Cross-sectional Study

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Novel echocardiographic markers for left ventricular filling pressure prediction in heart failure with preserved ejection fraction (ECHO-PREDICT): a prospective cross-sectional study

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Abstract

Heart failure with preserved ejection fraction is a complex clinical syndrome associated with a high level of morbidity and mortality, constituting 56% of heart failure cases and showing an increasing prevalence. The E/Ea ratio, used for echocardiographic assessment of left ventricular (LV) filling pressure, has been commonly recommended as a noninvasive measure. However, its validity lacks robust prospective validation in patients with preserved LV ejection fraction, and its accuracy has been questioned in comparison to patients with reduced LV ejection fraction. The objective of this study was to evaluate the accuracy of novel echocardiographic markers incorporating peak E velocity, left atrial volume index (LAVi), and pulmonary artery systolic pressure (PAP) for noninvasive estimation of LV end-diastolic pressure (LVEDP) against invasive measurement. In this cross-sectional study conducted at a tertiary care hospital, a sample size of 122 participants was utilized. Statistical analyses including independent samples *t*-test, χ^2 test, and linear regression analysis were employed to explore correlations and predict outcomes. The results indicated that Group 1 (LVEDP <20 mmHg) had a mean age of 59.25 years, while Group 2 (LVEDP > 20 mmHg) had a mean age of 56.93 years. Mitral E velocity positively predicted LVEDP, while Mitral E/A ratio showed a negative association. Notably, (E + PAP)/2, (E + LAVi)/2, and Mitral E exhibited good discriminative ability, with respective area under the curve values of 0.840, 0.900, and 0.854. (E + LAVi)/2 demonstrated the highest discriminatory power, with a threshold of 40.100, yielding high sensitivity (0.971) but relatively low specificity (0.302) in predicting LVEDP greater than 20. These findings emphasize the accuracy and utility of combining diastolic variables and peak E velocity as markers for left ventricular filling pressure in patients with a high burden of cardiac disease. Additionally, the study highlights the importance of these parameters in assessing cardiac abnormalities and supports the potential of novel echocardiographic parameters, particularly (E + LAVi)/2, in predicting LVEDP greater than 20. Further research is warranted to validate and explore the prognostic implications of these parameters in larger patient populations, ultimately improving the diagnosis and management of cardiac disease and enhancing clinical outcomes.

Keywords: area under curve, Cross-sectional studies, echocardiography, heart failure, stroke volume

Introduction

Heart failure represents a clinical syndrome characterized by cardinal symptoms like breathlessness, ankle swelling, and fatigue, potentially accompanied by signs such as elevated jugular venous pressure, pulmonary crackles, and peripheral oedema. This syndrome arises from structural and/or functional abnormalities in the heart, leading to increased intracardiac pressures and/or insufficient cardiac output both at rest and during physical exertion[1]. Management strategies involving the modulation of the renin-angiotensin-aldosterone system and the sympathetic nervous system using medications like angiotensin-converting enzyme inhibitors (ACE-I), angiotensin receptor-neprilysin inhibitors, beta-blockers, and mineralocorticoid receptor antagonists, have demonstrated efficacy in enhancing survival, lowering the risk of heart failure hospitalizations, and alleviating symptoms in individuals with heart failure with reduced ejection fraction[1].

Heart failure with preserved ejection fraction (HFpEF) is a complex clinical syndrome that is associated with a high level of

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illness and death. It now makes up 56% of cases of heart failure and its prevalence is on the rise[2]. HFpEF is characterized by the presence of symptoms and/or signs of heart failure, a preserved left ventricular ejection fraction (LVEF) of over 50%, elevated levels of natriuretic peptides (NPs), and evidence of cardiac functional and structural abnormalities that underlie heart failure[1]. Structural abnormalities may include an increased left atrial volume index (LAVI) or left ventricular mass index (LVMI), while functional abnormalities typically involve left ventricular diastolic dysfunction (LVDD). LVDD refers to impaired relaxation of the left ventricle and increased stiffness of the LV chamber, resulting in elevated left ventricular filling pressures (LVFP)[1]. LVDD can be diagnosed invasively using rest or exercise right-sided heart catheterization, or noninvasively using echocardiography[1]. No single echocardiographic measure can definitively diagnose LVDD; instead, a combination of multiple abnormal indices is recommended to assess left ventricular diastolic function. The currently recommended variables include tissue Doppler indices (E/e' ratio and e' velocities), LAVI, and tricuspid regurgitation velocity[3]. However, only a limited number of studies have validated the use of these echocardiographic indices, showing only a moderate correlation with invasive hemodynamic parameters and limited ability to distinguish HFpEF from other conditions[4]. Furthermore, the echocardiographic indices suggested by guidelines are normal in 40–75% of individuals with confirmed HFpEF using invasive methods[5,6]. These indices also demonstrate reduced accuracy in individuals in the early stages of the disease. In fact, these individuals often exhibit normal or inconclusive diastolic function during resting echocardiography due to either normal LVFP levels or fluctuating LVFP depending on their volume status[7]. The Heart Failure Association (HFA) of the European Society of Cardiology (ESC) has recently proposed a new diagnostic approach called the HFA-PEFF score. This approach aims to integrate various clinical, laboratory, and imaging tests in a stepwise manner to enhance the identification of individuals with HFpEF at different stages[8]. The HFA-PEFF score incorporates novel techniques that are currently under evaluation as potential diagnostic tools for improving the diagnosis and staging of HFpEF. These techniques include the assessment of left ventricular (LV) deformation using two-dimensional speckle tracking echocardiography and parameters derived from the diastolic stress test[8]. Additionally, the evaluation of left atrial (LA) functional parameters, such as LA strain, has shown a significant correlation with clinical status and invasive measurements of LVFP in individuals with HFpEF, suggesting its potential to enhance the diagnosis of HFpEF[9].

Echocardiographic assessment of LVFP using the E/Ea ratio has been commonly recommended as a noninvasive measure[10]. However, there is a lack of robust prospective validation specifically in patients with preserved LVEF. Moreover, the accuracy of E/Ea in patients with preserved LVEF has been questioned compared to those with reduced LVEF[10]. Many laboratories do not routinely calculate E/Ea, and even when it is calculated, its estimation of LVFP is imperfect[10]. The comparison of left ventricular end-diastolic pressure (LVEDP) levels and the examined variables is crucial in the field of cardiology as it provides valuable insights into the hemodynamic status and functioning of the heart. LVEDP is a key indicator of left ventricular filling pressure, reflecting the pressure exerted on the ventricle during diastole when it is relaxed and filled with blood. By analyzing LVEDP levels and correlating them with various variables such as cardiac output, ejection fraction, and pulmonary capillary wedge pressure, clinicians can assess cardiac performance, evaluate diastolic function, detect abnormalities in ventricular relaxation or compliance, and diagnose and monitor conditions such as heart failure, myocardial infarction, valvular diseases, and hypertension. This comparison helps guide treatment decisions, monitor patient response to therapy, and improve overall management of cardiovascular disorders. Therefore, we aimed to explore the accuracy of novel and simplified echocardiographic indexes that incorporate E velocity, LAVi, and pulmonary artery systolic pressure (PAP) as alternative measures for estimating LV filling pressure. This is particularly significant given the uncertainties surrounding the predictive value of several conventional echocardiographic variables in determining LVFP in patients with preserved LVEF. In our study, we hypothesized two key points: firstly, combining two separate "conventional" diastolic variables would enhance the accuracy of LVFP estimation compared to using either variable alone in this patient population, and secondly, peak E velocity alone would serve as a more useful marker of LVFP in a population with a high burden of cardiac disease, as abnormal LV relaxation could be assumed, reducing ambiguity between normal and pseudo-normal diastolic filling patterns observed in these patients.

