RESEARCH ARTICLE

DOI: 10.4274/ijca.2025.78309
Int J Cardiovasc Acad

Biomarkers in the Pathogenesis of Heart Failure with Preserved as Well as Reduced Ejection Fraction- A Cross-sectional Study

Sowmiya Thiyagarajan[1], Jasmine Chandra A[1], Karthikeyan Rajamani[2], Santhi Silambanan[1]

[1]Department of Biochemistry, Sri Ramachandra Institute of Higher Education and Research, Chennai, India
[2]Department of Public Health, Sri Ramachandra Institute of Higher Education and Research, Chennai, India

Abstract

Background and Aim: Heart failure (HF) is a multifaceted cardiovascular condition characterized by various pathophysiological mechanisms that lead to impaired ventricular structure or function. Diagnosing HF with preserved ejection fraction (HFpEF) and reduced EF (HFrEF) presents significant challenges due to overlapping symptoms and distinct underlying causes. This study aimed to investigate metabolic and inflammatory markers in patients with HFrEF and HFpEF.

Materials and Methods: The study included 80 HF patients, comprising HFpEF (n=40) and HFrEF (n=40), aged 30-90 years, of both genders. Participants were recruited from the Department of Cardiology at a tertiary care hospital. Blood samples were collected to analyze biomarker levels and statistical analysis was conducted considering a *P*-value of ≤0.05 as statistically significant.

Results: Patients with HFpEF had lower levels of total cholesterol, plasma glucose, glycated hemoglobin, N-terminal pro brain natriuretic peptide (NT-proBNP), and high sensitivity C-reactive protein (hsCRP), compared to those with HFrEF. There were significant differences in echocardiography variables when compared among the groups. hsCRP showed a cut-off value of 3.15 mg/L, whereas NT-proBNP showed 437.8 pg/mL.

Conclusion: The study identified notable differences in metabolic and inflammatory marker profiles between HFpEF and HFrEF patients. HFpEF was associated with less severe dyslipidemia and inflammation, as indicated by lipid profiles, NT-proBNP and hsCRP levels, compared to HFrEF. Understanding these biomarker variations may aid in developing personalized treatment strategies and enhancing patient care.

Keywords: Heart failure, reduced ejection fraction, preserved ejection fraction, biomarkers, inflammation.

INTRODUCTION

Heart failure (HF) is a multifaceted cardiovascular disorder in which there is impairment of blood supply to various organs of the body, leading to multiorgan dysfunction. It is a major global health concern, affecting millions of individuals and contributing to rising morbidity, mortality, and healthcare costs associated with its diagnosis and treatment.[1,2] In 2017, it was found that 64.3 million are suffer from HF globally.[3] In Asia, the prevalence of HF is 1.3-6.7%. In China, the prevalence is 1.3%, which amounts to 4.2 million.[4] Other Asian countries also report varying prevalence rates: Hong Kong (2-3%), the Philippines (1-2%), Indonesia (5%), Taiwan (6%), South Korea (0.6%), Japan (1%), and Thailand (0.4%). In Southeast Asia, approximately nine million people are affected, with prevalence rates of 6.7% in Malaysia and 4.5% in Singapore.[5]

To cite this article: Thiyagarajan S, Chandra A, Rajamani K, Silambanan S. Biomarkers in the pathogenesis of heart failure with preserved as well as reduced ejection fraction- a cross-sectional study. Int J Cardiovasc Acad. [Epub Ahead of Print]

Address for Correspondence: Santhi Silambanan, Department of Biochemistry, Sri Ramachandra Institute of Higher Education and Research, Chennai, India
E-mail: santhisilambanan@gmail.com
ORCID ID: orcid.org/0000-0001-8908-9432

Received: 11.03.2025
Accepted: 14.05.2025
Epub: 02.06.2025

India has reported a significant increase in HF prevalence, affecting between eight and ten million people. Unlike Western countries, where HF primarily affects the elderly, in India, it tends to impact younger individuals. States such as Punjab, Tamil Nadu, and Haryana report the highest HF cases. Since 1990, India's HF burden has increased by 104%, contributing to 17.8% of deaths in 2016.[6,7] In rural areas, HF prevalence is estimated at 1.2 cases per 1,000 people, with cardiovascular diseases (CVD) being less common compared to urban regions.[8]

