 1.1 times with a unit increase of systolic blood pressure.

Conclusion. HFpEF is the predominant form of heart failure in haemodialysis patients. Haemoglobin and calcium were positively associated with ejection fraction. Advancing age, elevated creatinine and diabetes mellitus levels are independent predictors of diastolic dysfunction in haemodialysis patients.

KEYWORDS: HFpEF, E/ Lateral e, E/A ratio, 2D ECHO, hemodialysis, cardiac failure

Introduction and Background

Cardiac failure is a predominant cardiovascular complication in the chronic kidney disease (CKD) population and it increases in prevalence with advancing renal failure [1]. The presence of cardiac failure in the dialysis population is predictive of short and long-term mortality in haemodialysis [2, 3]. The most prominent cause of mortality among haemodialysis patients is cardiovascular disease, which accounts for nearly 44% of the overall mortality [4].

Heart failure is classified into three major types: heart failure with reduced ejection fraction (HFrEF), mid-range ejection fraction (HFmrEF), and preserved ejection fraction (HFpEF). HFpEF is a clinical syndrome characterized by symptoms and signs of cardiac failure, presence of diastolic dysfunction (DD), and near-normal or normal left ventricular (LV) systolic function (EF≥50%) [5]. Diastolic dysfunction can manifest as impaired left ventricle relaxation or increased filling pressure.

The prevalence of HFpEF in the maintenance haemodialysis population is unclear. Echocardiography (2D ECHO) is of great utility in guiding and monitoring therapy in dialysis patients with cardiac dysfunction [6]. Hence, this study was designed to estimate the prevalence of heart failure with preserved ejection fraction and its clinical implications in patients undergoing haemodialysis.

Aims and Objectives

- Estimate the prevalence of cardiac failure with preserved ejection fraction (HFpEF) in haemodialysis study group
- Classify cardiac failure and ascertain the risk factors influencing cardiac failure with preserved ejection fraction (HFpEF) in haemodialysis patients.

Patients and Methods

Study Design

All consenting haemodialysis patients aged > 18 years with a minimum dialysis vintage of 3 months, urea reduction ratio (URR) greater than 65%, functioning arteriovenous fistula, and no evidence of overt fluid overload as assessed by lung comets on ultrasound were included.

Exclusion criteria included unwillingness of the patient, lung comets >15 on thoracic ultrasonography, consolidation or fibrosis on chest radiography (CXR), recent HD initiation (<3 months), interstitial lung disease (ILD), new-onset acute coronary syndrome (within 4 weeks), hemodynamic instability, prior heart or lung transplantation, significant valvular disease, and structural cardiac disease. The study was approved by institutional ethics committee (Ethics clearance number: 3093/IEC/2021).

The study volunteers underwent pre-dialysis blood investigations, which included serum creatinine, urea, pre-dialysis blood urea levels, haemoglobin, and transferrin saturation. Only patients with a URR consistently greater than 65% for three consecutive months were included. The average interdialytic weight gain of the preceding one month inclusive of the last dialysis session, was recorded. Pre- and post-dialysis urea levels were estimated in the last dialysis session prior to echocardiography to calculate URR. The dialysis was a standard bicarbonate-based haemodialysis with blood flow of 200 ml/min, dialysate flow of 500 ml/min and ultrafiltration volume was set as clinically indicated and focused on the attaining dry weight of the patients. The average pre-dialysis calcium and phosphorous levels in the last three months were used for the study analysis. N-terminal pro hormone Brain Natriuretic peptide (NT pro BNP) levels were measured prior to

echocardiography. NT-pro BNP values greater than 7200 pg/ml were considered significant to substantiate the presence of heart failure in the dialysis population [7]. Baseline ECG was obtained for all participants. Left Ventricular hypertrophy (LVH) on electrocardiogram (ECG) was defined based on the Sokolov Lyon criteria. Clinical details with comorbidities were noted with measurements of height, weight, and body mass index (BMI) of the study participants.

Lung comets were assessed in real-time B mode using Siemens Acuson X 300TM (Netherlands) ultrasound with a 6C2 curved transducer probe. Ultrasonography of the anterolateral chest was performed by an assistant professor in nephrology. The 2nd to 4th intercostal spaces in the left hemithorax and the 2nd to 5th intercostal spaces in the right hemithorax at the anterior axillary, parasternal, mid-axillary, and mid-clavicular lines were scanned individually using ultrasound. B-lines were counted from 0 to 10, with 0 indicating the absence of B-lines and a complete white screen corresponding to 10 B-lines. Patients with ultrasound B-lines >15 were excluded from the study because they indicated moderate extravascular lung water accumulation according to the methodology employed in the LUST study [8].