HIGHLIGHTS

- Heart failure with preserved ejection fraction involves complex clinical syndrome, constituting 56% of heart failure cases with rising prevalence and high morbidity/mortality.
- Combining diastolic variables improves left ventricular (LV) filling pressure estimation, particularly peak E velocity, in high cardiac disease burden population.
- Significant differences between patient groups emphasize the importance of echocardiographic parameters in assessing cardiac abnormalities and predicting LV end-diastolic pressure.
- Novel echocardiographic parameter (E + left atrial volume index)/2 shows potential in predicting LV end-diastolic pressure greater than 20 mmHg, urging further research for prognostic implications in larger populations.

Methods

Population

In this cross-sectional study, we recruited 122 participants at a tertiary care hospital over a period of 1-month from April 2023 to May 2023. The sample size of 122 participants, used in this study, based on previous studies done on this topic[10]. We recruited consecutive patients who were referred to the cardiac catheterization laboratory for coronary angiography upon clinical indications. We aimed to recruit a diverse range of cardiac patients undergoing angiography including patients with different cardiac conditions but excluding those with conditions that could impact Doppler measurements of LVFP such as non-sinus rhythm, severe mitral-regurgitation, mitral stenosis, tachyarrhythmias, or prosthetic mitral valve. All of the females included in the study were in the post-menopausal state. With this approach, we aimed to capture a representative sample of patients undergoing coronary

angiography allowing for a comprehensive assessment of cardiac parameters and LVEDP estimation.

The inclusion of study patients had diagnosis of HFpEF made using the H2FPEF score, which derives from four clinical parameters including body mass index (BMI) greater than 30 kg/m^2 , treatment involving two or more antihypertensive medications , presence of atrial fibrillation, and age exceeding 60 years along with two echocardiographic measures (E/e′ ratio >9 and PAP >35 mmHg[11]. This computation results in an assigned categorical H2FPEF score spanning from 0 to 9. H2FPEF scores within the range of 0–1 are linked with a lower likelihood of HFpEF (below 25%), whereas scores within the range of 6–9 are linked with a higher likelihood of HFpEF (exceeding 90%)[11].

Ethical approval

Institutional review board approval was obtained to comply with all ethical regulations that may apply to the study. Informed consent was obtained from all patients prior to their participation in the study. Ethical guidelines outlined in the Declaration of Helsinki were followed in this study. A Strengthening the Reporting of cohort, cross-sectional and case-control studies (STROCCS) checklist has been added as a supplementary file, Supplemental Digital Content 1, http://links.lww.com/MS9/A250.

Heart catheterization procedure

All the patients underwent left heart catheterization by inserting a guidewire through radial artery into the left ventricle. LV diastolic pressures were measured over 25 cardiac cycles and averaged followed by selective injection of the coronary ostia for coronary angiography. Angiography obtained the standard diagnostic views of the left and right coronary anatomy. An invasive cardiologist, blinded to other clinical and echocardiographic information, interpreted the invasive hemodynamics and angiographic readings. Venous blood samples (5 ml) were obtained during catheterization in a subset of patients to assess B-type natriuretic peptide (BNP) levels.

Echo-doppler studies

Following catheterization, patients underwent comprehensive transthoracic echo-doppler examination within 25 min in an identical supine position as the initial catheterization. Patients with conditions such as non-sinus rhythm, several mitral-regurgitation, etc., that could potentially impact the reliability of Doppler estimation of LVFP were excluded. Transthoracic echo-Doppler tests were performed using a General Electric Vivid 7 ultrasonography system. Two-dimensional measurements were obtained as per guidelines of the American Society of Echocardiography, including LVEF, maximal left atrial volume by the biplane method of discs, and LV by the area-length method.

Preserved LVEF was defined as 50% or greater. Pulsed wave Doppler recorded mitral inflow at the apical 4-chamber view to obtain peak early (E) and late (A) velocities, E/A ratio and E deceleration time. PAP can be calculated as tricuspid regurgitation velocity plus estimated right atrial pressure from inferior vena cava size and collapse. Tissue Doppler measured early diastolic (Ea) velocities at the septal and lateral annulus, averaged to calculate E/Ea ratio. An echocardiologist, blinded to the clinical and catheterization data, analyzed the echo-Doppler studies. Doppler measurements were averaged over three cardiac cycles.

Statistical analysis

Continuous data were presented as mean standard deviation and categorical data as numbers and percentages. Statistical analysis was performed using SPSS. Compared variables were compared using independent samples *t*-tests and categorical variables using χ^2 tests. Linear regression analyses were conducted to determine correlations between continuous variables. Sensitivity and specificity were calculated as per standard definitions to predict the outcome (LVEDP >20 mmHg). Receiver operating characteristic ROC curves were constructed to evaluate the performance of test result variables ((E + PAP)/2, (E + LAVi)/2, Mitral E velocity) in predicting elevated LVEDP. The area under the ROC curve (AUC) was calculated to determine the discriminative ability of these novel echocardiographic indexes to distinguish LVEDP greater than 20 mmHg. The significance level was set at a *p*-level of less than 0.05. ANOVA was used to compare the means of LVEDP levels between the two groups with LVEDP less than 20 mmHg and greater than 20 mmHg to find statistically significant difference between the two groups. Normality of data distribution was assessed through appropriate statistical tests. Following this verification, we proceeded with the necessary statistical analyses. ANOVA analysis was conducted to assess the significance of differences between multiple groups, and ROC curve analysis was performed to evaluate the diagnostic accuracy of our model. For the normality assessment, we utilized methods such as the Shapiro–Wilk test and visual inspection of Q-Q plots. The ANOVA analysis involved assessing the variation between groups and determining whether there were statistically significant differences. ROC analysis was utilized to evaluate the trade-off between sensitivity and specificity of the diagnostic model.

Results

In this prospective cross-sectional study, conducted with a sample size of 122 participants, results indicated that individuals with LVEDP less than 20 mmHg, a higher proportion of females (41.5%) was observed compared to males (31, 58.5%). Moreover, the prevalence of hypertension was significantly higher in the LVEDP greater than 20 mmHg group, with 73.6% of participants in this group having hypertension, in contrast to 26.4% of participants in the LVEDP less than 20 mmHg group who were free of hypertension. Another positive finding revealed a higher prevalence of hypercholesterolaemia in the LVEDP greater than 20 mmHg group (81.2%) compared to the LVEDP less than 20 mmHg group (69.8%). These findings highlight potential associations between sex, hypertension, and hypercholesterolaemia with LVFP in HFpEF, indicating their relevance in future investigations and clinical management. In the LVEDP less than 20 mmHg group, 22.6% of participants reported being current smokers, while 3% of participants in the LVEDP greater than 20 mmHg group were also current smokers. Furthermore, a higher proportion of individuals in the LVEDP less than 20 mmHg group (67.9%) reported using beta-blockers compared to the LVEDP greater than 20 mmHg group (69.6%). Similarly, in the LVEDP less than 20 mmHg group, 54.7% of participants reported using ACE-inhibitors or angiotensin receptor blockers

(ARBs), whereas 63.8% of participants in the LVEDP greater than 20 mmHg group reported the same medication use. Another positive finding indicated that 9.4% of participants in the LVEDP less than 20 mmHg group and 11.6% of participants in the LVEDP greater than 20 mmHg group reported using calcium channel blockers. These findings provide insights into the potential associations between current smoking, beta-blocker use, ACE inhibitor or ARB use, and calcium channel blocker use with LVFP in HFpEF. Further exploration of these relationships may contribute to improved management strategies for this patient population as shown in Table 1.