HF is grouped into HF with preserved ejection fraction (HFpEF) and HF with reduced EF (HFrEF), and they have distinct pathophysiology, comorbidities, and treatment responses. In HFrEF, EF is less than 49% and is often linked to ischemic heart disease, leading to systolic dysfunction. Symptoms include reduced cardiac output, fatigue, shortness of breath, and fluid retention. Effective management includes various medications involving the renin-angiotensin-aldosterone system, beta-blockers, and diuretics.[8-10]

HFpEF, on the other hand, is defined by an EF of more than 50%, indicating normal heart contraction but impaired left ventricular relaxation and increased stiffness. This form of HF is primarily associated with dysfunction in left ventricular filling and with obesity, diabetes, hypertension, and dyslipidemia, among others In addition, high-sensitivity C-reactive protein (hsCRP), a general inflammatory marker, plays a significant role in CVDs hsCRP plays a major role in the adverse prognosis of HF, altered endothelial function, arrhythmias, cardiorenal syndrome and increased morbidity and mortality.[11] hsCRP levels of more than 2 mg/L are found to predict an increased risk of HF with preserved EF and a worse prognosis and poor cardiovascular outcomes.[12] N-terminal pro brain natriuretic peptide (NT-proBNP) levels and echocardiography (ECHO) are the guideline diagnostic indicators of HF. There is a significant association between NT-proBNP and diastolic dysfunction.[13]

Managing HFpEF poses a greater challenge than HFrEF, as conventional HF medications often fail to provide the same therapeutic benefits.[14,15] The distinct pathophysiology and treatment approaches for these HF subtypes highlight the importance of understanding their metabolic and inflammatory differences. This study was conducted to investigate metabolic and inflammatory markers in HFrEF and HFpEF patients.

METHODS

HF patients were enrolled from the Department of Cardiology, and further analyses were carried out in the Department of Biochemistry at Sri Ramachandra Institute. This study was carried out on a subsample of a larger study. Part of the larger study which has been previously published.[16] Approval was obtained from the institutional ethics committee (approval number: IEC-NI/19/FEB/68/09, date:10.11.2020). The participants provided voluntary written informed consent at the time of induction into the study.

The study was carried out during the coronavirus disease-2019 (COVID-19) pandemic. Only patients with HF were seeking medical advice at the hospital. Apparently healthy individuals who could serve as controls were not attending the hospital. Hence, the study did not consist of a control group.

Based on the study "DuBrock HM, AbouEzzeddine OF, Redfield MM (2018) hsCRP in HF with preserved EF. PLoS ONE 13(8): e0201836", sample size was calculated.

$\alpha = 0.05$

Power = 80%

$\sigma = 2.0$

$\Delta = 1.5$

The calculated sample size was 28, which was increased to 80.

Study Design

Cross-sectional study.

Study Participants

Patients with HFpEF (EF ≥50%) (n=40)

Patients with HFrEF (EF ≤49%) (n=40)

Inclusion Criteria

Individuals aged 30 to 90 years of both genders, diagnosed with HF based on the Framingham Heart Failure Diagnostic Criteria.

Exclusion Criteria

Patients with a history of acute HF in the past three months or acute myocardial infarction within the last six weeks.

Individuals with thyroid, lung, renal, or liver disorders, cancer, systemic infectious diseases, or connective tissue disorders.

Participants currently taking anticancer medications, steroids, anabolic steroids, or oral contraceptive pills.

Sample Collection and Biomarker Analysis

The study participants were subjected to transthoracic 2D Doppler ECHO. Venous samples were collected from the individuals, and the separated serum was aliquoted and stored at -80 °C for testing. The following biomarkers were measured using specific methods: total cholesterol (TC) was analyzed by cholesterol oxidase-peroxidase, triglyceride (TGL) by glycerol phosphate oxidase-peroxidase, high density lipoprotein (HDL) by polymer-polyanion, low density cholesterol (LDL) by direct

enzymatic method, blood urea nitrogen (BUN) by ultraviolet/urease-glutamate dehydrogenase, creatinine by Jaffe's, glucose by hexokinase, and glycated hemoglobin (HbA1c) by ion-exchange chromatography. hsCRP and NT-proBNP were measured by the enzyme-linked immunosorbent assay method.

Statistical Analysis

Statistical analysis was performed in SPSS software version 16. The Kolmogorov-Smirnov test was performed to assess the normality of data distribution. Results were expressed as means and standard deviations. The Student's t-test and Mann-Whitney U test were used to compare the continuous variables. Categorical variables were compared using the chi-square test or Fisher exact test. The variables were subjected to correlation analysis using either Pearson's or the Spearman Correlation test. Additionally, the receiver operating characteristic (ROC) curve was conducted to determine the cut-off value, area under the curve (AUC), 95% confidence interval, *P*-value, sensitivity, and specificity for hsCRP and NT-proBNP. A *P*-value of ≤0.05 was considered statistically significant.