Echocardiography was performed using a Philips EPIQ 7TM ultrasound machine for cardiology (U.S.A) in M-mode by a single assistant professor in cardiology. Echocardiography was performed when the patient was considered to be at or near “dry weight” based on clinical parameters and lung ultrasound findings. Ultrasound and 2D ECHO were performed one day after dialysis on a non-dialysis day, preferably midweek. The parameters measured in 2D ECHO included Left Ventricular Internal diameter at End Systole (LVIDs) expressed in millimetres (mm), Left Ventricular Internal diameter at End diastole (LVIDd) in mm, Left Atrial Diameter (LAD) in mm, Left Ventricular posterior wall Thickness in end diastole (LVPWd) in mm, Ejection Fraction (EF) expressed as percentage (%) and Fractional Shortening (FS) expressed as percentage (Figure 1).

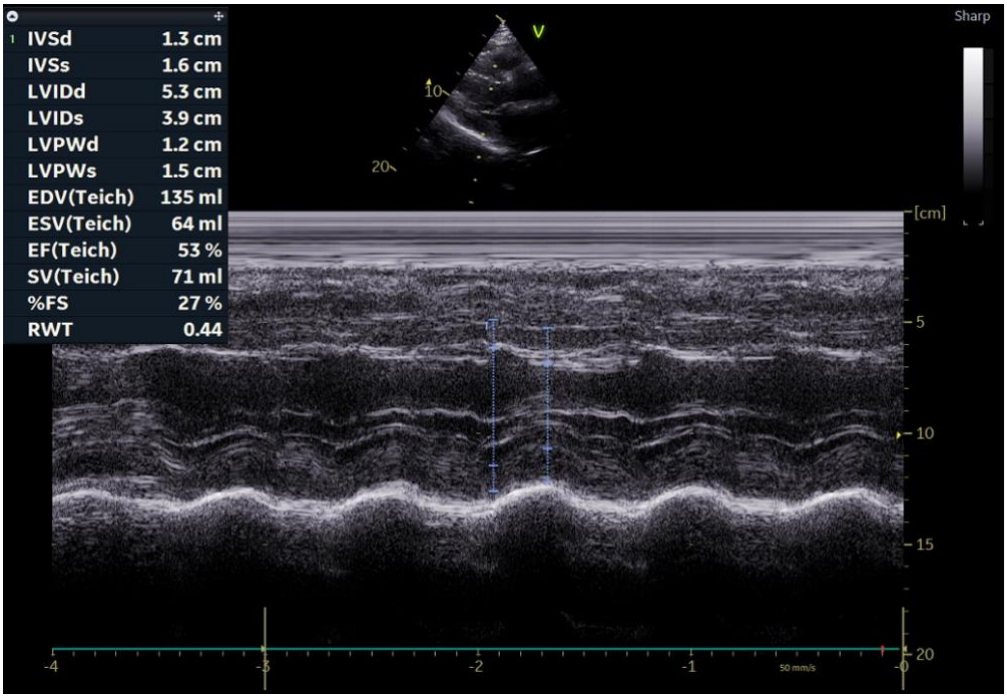

Figure 1. LVIDd, LVIDs, EF (%), LAD, LVPWd, FS (%) measurement during echocardiography (2170 × 1748 cm: 600 dpi).

The mitral peak E/A ratio describes the mitral inflow velocity, depicting the ratio of early versus late ventricular filling, computed with the Valsalva manoeuvre during 2D ECHO. Reversal of the E/A ratio to < 1 with a 50% reduction in E velocity is indicative of impaired ventricular relaxation [9] (Figure 2).