The independent samples *t*-test done to compare the means of various variables between two groups. Group 1 had LVEDP less than 20 mmHg, and Group 2 had LVEDP greater than 20 mmHg. The sample sizes for Group 1 and Group 2 were 53 and 69, respectively. The mean age in Group 1 was 59.25 years, while in Group 2 it was 56.93 years. The difference in means was statistically significant ($t = 2.3154$, $P = 0.030$), suggesting that the groups differed in terms of age. The proportion of males in Group 1 was 42%, whereas in Group 2 it was 62%. There was a significant difference between the groups in terms of sex distribution ($P = 0.049$). Body surface area: The mean body surface area in Group 1 was 2.470 square metres, and in Group 2 it was 2.531 square metres. The difference in means was not statistically significant ($t = -0.0609$, $P = 0.402$), indicating that the groups did not differ significantly in terms of body surface area. The proportions of hypertension, diabetes, hypercholesterolaemia, current smoking status, beta-blocker use, ACE-Inhibitor or ARB use, Calcium channel blocker, Statin, Diuretic, and Significant coronary artery disease did not show significant differences between Group 1 and Group 2. The mean heart rate measured using echocardiography in Group 1 was 70.193 beats per minute (bpm), while in Group 2 it was 68.755 bpm. The difference in means was not statistically significant ($t = 1.4382$, $P = 0.334$), indicating that the groups had similar heart rates. Various cardiac dimensions and indices such as the mean values of LVDD, LVMI, LAVi, right ventricular diastolic dimension (RVDD), right atrial volume index (RAVi), LVEF, and RV fractional area change differed significantly between Group 1 and Group 2 ($P < 0.001$ for all variables). Group 2 had larger dimensions and indices compared to Group 1, indicating possibly more severe cardiac structural and functional abnormalities. The means of Mitral E, Mitral A, Mitral E/A, Mitral deceleration time, Pulmonary artery systolic pressure, Mitral Ea average, Mitral E/Ea septal annulus, Mitral E/Ea lateral annulus, Mitral E/Ea average of annuli, (E + LAVi)/2, and (E + PAP)/2 were significantly different between the two groups ($P < 0.001$ for all variables). Group 2 exhibited higher values, suggesting impaired diastolic function and increased pulmonary pressure. The means of heart rate on cardiac catheterization, systolic blood pressure on cardiac catheterization, diastolic blood pressure on cardiac catheterization, LVEDP on cardiac catheterization, LV pre-A pressure on cardiac catheterization, and B-type natriuretic peptide levels differed significantly between Group 1 and Group 2 ($P < 0.001$ for all variables) with Group 2 having higher values. A consolidated table of baseline as well as independent samples *t*-test results is shown in Table 2.

The Pearson χ^2 correlations in Table 3 presents the correlations between various variables measured in two groups: those with LVEDP less than 20 mmHg ($n = 53$) and those with LVEDP greater than 20 mmHg ($n = 69$). The variables included in the table are age (years), Mitral E (early diastolic velocity), Mitral A (late diastolic velocity), Mitral E/A ratio, Mitral E/Ea (average of annuli), (E + LAVi)/2 (average of E velocity and left atrial volume index), (E + PAP)/2 (average of E velocity and pulmonary artery pressure), and LVEDP (measured through cardiac catheterization). The table provides Pearson correlation coefficients and corresponding *p* values (two-tailed) for each pair of variables in both groups. The Pearson correlation coefficient measures the strength and direction of the linear relationship between two variables, while the *p* value indicates the statistical significance of the correlation. In the LVEDP less than 20 mmHg group, significant correlations ($P < 0.05$) were found between Age and Mitral E (negative correlation), Age and LVEDP (positive correlation), Mitral E and Mitral E/A (negative correlation), and (E + PAP)/2 and Age (positive correlation). There were no significant correlations for other variable pairs in this group. In the LVEDP greater than 20 mmHg group, significant correlations ($P < 0.05$) were observed between Age and LVEDP (positive correlation), Mitral E and Mitral E/A (negative correlation), and

Table 1

Baseline categorical participant characteristics

	Group	
	LVEDP < 20 mmHg ($n = 53$)	LVEDP > 20 mmHg ($n = 69$)
	n (%)	*n* (%)
Sex		
Male	31 (58.5)	26 (37.7)
Female	22 (41.5)	43 (62.3)
Hypertension		
No hypertension	14 (26.4)	10 (14.5)
Hypertension	39 (73.6)	59 (85.5)
Diabetes		
No diabetes	32 (60.4)	42 (60.9)
Diabetes	21 (39.6)	27 (39.1)
Hypercholesterolaemia		
No hypercholesterolaemia	16 (30.2)	13 (18.8)
Hypercholesterolaemia	37 (69.8)	56 (81.2)
Current smoker		
No	41 (77.4)	55 (79.7)
Yes	12 (22.6)	14 (20.3)
Beta-blocker use		
No	17 (32.1)	21 (30.4)
Yes	36 (67.9)	48 (69.6)
ACE-inhibitor or ARB use		
No	24 (45.3)	25 (36.2)
Yes	29 (54.7)	44 (63.8)
Calcium channel blocker use		
No	48 (90.6)	61 (88.4)
Yes	5 (9.4)	8 (11.6)
Statin use		
No	22 (41.5)	16 (23.2)
Yes	31 (58.5)	53 (76.8)
Diuretic use		
No	37 (69.8)	35 (50.7)
Yes	16 (30.2)	34 (49.3)
Significant CAD on cardiac catheterization		
No	28 (52.8)	13 (18.8)
Yes	25 (47.2)	56 (81.2)

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CAD, coronary artery disease; LVEDP, left ventricular end-diastolic pressure.

Table 2

Consolidated table of baseline as well as independent samples *t*-test results; values are rounded off to the nearest tenth or 1 decimal point; *p* value was written as 0.01 if it was lower than that