Results

Table 1 illustrates the age distribution among HFpEF and HFrEF patients. Of the 80 participants, 25% were under 50 years old, with a higher proportion in the HFpEF group (40%) while the HFrEF group had 10%. In the 51-70 age range, which comprised 58.75% of the total study population, HFrEF patients were more prevalent (65%) than HFpEF patients (52.5%). Among those aged 71-90 years (16.25% of participants), 7.5% were HFpEF patients, whereas 25% were HFrEF patients.

Chi-square test analysis revealed a significant difference in age distribution between the two groups ($P = 0.01$), indicating that age is a key distinguishing factor between HFpEF and HFrEF. The age distribution of study participants is also represented in a bar diagram (Figure 1).

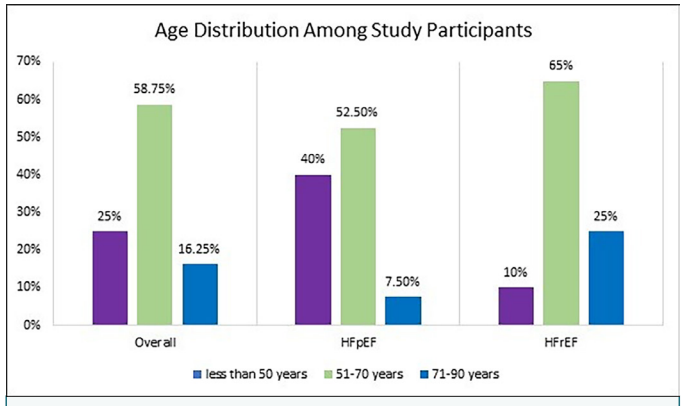

Figure 1: Bar diagram shows the age distribution among HFpEF and HFrEF patients

HFpEF: Heart failure with preserved ejection fraction, HFrEF: Heart failure with reduced ejection fraction

Table 1: Demographic details of the participants

Variables	Total (n=80)	HFpEF (n=40)	HFrEF (n=40)	*P*-value
Age (years)	58.93 (12.29)	53.17 (11.25)	64.68 (10.57)	<0.001**
Age distribution among participants (n/%)@				
<50	20 (25%)	16 (40%)	4 (10%)	0.003**
51-70	47 (58.75%)	21 (52.5%)	26 (65%)	
71-90	13 (16.25%)	3 (7.5%)	10 (25%)	
Gender distribution among participants (n/%)@				
Female	28 (35%)	13 (32.5%)	15 (37.5%)	0.007**
Male	52 (65%)	27 (67.5%)	25 (62.5%)	
Height (m)	1.60 (0.06)	1.59 (0.06)	1.60 (0.06)	0.45
Weight (kg)	65.99 (9.40)	66.23 (8.99)	65.75 (9.90)	0.82
BMI (kg/m²)	25.95 (3.79)	26.08 (3.64)	25.8 (4.0)	0.74
Waist (in)	36.46 (5.52)	37.47 (5.33)	35.45 (5.6)	0.1
Hip (in)	38.81 (5.13)	39.42 (5.25)	38.20 (5.00)	0.29
WHR	0.95 (0.04)	0.95 (0.03)	0.94 (0.05)	0.28
NYHAFC (n)#	I-38, II-2, III-17, IV-23	I-38, II-2	III-17, IV-23	<0.001**

P-value: *: Significant, **: Highly significant

Classification expressed as mean and SD. @Expressed frequency and percentage. #Epressed as frequency Student's t-test was used. @Chi-Square test was used. #Fischer's exact test used.

HFpEF: Heart failure with preserved ejection fraction, HFrEF: Heart failure with reduced ejection fraction, BMI: Body mass index, WHR: Waist hip ratio, NYHAFC: New York Heart Association Functional Classification

Of the 80 patients, 35% were female, with 32.5% in the HFpEF group and 37.5% in the HFrEF group. In contrast, 65% of the total participants were male, comprising 67.5% of HFpEF patients, and 62.5% of HFrEF patients. Statistical analysis using the chi-square test revealed a significant difference in gender distribution between the two groups ($P = 0.01$). The gender distribution of study participants is also illustrated in a bar diagram (Figure 2). Among patients with HFpEF, 38 belonged to class I, while 2 belonged to class II. Among HFrEF patients, 17 were in class III and 23 were in class IV according to New York Heart Association Functional Classification (NYHAFC).