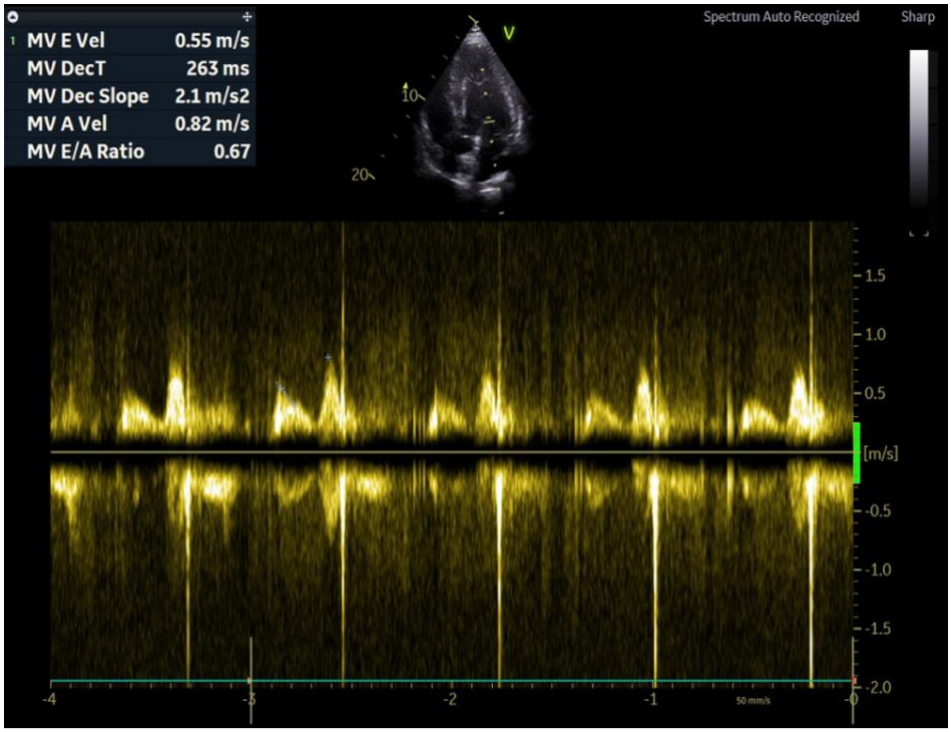

Figure 2. E/A measurement with Valsalva manoeuvre during 2D ECHO study (2455 × 1748 cm: 600 dpi).

Heart failure was defined as symptoms such as orthopnoea, dyspnoea on exertion, clinical signs of basilar rales with raised Jugular Venous Pressure (JVP), and associated echocardiographic parameters suggestive of diastolic dysfunction [7]. It is further classified as HFpEF (≥50%), HFmrEF (40%-49%) and HFrEF (<40 %) [10]. Cardiac Failure with significant diastolic dysfunction was defined as one having symptoms and clinical signs of cardiac failure with echocardiographic findings of elevated E/lateral e' values greater than 12 [11, 12]. E/lateral e', which denotes the left ventricular filling pressure, was computed using tissue Doppler (Figure 3).

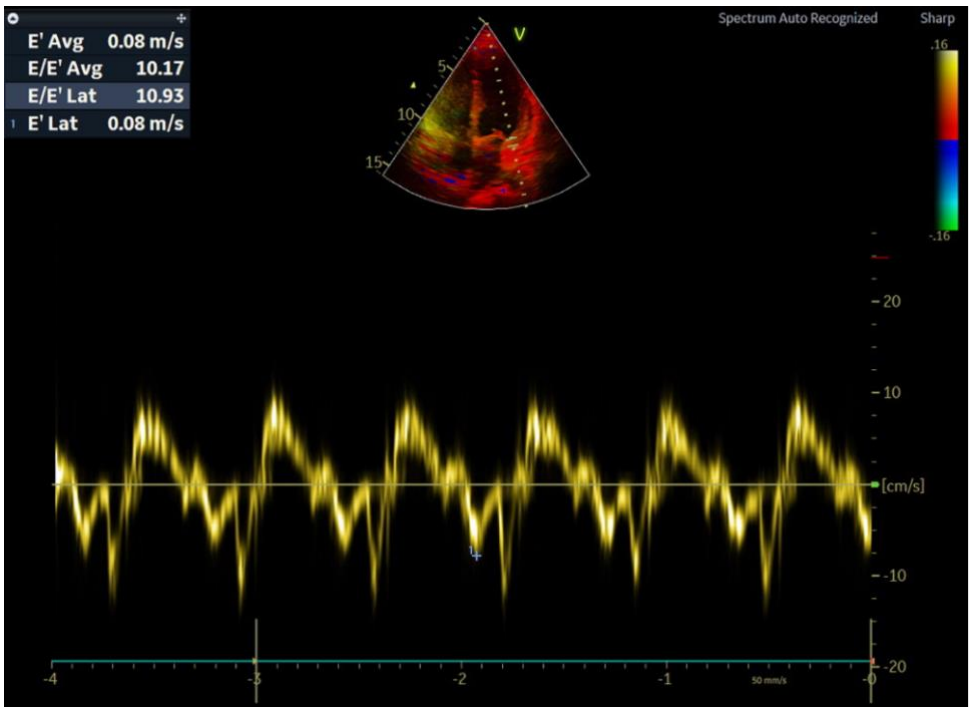

Figure 3. E/lateral e' reading using pulsed wave tissue doppler in 2D ECHO (2386 × 1769 cm: 600 dpi).

The e' velocity was calculated in the 4-chamber apical view using pulsed-wave (PW) tissue Doppler at end expiration using the optimal sweep speed. The lateral part of the mitral annulus was utilized in this study to compute the mean e' velocity. E/lateral e' value greater than 12 was indicative of definite diastolic dysfunction as per the algorithm proposed by Mitter et al. [12].