							t-test for equality of means (equal variances assumed)							
	LVEDP <20 (*n*=53)			LVEDP >20 (*n*=69)					95% CI of the difference		Levene's test for equality of variances (For equal variances assumed)			
Variables	**Mean**	**Std. deviation**	**Std. error mean**	**Mean**	**Std. deviation**	**Std. error mean**	**Mean difference**	**Std. error difference**	**Lower**	**Upper**	**F**	**sig.**	**t**	***P***
Age (year)	59.3	5.2	0.72	57.0	6.1	0.74	2.3	1.1	0.2	4.4	4.0	0.04	2.2	**0.03**
Body surface area in metre square	2.5	0.2	0.03	2.5	0.2	0.02	−0.06	0.04	−0.1	0.01	0.7	0.4	−1.7	0.1
Heart rate (bpm) on echocardiography	70.2	13.8	1.9	68.8	14.8	1.8	1.4	2.6	−3.8	6.6	0.9	0.3	0.5	0.6
LV diastolic dimension (cm)	4.3	0.8	0.1	4.7	0.5	0.1	−0.3	0.1	−0.6	−0.1	19.2	0.001	−2.8	**0.01**
Left ventricular mass index (g/m)	92.0	17.9	2.5	98.9	35.6	4.3	−7.0	5.3	−17.6	3.6	18.9	0.001	−1.3	0.2
Left atrial volume index (ml/m^2)	26.5	5.6	0.8	34.2	14.6	1.8	−7.7	2.1	−11.9	−3.5	33.3	0.001	−3.6	**0.01**
RV diastolic dimension (cm)	3.2	0.6	0.1	3.2	0.3	0.04	−0.02	0.1	−0.2	0.2	23.7	0.001	−0.2	0.9
Right atrial volume index (ml/m)	17.1	3.6	0.5	20.5	6.1	0.7	−3.4	0.9	−5.2	−1.5	18.6	0.001	−3.6	**0.01**
LV ejection fraction (%)	58.7	6.9	1.0	61.2	4.3	0.5	−2.5	1.0	−4.5	−0.5	18.9	0.001	−2.5	**0.01**
RV fractional area change (%)	40.8	6.2	0.9	41.2	6.6	0.8	−0.4	1.2	−2.7	1.9	0.2	0.7	−0.4	0.7
Mitral E (cm/s)	65.4	15.3	2.1	88.2	14.7	1.8	−22.8	2.7	−28.2	−17.4	0.2	0.7	−8.3	**0.01**
Mitral A (cm/s)	73.1	14.8	2.0	79.2	23.1	2.8	−6.1	3.6	−13.3	1.1	8.8	0.004	−1.7	0.1
Mitral E/A	0.7	0.2	0.02	0.6	0.1	0.01	0.09	0.03	0.04	0.1	12.4	0.001	3.4	**0.01**
Mitral deceleration time (cm/sec)	199.0	51.5	7.1	206.0	43.3	5.2	−7.0	8.6	−24.0	10.0	1.3	0.3	−0.8	0.4
Pulmonary artery systolic pressure (mmHg)	24.4	5.3	0.7	34.3	8.1	1.0	−9.9	1.3	−12.4	−7.4	10.3	0.002	−7.7	**0.01**
Mitral Ea average(cm/s)	6.8	1.5	0.2	7.1	2.4	0.3	−0.3	0.4	−1.1	0.4	12.2	0.001	−0.9	0.4
Mitral E/Ea septal annulus	12.5	3.5	0.5	18.3	7.2	0.9	−5.8	1.1	−7.9	−3.7	22.1	0.001	−5.4	**0.01**
Mitral E/Ea lateral annulus	9.2	1.9	0.3	15.1	5.4	0.6	−6.0	0.8	−7.4	−4.4	36.2	0.001	−7.7	**0.01**
Mitral E/Ea average of annuli	10.3	2.4	0.3	15.2	5.3	0.6	−4.9	0.8	−6.4	−3.3	31.3	0.001	−6.2	**0.01**
(E + LAVi)/2 (cm/sec + ml/m^2)	44.4	8.3	1.1	63.3	12.8	1.5	−19.0	2.0	−23.0	−15.0	5.6	0.02	−9.4	**0.01**
(E + PAP)/2 (cm/sec + mmHg)	25.8	5.2	0.7	35.8	8.6	1.0	−10.0	1.3	−12.7	−7.4	10.8	0.001	−7.5	**0.01**
Heart rate (bpm) on cardiac catheterization	72.4	13.3	1.8	71.3	9.7	1.2	1.1	2.1	−3.0	5.2	2.9	0.1	0.5	0.6
Systolic BP on cardiac catheterization	155.2	16.4	2.3	169.2	36.7	4.4	−14.1	5.4	−24.8	−3.3	20.0	0.001	−2.6	**0.01**
Diastolic BP on cardiac catheterization	73.5	11.5	1.6	85.1	16.3	2.0	−11.6	2.6	−16.8	−6.3	5.0	0.027	−4.4	**0.01**
LVEDP (mmHg) on cardiac catheterization	14.8	1.7	0.2	27.5	6.3	0.8	−12.7	0.9	−14.5	−11.0	53.6	0.001	−14.3	**0.01**
LV pre-A pressure (mmHg) on cardiac catheterization	11.7	3.4	0.5	19.1	4.5	0.5	−7.37	0.7	−8.8	−5.8	2.0	0.2	−9.8	**0.01**
B-type natriuretic peptide levels (pg/ml)	45.9	17.9	2.55	700.6	12.5	1.5	−69.7	2.8	−75.1	−64.2	12.3	0.001	−25.3	**0.01**

BP, blood pressure; LAVi, left atrial volume index; LV, left ventricular; LVEDP, left ventricular end-diastolic pressure; PAP, pulmonary artery systolic pressure; RV, right ventricular; Sig., significance.
Bold value indicate statistically significant wtih *P* value less than 0.05.

Table 3

Pearson correlation analysis

Pearson χ2 correlations

		Group															
		LVEDP < 20 mmHg (n = 53)								LVEDP > 20 mmHg (n = 69)							
		Age (year)	Mitral E (cm/s)	Mitral A (cm/s)	Mitral E/A	Mitral E/Ea average of annuli	(E + LAVi)/2 (cm/s + mL/m^2)	(E + PAP)/2 (cm/s + mmHg)	LVEDP (mmHg) on cardiac catheterization	Age (year)	Mitral E (cm/s)	Mitral A (cm/s)	Mitral E/A	Mitral E/Ea average of annuli	(E + LAVi)/2 (cm/s + mL/m^2)	(E + PAP)/2 (cm/s + mmHg)	LVEDP (mmHg) on cardiac catheterization
Age (year)	Pearson correlation	1	−0.276[a]	0.057	−0.276[a]	−0.125	−0.070	0.291[a]	−0.111	1	−0.048	0.051	−0.048	−0.027	0.120	−0.005	−0.159
	Sig. (2-tailed)		0.046	0.684	0.046	0.371	0.618	0.034	0.428		0.693	0.679	0.693	0.826	0.326	0.966	0.192
Mitral E (cm/s)	Pearson correlation	−0.276[a]	1	−0.116	1.000[b]	0.130	0.060	−0.221	−0.156	−0.048	1	0.098	1.000[b]	−0.070	−0.034	0.164	−0.168
	Sig. (2-tailed)	0.046		0.408	0.000	0.353	0.669	0.111	0.264	0.693		0.422	0.000	0.567	0.781	0.177	0.168
Mitral A (cm/s)	Pearson correlation	0.057	−0.116	1	−0.116	0.200	−0.129	−0.151	−0.021	0.051	0.098	1	0.098	0.163	0.034	−0.003	0.094
	Sig. (2-tailed)	0.684	0.408		0.408	0.152	0.357	0.279	0.881	0.679	0.422		0.422	0.180	0.783	0.981	0.442
Mitral E/A	Pearson correlation	−0.276[a]	1.000[b]	−0.116	1	0.130	0.060	−0.221	−0.156	−0.048	1.000[b]	0.098	1	−0.070	−0.034	0.164	−0.168
	Sig. (2-tailed)	0.046	0.000	0.408		0.353	0.669	0.111	0.264	0.693	0.000	0.422		0.567	0.781	0.177	0.168
Mitral E/Ea average of annuli	Pearson correlation	−0.125	0.130	0.200	0.130	1	0.037	0.158	0.013	−0.027	−0.070	0.163	−0.070	1	−0.018	−0.051	0.008
	Sig. (2-tailed)	0.371	0.353	0.152	0.353		0.795	0.259	0.927	0.826	0.567	0.180	0.567		0.881	0.679	0.949
(E + LAVi)/2 (cm/s + mL/m2)	Pearson correlation	−0.070	0.060	−0.129	0.060	0.037	1	0.119	0.029	0.120	−0.034	0.034	−0.034	−0.018	1	−0.038	−0.114
	Sig. (2-tailed)	0.618	0.669	0.357	0.669	0.795		0.395	0.835	0.326	0.781	0.783	0.781	0.881		0.759	0.351
(E + PAP)/2 (cm/s + mmHg)	Pearson correlation	0.291[a]	−0.221	−0.151	−0.221	0.158	0.119	1	−0.067	−0.005	0.164	−0.003	0.164	−0.051	−0.038	1	0.109
	Sig. (2-tailed)	0.034	0.111	0.279	0.111	0.259	0.395		0.632	0.966	0.177	0.981	0.177	0.679	0.759		0.372
LVEDP (mmHg) on cardiac catheterization	Pearson correlation	−0.111	−0.156	−0.021	−0.156	0.013	0.029	−0.067	1	−0.159	−0.168	0.094	−0.168	0.008	−0.114	0.109	1
	Sig. (2-tailed)	0.428	0.264	0.881	0.264	0.927	0.835	0.632		0.192	0.168	0.442	0.168	0.949	0.351	0.372	

LAVi, left atrial volume index; LVEDP, left ventricular end-diastolic pressure; PAP, pulmonary artery systolic pressure.

[a]Correlation is significant at the 0.05 level (2-tailed).

[b]Correlation is significant at the 0.01 level (2-tailed).