ECHO showed measurements at the level of the left ventricle (LV) and the aortic valve to assess aortic root diameter, left atrial (LA) diameter, LA volume, fractional shortening (FS%), LV internal diameter at end diastole (LVIDd) and LVIDs cavity diameters, LV posterior wall diameter in diastole (LVPWd) and LVPW thickness in systole (LVPWs) diameters, diastolic IV septum diameter (IVSd), IV septum diameter systolic (IVSs), LV mass, LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), EF, and stroke volume (SV). Among the ECHO variables, EF, LVIDs, LVIDd, IVSs, IVSd, LVPWs, LVPWd, LVESV, LVEDV, SV, FS, LA, LV early diastole filling (E-wave), left ventricular late diastole caused by atrial contraction (A-wave) and E/A ratio were statistically significant between the groups. (Table 2)

Table 3 presents the levels of metabolic and inflammatory biomarkers in HFpEF and HFrEF patients. TC levels were significantly lower in HFpEF patients compared to those with HFrEF ($P = 0.01$). Similarly, fasting plasma glucose (FPG), postprandial PG (PPPG), HbA1c, BUN, creatinine, hsCRP, and NT-proBNP showed significant differences between the groups. HFpEF patients exhibited lower levels of FPG, PPPG, HbA1c, BUN, creatinine, hsCRP, and NT-proBNP compared to HFrEF

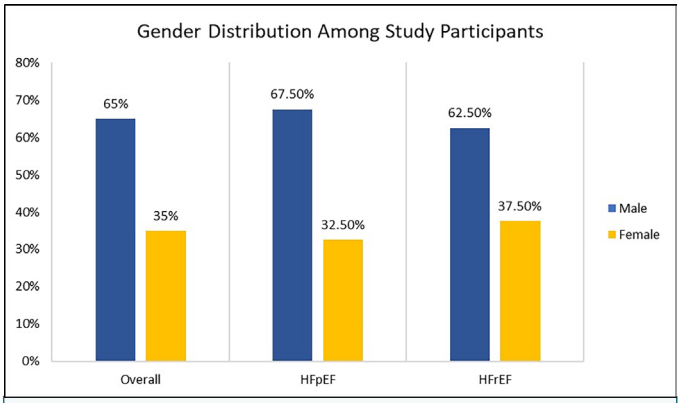

Figure 2: Gender distribution among HFpEF and HFrEF patients

HFpEF: Heart failure with preserved ejection fraction, HFrEF: Heart failure with reduced ejection fraction

Table 2: Echocardiography findings in the study participants

Variables	Total (n=80)	HFpEF (n=40)	HFrEF (n=40)	*P*-value
EF (%)	47.98 (15.27)	61.80 (2.40)	34.15 (8.63)	<0.001**
LVIDs (cm)	38.10 (6.39)	34.33 (3.31)	41.88 (6.52)	<0.001**
LVIDd (cm)	48.89 (5.97)	45.13 (2.17)	52.65 (6.19)	<0.001**
IVSs (cm)	10.43 (3.03)	11.80 (2.95)	9.05 (2.43)	<0.001**
IVSd (cm)	11.55 (2.88)	12.8 (2.84)	10.3 (2.35)	<0.001**
LVPWs (cm)	11.33 (2.78)	12.6 (2.62)	10.05 (2.34)	<0.001**
LVPWd (cm)	12.39 (2.71)	13.63 (2.63)	11.15 (2.19)	<0.001**
LVESV (mL)	58.56 (28.06)	34.65 (3.42)	82.48 (20.25)	<0.001**
LVEDV (mL)	109.19 (25.99)	88.20 (7.88)	130.2 (20.06)	<0.001**
SV (mL)	49.64 (8.06)	53.25 (3.3)	46.02 (9.68)	<0.001**
FS (%)	24.50 (7.71)	31.08 (1.83)	17.92 (5.31)	<0.001**
AO (mm)	29.08 (1.53)	28.93 (0.86)	29.22 (1.99)	0.4
LA (mL)	35.83 (5.97)	33.18 (3.88)	38.47 (6.53)	<0.001**
E-wave velocity (m/s)#	0.7 (0.6-0.9)	0.7 (0.6-0.8)	0.8 (0.65-0.9)	0.04*
A- wave velocity (m/s) #	0.7 (0.5-0.85)	0.8 (0.6-0.9)	0.6 (0.4-0.8)	0.006**
E/A ratio #	1.13 (0.75-1.5)	0.88 (0.73-1.26)	1.33 (0.81-2.12)	0.01*

P-value: *: Significant, **: Highly significant

Expressed as mean and SD. #Expressed as median and interquartile range Student's t-test was used. #Mann-Whitney U test used.