Patients with sinus tachycardia had an additional average of five E/e readings, and values greater than 14 were considered significant. To mitigate the impact of atrial fibrillation (AF) on E/e' ratio, additional readings of the septal E/e' ratio and ratio of left ventricular peak E wave velocity to flow propagation velocity (E/Vp) were performed. Septal E/e' >11 and E/Vp ratio > 1.4 were considered significant and were used as additional surrogate echocardiographic parameters for confirming significant diastolic dysfunction in haemodialysis patients [13].

Statistical Analysis

The data were evaluated using IBM SPSS Statistics for Windows, Version 28.0. (Armonk, NY: IBM Corp). All the continuous variables were tested for normal distribution using the Kolmogorov-Smirnov test. The median and interquartile range were used for continuous variables. Frequency, descriptive statistics, and percentage analyses were used for categorical variables. Pearson's correlation coefficient denoted by "r" was used to test the association between the variables. Statistical significance was set at $p \leq 0.05$. Differences in Lab and clinical parameters between the groups were assessed using the Kruskal-Wallis test. A binary logistic regression was performed with lateral E/e', and all laboratory and clinical parameters for evaluation of diastolic function and p value < 0.05 was considered significant. Binary logistic regression was performed with ejection fraction (EF), and all laboratory and clinical parameters for evaluation of systolic function and p value < 0.05 was considered significant.

Results

Clinical and Laboratory Parameters

This study included 102 patients (63 males (61.8 %) and 39 females (38.2 %)). The average age of the volunteers was 53 ± 13.1 years. All patients had functioning arteriovenous fistulas. 97 patients underwent haemodialysis twice a week and 5 patients underwent haemodialysis three times a week. Interdialytic weight gain was 4.05 + 1.04 kg.

URR of the study population calculated prior to 2D ECHO was 69.21 ± 2.76 %. The average dialysis vintage of the participants was 38.92 ± 6.947 months. 47 (46.1%) patients had diabetes and 88 (80.4%) had hypertension. 94 patients were on calcium channel blockers, 72 patients were on beta-blockers, 55 patients were on centrally acting sympatholytics, and 24 patients were on angiotensin receptor blockers. Coronary artery disease was documented using coronary angiography in 18 patients (17.6 %). Smokers were 4 (3.9%) in the study population. The average height of the patients was 157 ± 6.2 cm, and their weight was 58.2 ± 8.7 kg. The BMI of the study volunteers was 23.37 ± 2.82 kg/m^2. The median and interquartile range (IQR) for all variables were reported to ensure robustness against outliers and to facilitate consistent comparisons across all laboratory parameters listed in Table 1.

A subdivision of HFpEF (≥50%), HFmrEF(40%-49%) and HFrEF (<40 %) along with the lab parameters in each subgroup is enlisted in Table 2. Haemoglobin, Phosphorous, NT pro BNP, age and systolic blood pressure were significant variables among the different subdivisions of heart failure as outlined in Table 2.

Parameter	Median (IQR)
Creatinine	7.8 (7.4-8.4)
Albumin	3.4 (3.0-3.6)
Calcium	8.6 (8.1-8.9)
Phosphorous	5.5 (4.7-6.6)
Hemoglobin	8.7 (8.2-9.2)
Transferrin saturation	34 (26-39)
NT pro BNP*	8580 (6312-10187)
Pre Blood urea nitrogen	122 (108-134)
Post Blood urea nitrogen	38 (34-42)
Systolic Blood Pressure	144 (136-154)
Diastolic Blood Pressure	80 (76-88)

Table 1. Laboratory and clinical parameters of the research patients (n = 102).
*** N-Terminal pro hormone Brain Natriuretic peptide. IQR: Q1-Q3.**

Parameter	HFrEF (n=13)	HFmrEF(n=14)	HFpEF (n=44)	p value
Creatinine (mg/dl)	7.4 (6.9-7.6)**	7.5 (6.8-8)	7.9 (7.6-8.4)	0.016
Albumin (g/dl)	3.2 (2.8-3.6)	3.2 (3-3.5)	3.4 (3.2-3.6)	0.335
Calcium (mg/dl)	8.6 (8-8.7)	8.1 (7.9-8.8)	8.6 (8.4-9)	0.026
Phosphorous (mg/dl)(PO4)	6.7 (6.2-7)	5.75 (5.15-7.25)	5.2 (4.6-6)	0.007
Hemoglobin (g/dl)	8.3 (7.9-9)	8.2 (7.95-8.5)	8.9 (8.4-9.3)	0.002
Transferrin saturation (%)	26 (22-42)	26 (23-34)	36 (26-40)	0.037
NT pro BNP*(picograms/ml)	10340 (8420-10850)	9760 (8365-12265)	7900 (5680-9300)	0.003
Age (years)	61.5 (50.5-69.5)	61.5 (51.5-68)	50 (44-61)	0.007
Systolic BP (mm Hg)	134 (126-136)	144 (134-152)	146 (138-154)	0.011
Diastolic BP (mm Hg)	82 (76-84)	84 (76-91)	80 (76-88)	0.634