Mitral E and Mitral E/Ea (positive correlation). No other variable pairs showed significant correlations in this group. Additionally, for both groups, there was a significant negative correlation between Mitral E/Ea and (E + PAP)/2 ($P < 0.05$) as shown in detail in Table 3. Overall, these findings suggest that the variables included in the analysis exhibit varying degrees of association in relation to LVEDP levels and provide insights into potential relationships between age, mitral velocities, and other parameters in the context of LV function.

The regression analysis done to investigate the relationship between various predictors and LVEDP on cardiac catheterization as shown in Table 4. The model summary indicated that the regression model accounted for a significant proportion of the variance in LVEDP ($R^2 = 0.667$, adjusted $R^2 = 0.585$, $P < 0.001$). The ANOVA results showed that the regression model was statistically significant ($F(24, 97) = 8.110$, $P < 0.001$), suggesting the presence of at least one significant predictor. Examining the coefficients, it was found that Mitral E velocity (cm/sec) was a significant positive predictor of LVEDP ($B = 0.184$, $P = 0.048$), whereas Mitral E/A ratio exhibited a significant negative association ($B = -25.808$, $P = 0.012$). Other predictors, such as heart rate on echocardiography and LV diastolic dimension, did not reach statistical significance.

Table 4

Regression analysis

R	R^2	Adjusted R^2	Std. error of the estimate				
0.817[a]	0.667	0.585	5.1414				
			ANOVA[b]				
	Model	Sum of squares	Df	Mean square	F	Sig.	
1	Regression	5145.408	24	214.392	8.110	0.0001[c]	
	Residual	2564.144	97	26.434			
	Total	7709.551	121				
			Coefficients[d]				
	Model	Unstandardized coefficients		Standardized coefficients			95.0% CI for B
		B	Std. error	Beta	t	Sig.	Lower bound / Upper bound
1	(Constant)	3.287	13.284		0.247	0.805	−23.079 / 29.652
	Heart rate (bpm) on echocardiography	−0.032	0.035	−0.058	−0.909	0.366	−0.102 / 0.038
	LV diastolic dimension (cm)	0.973	0.821	0.079	1.185	0.239	−0.657 / 2.604
	Left ventricular mass index (g/m)	−0.003	0.017	−0.010	−0.150	0.881	−0.037 / 0.032
	Left atrial volume index (ml/m^2)	0.072	0.047	0.109	1.532	0.129	−0.021 / 0.165
	RV diastolic dimension (cm)	−0.402	1.089	−0.024	−0.369	0.713	−2.563 / 1.759
	Right atrial volume index (ml/m)	0.098	0.102	0.066	0.963	0.338	−0.105 / 0.301
	LV ejection fraction (%)	0.155	0.093	0.112	1.675	0.097	−0.029 / 0.340
	RV fractional area change (%)	−0.086	0.079	−0.069	−1.088	0.279	−0.242 / 0.071
	Mitral E (cm/s)	0.184	0.092	0.431	2.001	0.048	0.001 / 0.367
	Mitral A (cm/s)	0.013	0.026	0.034	0.515	0.608	−0.038 / 0.065
	Mitral E/A	−25.808	10.030	−0.469	−2.573	0.012	−45.714 / −5.902
	Mitral deceleration time (cm/s)	0.009	0.011	0.055	0.855	0.395	−0.012 / 0.031
	Pulmonary artery systolic pressure (mmHg)	0.097	0.079	0.104	1.224	0.224	−0.060 / 0.254
	Mitral Ea average(cm/s)	−0.093	0.251	−0.024	−0.371	0.712	−0.590 / 0.405
	Mitral E/Ea septal annulus	0.048	0.093	0.039	0.516	0.607	−0.136 / 0.232
	Mitral E/Ea lateral annulus	0.233	0.121	0.150	1.937	0.056	−0.006 / 0.473
	Mitral E/Ea average of annuli	0.069	0.121	0.043	0.572	0.569	−0.171 / 0.310
	(E + LAVi)/2 (cm/s + ml/m^2)	−0.030	0.045	−0.054	−0.664	0.508	−0.119 / 0.060
	(E + PAP)/2 (cm/s + mmHg)	0.049	0.071	0.055	0.694	0.489	−0.092 / 0.191
	Heart rate (bpm) on cardiac catheterization	0.036	0.047	0.051	0.771	0.442	−0.056 / 0.128
	Systolic BP on cardiac catheterization	−0.005	0.019	−0.020	−0.269	0.789	−0.043 / 0.033
	Diastolic BP on cardiac catheterization	−0.018	0.034	−0.035	−0.522	0.603	−0.086 / 0.050
	LV pre-A pressure (mmHg) on cardiac catheterization	−0.085	0.129	−0.058	−0.665	0.508	−0.341 / 0.170
	B-type natriuretic peptide levels (pg/mL)	0.033	0.031	0.154	1.057	0.293	−0.029 / 0.094

BP, blood pressure; LAVi, left atrial volume index; LV, left ventricular; LVEDP, left ventricular end-diastolic pressure; PAP, pulmonary artery systolic pressure; RV, right ventricular; Sig., significance.

[a]Predictors: (Constant), B-type natriuretic peptide levels (pg/ml), RVDD (cm), Mitral deceleration time (cm/s), heart rate (bpm) on cardiac catheterization, Mitral Ea average(cm/s), heart rate (bpm) on echocardiography, LVMI (g/m), RV fractional area change (%), Mitral A (cm/s), LVDD (cm), Mitral E/A, Systolic BP on cardiac catheterization, LVEF (%), Diastolic BP on cardiac catheterization, Right atrial volume index (ml/m), LAVi (ml/m^2), Mitral E/Ea septal annulus, Mitral E/Ea lateral annulus, Mitral E/Ea average of annuli, (E + PAP)/2 (cm/s + mmHg), (E + LAVi)/2 (cm/s + ml/m^2), LV pre-A pressure (mmHg) on cardiac catheterization, Pulmonary artery systolic pressure (mmHg), Mitral E (cm/sec).

[b]Dependent Variable: LVEDP (mmHg) on cardiac catheterization.

[c]Predictors: (Constant), B-type natriuretic peptide levels (pg/ml), RVDD (cm), Mitral deceleration time (cm/s), heart rate (bpm) on cardiac catheterization, Mitral Ea average(cm/s), Heart rate (bpm) on echocardiography, LVMI (g/m), RV fractional area change (%), Mitral A (cm/s), LVDD (cm), Mitral E/A, Systolic BP on cardiac catheterization, LVEF (%), Diastolic BP on cardiac catheterization, Right atrial volume index (ml/m), LAVi (ml/m^2), Mitral E/Ea septal annulus, Mitral E/Ea lateral annulus, Mitral E/Ea average of annuli, (E + PAP)/2 (cm/s + mmHg), (E + LAVi)/2 (cm/s + ml/m^2), LV pre-A pressure (mmHg) on cardiac catheterization, Pulmonary artery systolic pressure (mmHg), Mitral E (cm/s).

[d]Dependent Variable: LVEDP (mmHg) on cardiac catheterization.

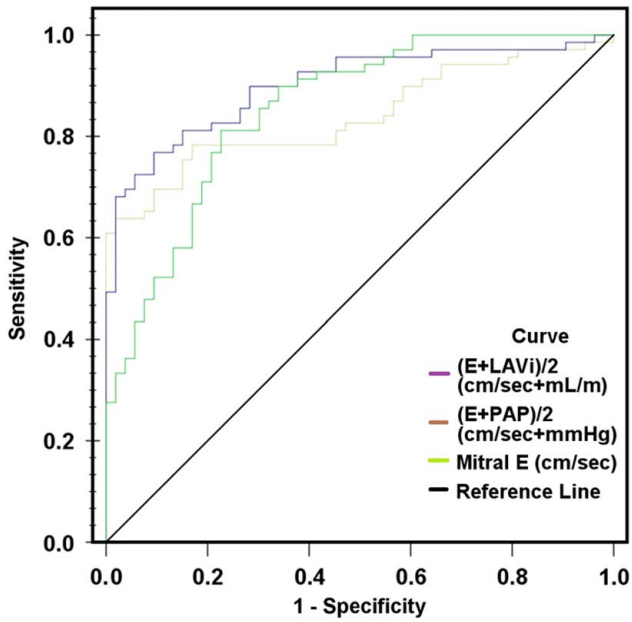

Figure 1. Receiver operating characteristic curves. LAVi, left atrial volume index; PAP, pulmonary artery systolic pressure.