EF: Ejection fraction, LVIDs: Left ventricular internal diameter at end systole, LVIDd: Left ventricular internal diameter at end diastole, IVSs: Interventricular septum thickness in systole, IVSd: Interventricular septum thickness in diastole, LVPWs: Left ventricular posterior wall in systole, LVPWd: Left ventricular posterior wall in diastole, LVESV: Left ventricular end-systolic volume, LVEDV: Left ventricular end diastolic volume, SV: Stroke volume, FS: Fractional shortening, AO: Aortic annulus, LA: Left atrial volume, E-wave: left ventricular early diastole filling, A-wave: left ventricular late diastole caused by atrial contraction

patients as indicated by statistically significant *P*-values. In contrast, hemoglobin (Hb) levels were higher in HFpEF patients than in HFrEF patients.

DISCUSSION

HF is a multiorgan debilitating disorder, precipitated by the inability of the heart to cope with the routine functioning, both at rest and during physical activity. Common clinical features include dyspnea, fatigue, and pulmonary edema.[17] HF arises from various cardiac and non-cardiac conditions that impair heart structure and function resulting in cardiac dysfunction. Common cardiac causes include acute myocardial infarction, myocarditis, aortic stenosis, hypertension, valvular regurgitation, and genetic cardiomyopathy.[18]

According to the World Health Organization, India significantly contributes to global CVD-related deaths, accounting for one-fifth of worldwide fatalities, particularly among younger individuals. The Global Burden of Disease study reports that India's mortality rate due to CVD stands at 272 per 100,000 individuals, exceeding the global average of 235 per 100,000. Furthermore, mortality from coronary artery disease (CAD) among Asians is 20-50% higher than other demographic groups.[19]

The age distribution of study participants revealed distinct trends in HFpEF and HFrEF prevalence. Most of the participants were in the 51-70 years age group (58.75%), followed by those under 50 years (25%) and those aged 71-90 years (16.25%). Among individuals aged 51-70 years, 52.5% of HFpEF cases and 65% of HFrEF cases were observed, suggesting that HF predominantly affects individuals between 50 and 75 years. (Table 1, Figure 1). Although clinical symptoms may manifest earlier, they tend to significantly impact daily life as age advances. The lower prevalence of HF in individuals over 75 years may be attributed to increased mortality or a reluctance to seek medical care.

There was a statistically significant difference in age distribution between HFpEF and HFrEF patients ($P = 0.01$), emphasizing that both conditions are more prevalent among older adults, particularly those aged 51-70 years. Notably, 40% of HFpEF patients were under 50 years old, whereas only 10% of HFrEF patients belonged to this younger age group, suggesting that HFpEF may have an earlier onset compared to HFrEF. In contrast, among the oldest age group (71-90 years), HFrEF was more prevalent (25%) compared to HFpEF (7.5%), indicating that reduced EF becomes more common in the elderly. These findings indicate that age is an important determinant in the diagnostic workup and further treatment of HF.

The significant differences in HFpEF and HFrEF prevalence across age groups suggest that age-specific management strategies may be necessary, particularly for middle-aged and older adults, who make-up the majority of HF patients. Additionally, the earlier onset of HFpEF in younger individuals underscores the importance of early intervention and preventive measures in high-risk populations to slow disease progression. The increasing prevalence of HF with age is attributed to prolonged exposure to deleterious effects of metabolic and inflammatory insults. Consequently, older individuals tend to have greater impairment in cardiac reserve and an elevated risk of HF due to the cumulative effects of these risk factors.[20]

Table 3: Metabolic and inflammatory biomarkers levels in HFpEF and HFrEF patients