Table 2. Laboratory and clinical parameters of HFrEF (<40 %), HFmrEF (40%-49%) and HFpEF (≥50%).
*** N-Terminal pro hormone Brain Natriuretic peptide**
****IQR is mentioned in parentheses**

Cardiac and Echocardiographic Parameters

ECG findings included normal sinus rhythm (51/102, 50%), sinus tachycardia (22/102, 21.6%), ST-T abnormalities (18/102, 17.6%), and atrial fibrillation (11/102, 10.8%). LVH was present in the ECG of 88 (80.4 %) patients. RWMA was found in 18 patients (17.6 %) using 2D ECHO. E/A ratio less than 1 with a reduction in E velocity < 50% was present in 77 patients (75.4%). Heart failure was detected in 71 of 102 patients (69.6%) according to the clinical criteria employed in the study ratio and LAD among the different subdivisions of heart failure which in outlined in Table 4.

Parameters	Median (IQR)
LVIDd (mm)[a]	47.8 (45.9-48.9)
LVIDs (mm)[b]	30.8 (29.8-31.9)
Ejection Fraction (EF %)	58 (48-60)
LVPWd (mm)[c]	11.8 (11.4-12)
E/A ratio [d]	0.98 (0.95-1)
LAD (mm)[e]	28.5 (27.9-29.4)
Fractional Shortening (FS%)	34.74 (33-37.42)
E/Lateral e′ ratio [f]	14 (11-14)

Table 3. 2D echo variables of hemodialysis patients (n = 102). a: Left Ventricular Internal diameter at End diastole; b: Left Ventricular Internal diameter at End Systole; c: Left Ventricular posterior wall Thickness in end-diastole; d: Trans-mitral inflow velocity ratio; e: Left Atrial diameter; f: Lateral aspect of the mitral annulus derived tissue Doppler ratio

Parameters	HFrEF	HFmrEF	HFpEF	P value
LVIDd (mm)[a]	48.4 (47.8-49.1)	47.2 (44.1- 49.15)	47.8 (46.3- 48.9)	0.351
LVIDs (mm)[b]	31.2 (30.4-31.8)	30.3 (29.35-31.45)	31.3 (29.6-32.3)	0.337
Ejection Fraction	30 (30-35)	45 (43-48)	58 (56-60)	<0.001
LVPWd (mm)[c]	12.1 (11.7-12.3)	11.8 (11.25-12.15)	11.7 (11.4-11.9)	0.193
E/A ratio [d]	0.947 (0.936-0.968)	0.938 (0.908-0.996)	0.985 (0.97-1)	<0.001
LAD (mm)[e]	28.8 (28.6-29.4)	29.5 (28.5-30.1)	28.3 (27.8-29.1)	0.011
Fractional Shortening (%)	34.29 (33.48-35.56)	35.81 (33.12-37.97)	34.67 (33-36.8)	0.616
E/Lateral e' ratio [f]	14 (14-15)	15 (13-16)	14 (11-14)	0.004

Table 4. Echo variables in HFrEF (<40 %), HFmrEF (40%-49%), and HFpEF (≥50%) (Median (IQR)). a: Left Ventricular Internal diameter at End diastole; b: Left Ventricular Internal diameter at End Systole; c: Left Ventricular posterior wall Thickness in end-diastole; d: Trans-mitral inflow velocity ratio; e: Left Atrial diameter; f: Lateral aspect of the mitral annulus derived tissue Doppler ratio

Correlation of Echocardiographic Parameters with Clinical and Laboratory Parameters

The E/A ratio had a weak positive correlation with haemoglobin (r = 0.27; p = 0.018) and serum calcium (r = 0.33; p = 0.004) and transferrin (r = 0.24; p = 0.040). The ejection fraction had a weak positive association with haemoglobin (r = 0.23; p = 0.044), and serum calcium (r = 0.25; p = 0.03). Serum phosphorus had a weak inverse correlation with ejection fraction (r = -0.38; p< 0.001). LAD had a weak positive correlation with systolic blood pressure (r = 0.31; p = 0.007) and diastolic blood pressure (r = -0.28; p = 0.016) and inverse correlation with calcium (r = -0.39; p < 0.001). Other correlations are listed in Table 5.