The ROC curves were generated to evaluate the performance of three test result variables in predicting the positive actual state of LVEDP greater than 20 mmHg as shown in Fig. 1.

AUC values for (E + PAP)/2 (cm/s + mmHg), (E + LAVi)/2 (cm/s + ml/m^2), and Mitral E (cm/s) were found to be .840 [SE = 0.036, $P < 0.001$, 95% CI (0.769, 0.911)], 0.900 [SE = 0.028, $P < 0.001$, 95% CI (0.846, 0.955)], and 0.854 [SE = 0.034, $P < 0.001$, 95% CI (0.787, 0.920)], respectively as shown in Table 5. These results suggest that all three variables have good discriminative ability in distinguishing between an LVEDP of greater than or lesser than 20 mmHg, with (E + LAVi)/2 exhibiting the highest discriminatory power. The findings support the utility of these variables as potential predictors of elevated LVEDP. A threshold of 40.100 for (E + LAVi)/2 (cm/s + ml/m^2) was selected as the threshold at which the sensitivity was 0.971 while the specificity was 0.302.

Discussion

The study compared various variables between two groups based on LVEDP levels. Group 1 had LVEDP less than 20 mmHg, while Group 2 had LVEDP greater than 20 mmHg. The mean age in Group 1 was 59.25 years, whereas in Group 2 it was 56.93 years. There was a statistically significant difference in age between the two groups, indicating that the groups differed in terms of age. Additionally, the proportion of males in Group 1 was 42%, while in Group 2 it was 62%. This difference in sex distribution was also found to be statistically significant. The study examined body surface area between the two groups and found that the mean body surface area did not differ significantly between Group 1 (2.470 square metres) and Group 2 (2.531 square metres). This suggests that body surface area was not a differentiating factor between the two groups. Moreover, the proportions of hypertension, diabetes, hypercholesterolaemia, current smoking status, beta-blocker use, ACE-inhibitor or ARB use, calcium channel blocker use, statin use, diuretic use, and significant coronary artery disease did not show significant differences between Group 1 and Group 2. Various cardiac dimensions and indices, such as LVDD, LVMI, LAVi, RVDD, RAVi, LVEF, and RV fractional area change, differed significantly between Group 1 and Group 2. Group 2 exhibited larger dimensions and indices, suggesting more severe cardiac structural and functional abnormalities compared to Group 1. Similarly, the means of several diastolic function parameters, including Mitral E, Mitral A, Mitral E/A, Mitral deceleration time, Pulmonary artery systolic pressure, Mitral Ea average, Mitral E/Ea septal annulus, Mitral E/Ea lateral annulus, Mitral E/Ea average of annuli, (E + LAVi)/2, and (E + PAP)/2, were significantly different between the two groups. Group 2 had higher values for these parameters, indicating impaired diastolic function and increased pulmonary pressure.

These findings have important practical implications in the field of cardiology. Firstly, the significant difference in age between the two groups suggests that age may play a role in the development of elevated LVEDP. This finding highlights the need for age-specific considerations when evaluating and managing patients with cardiac disorders. Additionally, the significant difference in sex distribution indicates that sex may influence LVEDP levels, emphasizing the importance of sex-specific approaches to diagnosis, treatment, and risk stratification in cardiology. Moreover, the lack of significant differences in comorbidities such as hypertension, diabetes, and hypercholesterolaemia between the two groups suggests that these conditions may not be the primary drivers of elevated LVEDP in this study population. This finding directs attention towards other factors that could contribute to the observed differences in cardiac dimensions, indices, and diastolic function parameters. By exploring these factors further, clinicians can gain insights into the underlying mechanisms leading to elevated LVEDP and tailor their therapeutic strategies accordingly. The significant differences observed in cardiac dimensions, indices, and diastolic function parameters between Group 1 and Group 2 have important implications for understanding the condition being studied. The larger dimensions and indices in Group 2 indicate more pronounced structural abnormalities, such as ventricular hypertrophy and increased atrial volumes. These findings suggest that elevated LVEDP may be associated with more advanced stages of cardiac remodelling and dysfunction. Additionally, the impaired diastolic function parameters and increased pulmonary pressure in Group 2 further support the notion of significant diastolic dysfunction and potential pulmonary hypertension in this group.

Table 5

Area under the curve

Test Result variable(s)	Area	Std. error[a]	Asymptotic Sig.[b]	Asymptotic 95% CI Lower bound	Asymptotic 95% CI Upper bound
(E + PAP)/2 (cm/s + mmHg)	0.840	0.036	0.001	0.769	0.911
(E + LAVi)/2 (cm/s + ml/m^2)	0.900	0.028	0.001	0.846	0.955
Mitral E (cm/s)	0.854	0.034	0.001	0.787	0.920

LAVi, left atrial volume index; PAP, pulmonary artery systolic pressure; Sig., significance.
[a]Under the nonparametric assumption.
[b]Null hypothesis: true area = 0.5.

The means of heart rate, systolic blood pressure, diastolic blood pressure, LVEDP, LV pre-A pressure, and B-type natriuretic peptide levels differed significantly between Group 1 and Group 2. Group 2 had higher values for these variables, suggesting a more severe cardiac condition in terms of hemodynamic parameters and B-type natriuretic peptide levels. Dokainish *et al.*[12] reported their study that in individuals with normal LVEF, incorporating LAVi greater than 31 ml/m^2 along with E/e' ratio (when E/e' falls within the intermediate range considerably improved the precision of estimating LVFP compared to relying solely on E/e' ratio. We found similar results as well[12].

The observed NT-proBNP levels of 700.6 ± 12.5 pg/ml in the group with increased LVFP could be attributed to the physiological response of the heart to the elevated pressure. When the left ventricle faces increased pressure during diastole, such as in cases of impaired relaxation or increased stiffness of the ventricle, it can result in greater stretching of the cardiac muscle fibres. This stretching triggers the release of natriuretic peptides, including NT-proBNP, from the cardiac cells as a compensatory mechanism to regulate fluid volume and maintain cardiovascular homoeostasis[13]. Elevated NT-proBNP levels are indicative of the heart's attempt to counteract the increased pressure and strain on the ventricle by promoting diuresis and vasodilation[13,14]. Therefore, the recorded NT-proBNP levels in the group with increased LVFP can be seen as a reflection of the heart's response to the increased LVFP, serving as a diagnostic and prognostic marker for the underlying cardiovascular condition[13].

Pearson chi-square correlations were performed to assess the relationships between various variables and LVEDP levels in both groups. In Group 1, significant correlations were observed between age and Mitral E, age and LVEDP, Mitral E and Mitral E/A, and (E + PAP)/2 and age. In Group 2, significant correlations were found between Age and LVEDP, Mitral E and Mitral E/A, and Mitral E and Mitral E/Ea. Additionally, there was a significant negative correlation between Mitral E/Ea and (E + PAP)/2 in both groups.

A regression analysis was done to investigate the relationship between predictors and LVEDP on cardiac catheterization. The model accounted for a significant proportion of the variance in LVEDP, suggesting the presence of at least one significant predictor. Mitral E velocity was found to be a significant positive predictor of LVEDP, while Mitral E/A ratio exhibited a significant negative association. Other predictors, such as heart rate on echocardiography and LVDD, did not reach statistical significance. As per Ozer *et al.*[15], among the various echocardiographic parameters, both septal E/e' (≥ 15) and LAVi (≥ 34 ml/m^2) emerged as stronger indicators for predicting elevated LVEDP. Significant moderate positive associations were observed between LVEDP and septal E/e' as well as LAVI. Combining LAVI and septal E/e' proves to be valuable in identifying diastolic dysfunction. This is in line with our findings as well. Our findings also agree with the results of the Euro-Filling study[16] in which noninvasive assessment of LVFP was found to be reliable and clinically useful[16].