Variables	Total (n=80)	HFpEF (n=40)	HFrEF (n=40)	*P*-value
TC (mg/dL)	203.37 (47.38)	190.08 (38.99)	216.67 (51.61)	0.005**
TGL (mg/dL)	152.76 (62.68)	144.20 (60.16)	161.32 (64.72)	0.112
HDL (mg/dL)	43.33 (11.44)	42.68 (8.50)	44 (13.86)	0.303
LDL (mg/dL)	128.7 (39.75)	124.85 (32.72)	132.55 (45.82)	0.194
FPG (mg/dL)	116.26 (44.99)	107.34 (14.87)	140.5 (80.29)	0.008**
PPPG (mg/dL)	158.01 (73.99)	116.29 (25.11)	188.36 (82.89)	<0.001**
HbA1C (%)	6.95 (2.11)	5.80 (0.53)	8.11 (2.46)	<0.001**
BUN (mg/dL)	12.8 (6.98)	10.43 (2.88)	15.17 (8.88)	<0.001**
Creatinine (mg/dL)	0.95 (0.38)	0.88 (0.26)	1.03 (0.46)	0.03*
Hb (g/dL)	12.79 (2.07)	13.30 (1.87)	12.29 (2.15)	0.01*
hsCRP (mg/L)	3.50 (1.59)	2.28 (1.07)	4.72 (0.97)	<0.001**
NT-proBNP (pg/mL)	394.02 (134.25)	287.27 (103.18)	500.80 (49.91)	<0.001**

Expressed in mean and SD. Student's t-test was used. P-value: *: Significant; **: Highly signific

TC: Total Cholesterol, TGL: Triglycerides, HDL: High density lipoprotein, LDL: Low density lipoprotein, FPG: Fasting plasma glucose, PPPG: Postprandial plasma glucose, HbA1c: Glycated hemoglobin, BUN: Blood urea nitrogen, Hb: Hemoglobin, hsCRP: High sensitivity C-reactive protein, NT-proBNP: N-terminal-pro brain natriuretic peptide

In India, HF manifests at a younger age compared to Western populations. For instance, HF patients in the Thai Heart Failure Registry (THFR) and International Congestive HF (Indian subset) studies had a median age of 61.2 years and 56 years, respectively. The male-to-female gender distribution (70:30, according to the THFR) also differs from that in the USA and Africa (approximately 50:50). This discrepancy may be partly explained by the fact that, unlike in Western countries, men in India are more likely to seek healthcare compared to women. Additionally, risk factor prevalence varies between India and the West, with diabetes mellitus being significantly more common among Indians, as reported in the THFR data.[21-23]

In the present study, gender distribution indicated that 65% of HF patients were males, and 35% were women. When comparing HF subtypes, females accounted for 32.5% of the HFpEF group and 37.5% of the HFrEF group, while males comprised 67.5% and 62.5% of these groups, respectively ($P = 0.01$) (Table 1, Figure 2). Traditionally, HF has been more prevalent in men due to their higher risk of CAD; however, women tend to develop HF more frequently at an advanced age. In this study, the proportion of patients in the HFrEF group was women; women in general have a longer survival rate and a lesser chance of sudden death compared to men.

The underlying causes of HF also vary by gender. In men, CAD is the underlying etiology, whereas in women, uncontrolled diabetes and hypertension play more significant roles. Notably, type 2 diabetes mellitus increases the risk for women with HFpEF compared to men.[24] Women also tend to have stiffer and smaller LVs with higher EFs than men. This increased stiffness may result from greater fibrosis, particularly as they age. Estrogen has an effect on collagen synthesis; in women, there is decreased formation. On the contrary, there is increased collagen production and further damaging effects on the heart. Furthermore, under stressful conditions, energy metabolism is maintained in women's hearts more effectively compared to male hearts, thus contributing to sex-based differences in HF progression and outcomes.[25]

When the study participants were classified according to the NYHAFC, among HFpEF, 38 patients belonged to class I, while 2 belonged to class II. Seventeen participants among those with HFrEF were in class III, while 23 were in class IV. NYHAFC is used to assess the functional capacity of HF patients (Table 1). NYHAFC came into existence in 1921, and has undergone remarkable change from an assessment of symptoms during activity to being used as a benchmark inclusion criterion in contemporary HF clinical trials. Thus, the treatment recommendations are mainly based on the NYHAFC.[26]

Among the ECHO variables EF, LVIDs, LVIDd, IVSs, IVSd, LVPWs, LVPWd, LVESV, LVEDV, SV, FS, LA, E-wave, A-wave and E/A ratio were statistically significant between the groups. (Table 2) ECHO is a fundamental diagnostic tool used to detect early cardiac dysfunction and offers vital support and management for cardiovascular patients.[27] Two-dimensional assessments of LV cavity diameter, wall thickness, and mass are performed according to the criteria of the American Society of ECHO and the European Association of Cardiovascular Imaging.[28] Thus, there were structural and functional alterations in ECHO parameters.