	LVEDV (mm)[1]	LVESV (mm)[2]	EF[3]	LVPWd [4]	E/A[5]	LAD (mm)[6]	FS (%)[7]
Creatinine	0.14 (0.251)	0.08 (0.489)	0.149 (0.214)	0.19 (0.102)	0.15 (0.192)	0.09 (0.435)	-0.024 (0.841)
Albumin	-0.03 (0.78)	-0.11 (0.359)	0.16 (0.174)	-0.050 (0.676)	0.07 (0.529)	-0.05 (0.65)	0.10 (0.365)
Calcium	0.24 (0.039*)	0.05 (0.672)	0.25 (0.03*)	-0.17 (0.148)	0.33 (0.004*)	0.39 (<0.001)*	-0.15 (0.186)
Po4	0.07 (0.55)	0.067 (0.604)	-0.38 (<0.001*)	0.26 (0.022)*	-0.12 (0.293)	0.17 (0.140)	-0.019 (0.871)
Hemoglobin	0.20 (0.09)	0.13 (0.2705)	0.23 (0.044*)	-0.22 (0.06*)	0.27 (0.018)	-0.01 (0.871)	0.022 (0.849)
Transferrin	0.22 (0.055)	0.24 (0.036*)	0.17 (0.153)	-0.08 (0.497)	0.24 (0.040*)	0.18 (0.113)	-0.13 (0.25)
Systolic	0.08 (0.49)	0.19 (0.110)	0.20 (0.081)	0.19 (0.102)	-0.04 (0.718)	0.31 (0.007*)	-0.16 (0.181)
Diastolic	-0.07 (0.55)	0.05 (0.638)	-0.01 (0.91)	0.03 (0.781)	-0.22 (0.064)	0.28 (0.016*)	-0.15 (0.189)

Table 5. Correlation of echocardiographic parameters with laboratory markers in heart failure patients (N = 71). *; Statistical significance. At 95% CI. p-value is provided in the parenthesis ()
1: Left Ventricular Internal diameter at End diastole; 2: Left Ventricular Internal diameter at End Systole; 3: Ejection Fraction; 4: Left Ventricular posterior wall Thickness in end diastole; 5: Trans mitral Inflow velocity ratio; 6: Left Atrial Diameter; 7: Fractional Shortening.

Correlation of E/lateral e' with Clinical and Laboratory Parameters

The E/lateral e' ratio had a strong positive correlation with NT pro-BNP levels (r = 0.63; p < 0.001). There was a weak inverse correlation with transferrin saturation (r = -0.33; p = 0.027). E/lateral e' had a weak positive correlation with age (r = 0.353; p = 0.003). There was no correlation between the choice of antihypertensives and lateral E/e' in our study.

There was weak correlation with systolic blood pressure and E/lateral e' (r = 0.44; p = 0.003). The relationships between E/lateral e' and various laboratory and clinical parameters are listed in Table 6.

Parameter	r (p value)
Age	0.353 (0.003)
Creatinine	-0.03 (0.834)
Albumin	0.13 (0.370)
Calcium	0.04 (0.760)
Phosphorous	-0.25 (0.092)
Haemoglobin	-0.13 (0.395)
Transferrin	-0.33 (0.027*)
NT pro BNP	0.63 (<0.001*)
Weight gain	-0.12 (0.438)
BMI	-0.11 (0.443)
Systolic BP	0.44 (0.003*)
Diastolic BP	-0.31 (0.040*)

Table 6. Correlation of E/lateral e' with clinical and laboratory parameters in heart failure with preserved ejection fraction (n = 44).
r-Pearson's correlation coefficient.
***-Statistical significance.**

Binary Logistic Regression of Clinical and Laboratory Parameters on Diastolic and Systolic Function

On application of binary logistic regression involving Lateral E/e' and all laboratory and clinical parameters, it was found that the odds of diastolic dysfunction increased by 2.3 times with a unit increase of creatinine, and patients with diabetes have 7.66 times higher risk for diastolic dysfunction (Table 7). The Nagelkerke R^2 of the model evaluating Lateral E/e' was 76.8%. Binary logistic regression involving ejection fraction and all laboratory and clinical parameters (Table 8) revealed that the odds of HFpEF increased by 1.93 times with a unit increase in age (p = 0.02), 1.53 times with a unit increase in phosphorus (p = 0.01), and 1.1 times with a unit increase in systolic blood pressure (p = 0.01). The Nagelkerke R^2 of this model was 52.0%.

Diastolic dysfunction (n = 102)				
	P value	OR	95% C.I. for EXP(B)	
			Lower	Upper
Creatinine	0.03	2.30	1.08	4.94
Diabetes	0.04	7.66	1.08	54.54
Hypertension	0.12	0.12	0.01	1.68
NT pro BNP	<0.001	1.00	1.00	1.00
Diastolic blood pressure	0.06	1.11	0.99	1.24
Constant	<0.001	0.00		

Table 7. Logistic regression showing clinical and lab parameters associated with diastolic dysfunction (Lateral E/e' ratio).