The practical implications of these findings in the field of cardiology are significant. Understanding the differences and correlations identified in this study helps clinicians in several ways when it comes to the condition being studied, which is elevated LVEDP. Firstly, the differences observed in variables such as heart rate, blood pressure, LVEDP, LV pre-A pressure, and B-type natriuretic peptide levels between Group 1 and Group 2 provide valuable insights into the severity of the cardiac condition associated with elevated LVEDP. Group 2, with higher values in these variables, indicates a more severe cardiac impairment in terms of hemodynamic parameters and biochemical markers. This understanding is crucial for risk stratification, treatment planning, and determining the appropriate level of intervention needed for patients with elevated LVEDP. Furthermore, the correlations between various variables and LVEDP offer valuable information on the interrelationships between different parameters in the context of this condition. For example, the significant correlations found between age and several variables in both groups highlight the impact of age on LVEDP and cardiac function. These correlations can assist in identifying additional risk factors and aid in individualized patient management. The regression analysis conducted to investigate the relationship between predictors and LVEDP provides insights into the specific parameters that influence LVEDP levels. The positive association between Mitral E velocity and LVEDP suggests that higher E velocity corresponds to increased LVFP, indicating impaired diastolic function. Conversely, the negative association between Mitral E/A ratio and LVEDP suggests that a higher E/A ratio is associated with lower LVFP, indicating better diastolic function. These findings contribute to a deeper understanding of the underlying pathophysiology of elevated LVEDP and guide clinicians in assessing diastolic dysfunction and its severity.

ROC curves were generated to assess the performance of three test result variables in predicting LVEDP greater than 20 mmHg. The variables (E + PAP)/2, (E + LAVi)/2, and Mitral E exhibited good discriminative ability, with AUC values of 0.840, 0.900, and 0.854, respectively. (E + LAVi)/2 demonstrated the highest discriminatory power. The study identified a threshold of 40.100 for (E + LAVi)/2, which yielded high sensitivity (0.971) but relatively low specificity (0.302) in predicting LVEDP greater than 20 mmHg. Cameli *et al.*[17] reported that among individuals with preserved or mildly reduced LVEF, both global longitudinal peak systolic strain and the average E/E' ratio exhibited strong associations with LVEDP. However, in patients with moderate or severe reduction in ejection fraction, the E/E' ratio demonstrated a weak correlation with invasively measured LV filling pressures. In this subgroup, global peak systolic strain offered a more accurate estimation of LV filling pressures overall. Although we did not do a subgroup analysis as Cameli *et al.*[17], we found analysis of our variables tending to show similar associations as well. A recent meta-analysis by Jones *et al.*[18] reported that Echocardiographic parameters exhibit a moderate collective correlation with invasively measured LVFP, although this association varies significantly depending on the underlying disease condition. In patients with HFpEF, none of the individual echocardiography-based metrics can reliably provide an accurate estimation of LVFP. However, in heart failure cases associated with reduced ejection fraction, metrics derived from mitral inflow analysis demonstrate reasonable clinical relevance for estimating LVFP. While adopting an integrated approach that combines multiple echocardiographic metrics holds the most potential for accurately estimating LVFP, these strategies require further validation through extensive studies involving larger patient cohorts. The validation process should encompass specific patient characteristics to ensure the reliability and applicability of these strategies in clinical practice[18]. In our study, we included participants with clinical indications for coronary angiography. Our

study is in agreement with the findings of the meta-analysis as multiple echocardiographic metrics had the most potential for accurately estimating LVFP, especially the added equation of mitral E velocity and LAVi. Sharifov *et al.*[19] analyzed and reported that the available evidence did not provide enough support to confidently assert that the E/e' ratio could reliably estimate LVFP in cases of preserved EF. We had similar findings in our study as well. Accurate analysis of LVEDP can be highly useful in assessment of volume status as well. For instance, a study by Santosa *et al.*[20] revealed LVEDP was reported to be a crucial measure for assessing cardiac function, but its direct measurement posed challenges and risks, similar to our study. As an alternative, correlates of LVEDP obtained through transesophageal echocardiography (TEE) or pulmonary artery catheterization were used. TEE is less invasive than other methods, but estimating LVEDP using TEE-based measures such as LVEDV has limitations. Santosa *et al.*[20] used a controlled haemorrhagic model. Mitral flow parameters and three-dimensional reconstructions of left atrial volume were examined as potential substitutes for LVEDP. The results showed that peak E wave velocity and LAEDV correlated with changes in intravascular volume. Their findings suggested the potential for using TEE, along with Doppler images of flow, to optimize intraoperative fluid management. In the study conducted by Iannaccone *et al.*[21], it was found that lower values of LA reservoir and pump strain had stronger predictive capability for LVEDP in the acute phase of Takotsubo syndrome compared to conventional echocardiographic parameters. Additionally, LA reservoir strain emerged as an independent predictor of unfavourable outcomes during hospitalization. This means that in some subsets of patients like those with Takotsubo syndrome, echocardiographic parameters, like the ones presented by us may not be that helpful in assessment of LVEDP.

In comparison to the study by Güvenç *et al.*[22], which focused on the estimation of LVEDP using parameters of pulmonary venous flow measured through transthoracic echocardiography, our study examined a broader range of cardiac dimensions, indices, and diastolic function parameters to assess cardiac abnormalities and LVEDP levels. We found that various cardiac dimensions and indices, including LVDD, LVMI, LAVi, RVDD, and RAVi, were significantly different between two groups. Similarly, several diastolic function parameters, such as Mitral E, Mitral A, Mitral E/A, Mitral deceleration time, and Pulmonary artery systolic pressure, were also significantly different between the groups. These findings indicate that our study provides a comprehensive assessment of cardiac structural and functional abnormalities, along with LVEDP estimation. Moreover, our study revealed significant differences in heart rate, blood pressure, LVEDP, and B-type natriuretic peptide levels between the two groups, which further substantiated the severity of cardiac conditions. In terms of correlations with LVEDP levels, our study identified age, Mitral E, Mitral E/A, and (E + PAP)/2 as significant factors in Group 1, and age, Mitral E, Mitral E/A, and Mitral E/Ea in Group 2. We also observed a negative correlation between Mitral E/Ea and (E + PAP)/2 in both groups. While Güven' *et al.*'s[22] study primarily focused on the use of pulmonary venous flow parameters and the ASE/EACVI algorithm to estimate LVEDP, our study expanded upon their findings by considering a broader range of cardiac parameters and exploring their correlations with LVEDP levels. Our results provide a more comprehensive understanding of cardiac abnormalities and LVEDP estimation in relation to various cardiac dimensions, indices, diastolic function parameters, and clinical variables.