The variations in biomarker levels observed in this study highlight the distinct pathophysiological mechanisms underlying HFpEF and HFrEF, which have important implications for diagnosis, treatment, and prognosis. A significant difference in TC levels was observed, with HFrEF patients exhibiting higher levels than HFpEF patients ($P = 0.01$) (Table 3). This finding suggests that dyslipidemia may be more pronounced in HFrEF, potentially accelerating the progression of CAD, a major contributor to HFrEF. Although TGL and LDL levels were also higher in the HFrEF group, these differences were not statistically significant. HDL levels were nearly identical in both groups. Dyslipidemia is a well-recognized modifiable risk factor for CVD, with elevated LDL and reduced HDL levels being associated with impaired cardiac function. Inflammation linked to dyslipidemia further exacerbates HF progression.[29]

HFrEF patients exhibited significantly higher levels of FPG ($P = 0.01$), PPPG ($P = 0.001$), and HbA1c ($P = 0.001$) compared to HFpEF patients (Table 3). This suggests that poor glycemic control is more prevalent among HFrEF patients, reinforcing the strong link between diabetes and HFrEF. These findings emphasize the importance of blood glucose management in HFrEF patients to potentially slow HF progression. In diabetes mellitus, lipid accumulation, including TGL, ceramides, and diacylglycerols, within the myocardium contributes to cardiac dysfunction.[30] Diabetes also impairs cellular glucose uptake, increases serum glucose concentrations, and disrupts mitochondrial oxidative phosphorylation, resulting in a toxic environment that damages myocardial cells and alters cardiac relaxation patterns, which are characteristic of HFpEF.[31,32]

Additionally, BUN ($P = 0.001$) and creatinine ($P = 0.03$) levels were significantly higher in HFrEF patients compared to HFpEF patients (Table 3), indicating more severe renal impairment in HFrEF. Renal dysfunction is a well-established predictor of poor HF outcomes, highlighting the need for vigilant renal function monitoring in HFrEF patients. BUN, which reflects renal perfusion changes, serves as a more accurate marker of HF progression than creatinine. Notably, for every 10 mg/dL increase in BUN, HF mortality risk rises by 21%.[33] HFrEF patients also had significantly lower Hb levels than HFpEF patients ($P = 0.01$), indicating a higher prevalence of anemia in HFrEF. Anemia is a common comorbidity in HF and is linked

to worse clinical outcomes. Its precise etiology in HF remains unclear, but is considered multifactorial, with iron deficiency anemia and inflammation playing major roles.[34]

hsCRP, a key inflammatory biomarker, was significantly elevated in HFrEF patients compared to HFpEF patients (P = 0.001) (Table 3). CRP is synthesized in the liver in response to inflammation via IL-1/IL-6 pathway activation; it is a commonly used clinical marker. HF patients frequently exhibit increased hsCRP levels, particularly during acute exacerbations, reflecting systemic inflammation.[35] Chronic inflammation contributes to endothelial dysfunction, activation of the renin-angiotensin and sympathetic nervous systems, reduced myocardial contractility, and interstitial fibrosis, all of which promote HF progression. While hsCRP levels typically decline following HF stabilization, they remain elevated compared to the general population, underscoring the chronic inflammatory nature of HF.[36] Figure 3 and Table 4 illustrate the ROC curve for hsCRP, showing a strong predictive value with an AUC of 0.946 (95% confidence interval: 0.890-0.994). The optimal cut-off value for hsCRP was determined to be 3.157 mg/L, with a sensitivity of 100% and specificity of 85% ($P < 0.001$). Patients with hsCRP ≥2 mg/L experience frequent HF hospitalizations, poorer health-related quality of life, and increased mortality risk.[12] Elevated hsCRP at the time of risk assessment correlates with a worse prognosis in HF patients.[35] Rather than being a static marker, hsCRP fluctuates over time, acting as a dynamic risk indicator. Recent studies suggest that cumulative hsCRP burden is a stronger predictor of new-onset HF than a single baseline measurement.[37]