	P value	OR	95% C.I. for ODDS ratio	
			Lower	Upper
Age	0.02	1.93	1.87	1.99
Albumin	0.07	8.61	0.82	90.59
Po4	0.03	1.53	1.30	1.92
NT pro BNP	0.03	1.00	1.00	1.00
Systolic	0.01	1.11	1.03	1.20
Constant	0.05	0.00		

Table 8. Logistic regression showing clinical and lab parameters associated with ejection fraction.

Discussion

This was a prospective observational study involving 102 haemodialysis patients, with 63 males (61.8%) and 39 females (38.2%) from a single centre. The average age of study volunteers was 53 + 13.1 years, which was similar to the work done by Kamal et al., which reported a mean age of 53.29 ± 6.79 years indicative of the higher burden of CKD in the middle-aged and elderly population [13]. This study stands out because the vast majority (97/102) of patients ay our centre were on twice-weekly dialysis, a protocol that deviates significantly from those used in studies by Kamal et al. [14] and Laddha et al. [15]. The enrolled study participants had optimal URR, and since the practice of incremental dialysis is prevalent in our setup, the majority of them underwent twice-weekly haemodialysis at our institute. The average dialysis vintage of participants was 38.92 ± 6.9 months and diabetics constituted 46.1% of the study population. Our research showed higher proportion of diabetics compared to a similar study on diastolic dysfunction done by De Bie et al. [16], which reflects the pathological effects of diabetes on myofibrillar protein contractility, sarcolemmal calcium transport and decreased carbohydrate metabolism in the heart muscles thereby leading to imminent heart failure [17].

The haemoglobin was 8.7 ± 0.9 gm/dl in our research which showed correlation with E/A ratio similar to the study done by Shivendra et al. [18]. We also had a higher baseline creatinine level than that a in previous study [18]. Chronic uremic milieu can be responsible for alterations in mineral metabolism, cardiotonic steroids, insulin resistance, anaemia, endothelial dysfunction, and high fibroblast growth factor 23 [19], thereby contributing to the increased prevalence of heart failure. In our study, lower haemoglobin levels and increased baseline creatinine levels due to the twice-weekly haemodialysis regimen may have contributed to the increased burden of heart failure in our research volunteers. The low haemoglobin in our study is attributed to the suboptimal adherence to erythropoietin and intravenous iron supplementation in our patients due to their poor socioeconomic status. The higher creatinine level in our study leading to increased LVPWd probably reflects the long-term effects of uraemia on left ventricle remodelling [19].

LVH was present in ECG of 88 patients (80.4%) which was higher compared to the work done by Zocali et al. [20] and Shivendra S. et al. [18]. Chronic hypertension is an important factor responsible for left ventricular remodelling, and neurohormonal factors associated with persistent elevated blood pressure are responsible for diastolic dysfunction [21], leading to an increased percentage of haemodialysis patients (67.64%) in our cohort with heart failure. We were unable to find a positive impact of angiotensin receptor blockers (ARB's) on heart failure with a preserved ejection fraction in our study; only a small percentage of our patients (23.5%) were on ARB due to the fear of possible hyperkalaemia in the twice-weekly haemodialysis population, which may have contributed to the statistical insignificance of ARB's in our HFpEF study group.

E/A ratio less than 1 with reduction in E velocity less than 50 percentage was present in 77 patients (75.4%) which was indicative of impaired early diastolic relaxation of left ventricle similar to study done by Nazneen et al. [22]. This study is unique in the implementation of scientific definition of Heart failure as proposed by McDonagh TA et al. [11] and Mitter et al. [12]. This research used a practical algorithm incorporating clinical signs, laboratory parameters such as NT pro-BNP, and objective echocardiographic parameters such as Lateral E/e' for defining heart failure with significant diastolic dysfunction.

Our analysis demonstrated that the E/A ratio had a weak positive correlation with haemoglobin and calcium levels. The ejection fraction had a weak positive association with haemoglobin, transferrin saturation, and serum calcium levels. Iron is an important micronutrient for beta oxidation of fatty acids and the survival of cardiomyocytes [23], which implies that iron deficiency anaemia is a major

cause of heart failure. This finding of better haemoglobin associated with better left ventricular function was also observed in the work done by Nazneen S et al. [22]. Our study showed weak positive association of calcium with statistical significance with E/A ratio which was discordant with findings of De Bie et al. [16]. Calcium is an important element for cardiac muscle contractility, and deranged calcium homeostasis in CKD can contribute to impaired left ventricular relaxation, as was evident in our study [24].