In comparison to the study by Anthony *et al.*[23], which focused on the evaluation and diagnosis of diastolic dysfunction using non-invasive Doppler echocardiography techniques, our study primarily examined the relationship between various cardiac dimensions, indices, diastolic function parameters, and LVEDP levels. While Anthony *et al.*[23] highlighted the limitations of previous guidelines in terms of complexity, diagnostic performance, and interobserver variability, our study aimed to explore a wider range of cardiac parameters and their correlations with LVEDP, providing a more comprehensive understanding of cardiac abnormalities and LVEDP estimation. Additionally, our study expanded beyond the review of echo-derived Doppler parameters by considering a broader set of cardiac dimensions, indices, and clinical variables to assess the severity of cardiac conditions. By incorporating these parameters, we aimed to enhance the accuracy of estimating LVEDP and improve the overall diagnosis and gradation of diastolic dysfunction. While both studies focused on the non-invasive assessment of cardiac function, our study delved into a more comprehensive evaluation of cardiac abnormalities and their correlations with LVEDP, providing a deeper insight into the understanding of diastolic dysfunction and its clinical implications. In contrast to Matsushita *et al.*[24] study, our study focused on a broader range of cardiac dimensions, indices, diastolic function parameters, and LVEDP levels to assess patients with acute decompensated HF. In the study conducted by Matsushita *et al.*[24], the prognostic utility of lateral e' was compared to that of septal e' in patients hospitalized for acute decompensated HF. The data of 193 consecutive patients with acute decompensated HF were retrospectively analyzed. The findings revealed that lateral e'less than 10 was significantly correlated with higher 90-day mortality, whereas septal e'less than 7 did not show a significant association with 90-day mortality. Receiver operating characteristic curve analyses identified the optimal cut-off values for lateral e' and septal e' as 10 and 6 cm/s, respectively. However, even septal e'less than6 did not exhibit a significant association with 90-day mortality. The study concluded that lateral e' demonstrated better prognostic utility compared to septal e' in patients with acute decompensated HF. The results suggested that when a dissociation between lateral e' and septal e' is observed, the value measured at the lateral site may be more reliable for determining LVFP in HF. While Matsushita *et al.*[24] compared the prognostic utility of lateral e' and septal e' in relation to 90-day mortality, our study aimed to provide a more comprehensive understanding of cardiac abnormalities and their implications for patients.

Comparing the findings of Mele *et al.*'s[25] review with our own results, there are some similarities and differences. In our study, body surface area and the presence of comorbidities such as hypertension, diabetes, and hypercholesterolaemia did not show significant differences between the groups based on LVEDP levels, which aligns with Mele *et al.*'s[25] emphasis on the limitations of classifying HF patients solely based on these factors. However, Mele *et al.*[25] focused on the feasibility and reliability of echocardiographic techniques for assessing LV hemodynamics, whereas our study examined various cardiac dimensions, indices, and diastolic function parameters to differentiate between the two groups. We found significant differences in these parameters, indicating more severe cardiac structural and functional abnormalities in Group 2 compared to Group 1, which

supports the need for a more comprehensive hemodynamic categorization.

In the study by Jentzer *et al.*[26], which focused on ICU patients, the researchers investigated the relationship between left ventricular stroke work index (LVSWI) measured by transthoracic echocardiography and mortality risk stratification based on the Society for Cardiovascular Angiography and Intervention (SCAI) shock classification[26]. They found that LVSWI progressively decreased with increasing shock severity, as defined by the SCAI shock stage[26]. Furthermore, lower LVSWI and higher SCAI shock stage were associated with higher in-hospital mortality[26]. The study suggested that LVSWI measured by transthoracic echocardiography could noninvasively characterize the severity of shock and identify low-risk and high-risk patients at each level of clinical shock severity[26].

In comparison, our study did not specifically focus on ICU patients or the SCAI shock classification. However, we observed significant differences in echocardiographic measurements related to cardiac structure, function, and hemodynamics based on LVEDP levels. These findings suggest the presence of cardiac abnormalities in the group with higher LVEDP. Although the contexts and objectives of the two studies differ, both studies highlight the potential value of echocardiographic measurements in assessing cardiac function and hemodynamics. Therefore, echocardiographic techniques, including LVSWI and other relevant parameters, may hold promise in evaluating and managing critically ill patients in ICU settings. Further research is needed to explore the specific applications and predictive capabilities of echocardiography in ICU patient populations.

In comparison to the study by Dini *et al.*[27], our study focused on a different patient population and objective. However, there are notable similarities and differences between the findings. In Group 1 of our study, we observed significant correlations between age and Mitral E, age and LVEDP, Mitral E and Mitral E/A, and (E + PAP)/2 and age. These findings align with the emphasis on age-related associations found in Dini's study[27], where age was also correlated with Mitral E and Mitral E/A in both Group 1 and Group 2. Additionally, Dini *et al.*[27] reported the association between Mitral E and Mitral E/Ea, which we also found significant in Group 2. Moreover, both studies identified the importance of echocardiographic parameters in predicting LVFP. In our regression analysis, Mitral E velocity emerged as a significant positive predictor of LVEDP, consistent with Dini *et al.*'s findings of E/e' ratio as a significant predictor of elevated LVFP[27]. The practical implications of these findings in the field of cardiology are significant. Understanding the differences and correlations identified in this study provides valuable insights into the condition being studied, which is elevated LVEDP. The ROC curves generated in this study indicate that variables such as (E + PAP)/2, (E + LAVi)/2, and Mitral E have good discriminative ability in predicting LVEDP levels. These findings have practical implications in clinical settings as they suggest that these variables can serve as useful markers in assessing and predicting elevated LVEDP. The correlations observed between various variables and LVEDP further enhance our understanding of the condition. For example, the correlations between age and various parameters suggest that age plays a role in the development and severity of elevated LVEDP. These correlations can guide clinicians in risk stratification and tailoring treatment strategies based on individual patient characteristics. The regression analysis conducted in this study helps identify significant predictors of LVEDP. The positive association between Mitral E velocity and LVEDP, along with the negative association between Mitral E/A ratio and LVEDP, provides insights into the hemodynamic status of the heart. These findings aid in the assessment of diastolic function and can guide treatment decisions for patients with elevated LVEDP.

The study's findings indicate that age, sex, cardiac dimensions, indices, diastolic function parameters, hemodynamic variables, and certain echocardiographic variables are associated with LVEDP levels. The results provide insights into potential relationships between these variables and left ventricular function, highlighting the importance of considering these factors when assessing cardiac health.

Limitations

The study's findings on the prediction of LVFP in HFpEF using novel echocardiographic markers should be interpreted in light of certain limitations. The small sample size, cross-sectional design, potential biases, confounding factors, and measurement limitations may affect the validity and generalizability of the results. A larger sample size and longitudinal design would have enhanced the statistical power and ability to establish causal relationships. Selection bias and unmeasured confounders may have influenced the findings, and the reliance on echocardiographic techniques introduces measurement errors. The generalizability of the findings to other populations or settings should be considered cautiously. Further studies addressing these limitations are needed to validate and extend the current findings.

Conclusion

Our study's findings have important implications for patient management and diagnostic approaches in the field of cardiology. The identified differences, correlations, and predictors of LVFP provide valuable insights into cardiac structural, functional, and hemodynamic abnormalities. The significant utility of combining diastolic variables and peak E velocity as markers for LVFP highlights their importance in assessing cardiac health. The promising performance of novel echocardiographic parameters, particularly (E + LAVi)/2, in predicting elevated LVEDP suggests their potential for clinical use. However, further research is needed to validate these findings in larger patient populations and explore their prognostic implications. Incorporating these parameters into routine clinical practice has the potential to enhance diagnostic accuracy and improve patient outcomes in heart failure patients.

Ethics approval and consent to participate

Written informed consent was obtained from all study participants prior to enrolment in study.

Consent

Not applicable.

Sources of funding

Not applicable.

Author contribution

All authors contributed significantly to the study. All authors contributed to conceptualization of the research design and methodology, collection and compilation of the data, statistical analysis, interpretation of the results and drafting of the manuscript. All authors critically reviewed and provided intellectual input throughout the manuscript preparation. All authors approved the final version of the manuscript for submission.

Conflicts of interest disclosure

There are no conflicts of interest.

Research registration unique identifying number (UIN)

This study has been registered in Research Registry with UIN = researchregistry9081. The registration can be accessed online from: https://www.researchregistry.com/browse-the-registry#home/registrationdetails/6470b24f551de60027fefe06/.

Guarantor

Hassan Mumtaz.

Availability of data and materials

Deidentified data are available from the corresponding author upon reasonable request.

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