The E/lateral e' ratio has a positive correlation with age, NT pro-BNP levels and systolic blood pressure along with a weak inverse correlation with transferrin saturation. E/lateral e' had a weak positive correlation with age, indicating that increasing age may contribute to diastolic dysfunction. NT pro BNP had positive co relation with Lateral E/e', which is consistent with the findings of a seminal study by Carsten Tschope et al. [25]. However, there was no association of NT pro BNP with the degree of diastolic dysfunction in binary logistic regression as denoted by odds ratio of 1 in our study. This finding is concordant with the study of Yin L et al. [26] which demonstrated the non-reliability of NT pro BNP as a reliable marker of heart failure in end stage renal disease and haemodialysis population. Advancing age was a potential risk factor for diastolic dysfunction in our study population which follows a similar trend observed even in the general population [27]. Aging accelerates cardiac apoptosis and hinders cardiomyocyte regenerative potential, thereby contributing to an increased prevalence of heart failure [28]. Our study also showed that there is a weak positive corelation of E/Lateral e' with systolic blood pressure, consistent with the universal understanding that patients with higher central systolic blood pressure and larger left atrial diameter tend to have a higher degree of diastolic dysfunction, contributing to cardiovascular mortality in individuals with preserved systolic function [29]. Our study showed that diabetics and elevated creatinine levels are significant indicators of diastolic dysfunction, which are associated with increased systemic inflammation, impaired oxygen delivery, renin angiotensin aldosterone system activation, chronotropic incompetence and micro vasculopathy, thereby contributing to increased incidence of HFpEF [30].

Conclusion

HFpEF is the predominant subtype of heart failure in haemodialysis patients. Haemoglobin and calcium were positively associated with ejection fraction. Elevated creatinine, diabetes mellitus and advancing age are independent risk factors for diastolic dysfunction in the haemodialysis population.

Merits of the Study

The merits of this study include a meticulous, scientifically executed, practical algorithm using the LUST protocol for the evaluation of cardiac failure in the haemodialysis population.

This study on the prevalence of HFpEF involved maximum participants on twice-weekly haemodialysis with adequate URR, which in itself is a novelty.

This study explored the possibility of using E/lateral e' as a potential echocardiographic parameter for defining diastolic dysfunction in patients undergoing haemodialysis.

Limitations of the Study

The limitations of this study included the absence of follow-up, lack of multifactorial analysis among patients without heart failure and with heart failure, primary focus only on HFpEF risk factors, lack

of critical appraisal of the potential limitations of E/ Lateral e' and E/A ratio in the prediction of diastolic dysfunction [31] in the dialysis population, low percentage of haemodialysis patients on ARB's and lack of grading of diastolic dysfunction based on E/A values.

Dyslipidaemia is major contributor for Heart failure, and we had logistic constraints for the study so we couldn't explore the role of dyslipidaemia in heart failure with preserved ejection fraction.

Kt/V would have been a better measure of adequacy in biweekly dialysis, which was not used in this study, but adequate URR was ensured before inclusion in the study. In addition, ultrafiltration volume was not included in the analysis because we ensured optimal ultrafiltration prior to echocardiography by lung ultrasound in all study participants.

HFpEF was the predominant phenotype in our study, probably because of a bias related to the age of patients selected (40-66 years), short dialysis vintage (2-3 years), and lack of consecutive patients, which is acknowledged as a limitation of our study.

Ethical Issues and Informed Consent

This study was conducted in a medical college hospital after written informed consent of the participants and institutional ethics committee approval (Ethics no: 3093/IEC/2021). All research protocols, including adherence to the principles outlined in the Declaration of Helsinki, were strictly followed in this study.

Abbreviations

CKD: Chronic Kidney Disease, **HFpEF:** Heart Failure with preserved Ejection Fraction, **HFmidrEF:** Heart Failure with mid-range Ejection Fraction, **HFrEF:** Heart Failure with reduced Ejection Fraction, **URR:** Urea reduction ratio, **LVIDs:** Left Ventricular Internal diameter at End Systole expressed in millimetres (mm), **LVIDd:** Left Ventricular Internal diameter at End diastole in mm, Left Atrial Diameter(LAD) in mm , **LVPWd:** Left Ventricular posterior wall Thickness in end diastole in mm, **EF:** Ejection Fraction expressed as percentage(%), **FS:** Fractional Shortening expressed as percentage, **E/A:** Early vs late filling ratio, **E/Lateral e':** Ratio denoting left ventricular filling pressure, **E/Vp:** ratio of left ventricular peak E wave velocity to flow propagation velocity, **ARB's:** Angiotensin receptor blockers.

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