The mean NT-proBNP levels in HFpEF and HFrEF were 287.27 and 500.80 pg/mL, which was statistically significant ($P < 0.001$). (Table 2) The cut-off level of NT-proBNP was 437.8 pg/mL with an AUC) of 0.995; sensitivity and specificity were 100% and 97%, respectively (Table 4, Figure 3). HFpEF is a common condition due to its prevalence in an ageing western population. HFpEF is associated with significant morbidity and mortality and has outcomes similar to HFrEF. NT-proBNP levels and ECHO are used as the guidelines diagnostic indicators of HF. The National Institute for Health and Care Excellence and European guidelines recommend a single NT-proBNP threshold of >400 ng/L and >125 ng/L, respectively, to use ECHO assessment of HF in the outpatient setting. A significant relationship between NT-proBNP levels and diastolic dysfunction has been established. NT-proBNP has a high negative predictive value, which increases its use in clinical medicine.[13]

EF, LVID, IVS, LVPW, EDV, ESV, FS, and LA showed correlation with other ECHO parameters in both groups. (Table 5) hsCRP showed correlation with NT-proBNP and ECHO parameters such as EF, LVID, IVS, LVPW, EDV, FS and E-wave, which were statistically significant. Even though NT-proBNP is a gold standard marker of HF, it showed correlation only with a few ECHO parameters, such as LVID, EDV, ESV, FS and LA. (Table 6) Even though NT-proBNP performed well in the ROC curve, the correlation of hsCRP with ECHO variables was better than that of NT-proBNP. ECHO combined with NT-pro BNP had higher accuracy in NYHAFC class and prognostic assessment of Diastolic HF than the separate applications of ECHO and NT-proBNP.[38] High hsCRP during hospital admission may help identify patients with a higher morbidity risk in the long-term follow-up. In many studies, an elevated hsCRP (>2 mg/L) is one the key inclusion criteria. Thus, hsCRP may aid in risk stratification in HF and identify patients with an inflammatory phenotype who may benefit from specific anti-inflammatory therapies.[39]

These biochemical variations between HFpEF and HFrEF emphasize the need for a distinct management approach for each HF subtype. The elevated levels of glucose, lipids, renal markers, and inflammatory biomarkers in HFrEF patients indicate a more advanced disease state that may necessitate aggressive treatment strategies.

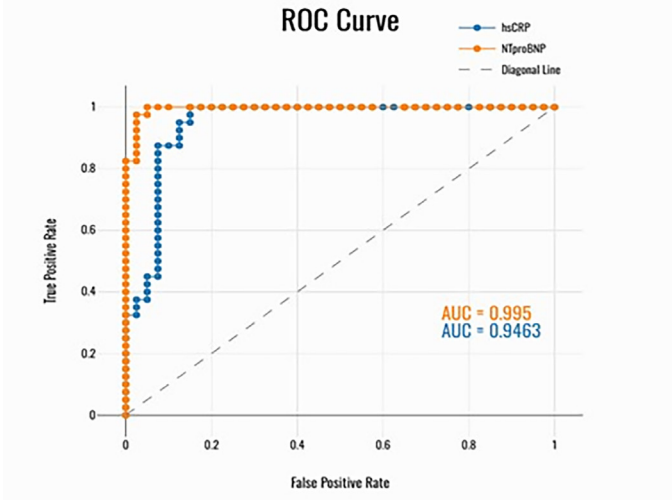

Figure 3: ROC curve of hsCRP and NT-proBNP in heart failure patients

ROC: Receiver operating characteristic, hsCRP: High sensitivity C-reactive protein, NT-proBNP: N-terminal pro brain natriuretic peptide

Table 4: ROC curves of hsCRP and NT-proBNP in heart failure patients

Variable	AUC	95% CI	Cut-off	Sensitivity	Specificity	*P*-value
hsCRP (mg/L)	0.946	0.890-0.994	3.157	100%	85%	<0.001
NT-proBNP (pg/mL)	0.995	0.899-0.999	437.8	100%	97%	<0.001

ROC: Receiver operating characteristic, hsCRP: High sensitivity C-reactive protein, NT-proBNP: N-terminal pro brain natriuretic peptide

Table 5: Comparisons among ECHO parameters of study participants

		EF	LVIDd	LVIDs	IVSs	IVSd	LVPWs	LVPWd	EDV	ESV	SV	FS	AO	LA	E	A
LVIDd	*R*-value	**-0.77**	**1**													
	P-value	**<0.001**	**1**													
LVIDs	*R*-value	**-0.75**	**0.91**	**1**												
	P-value	**<0.001**	**<0.001**	**1**												
IVSs	*R*-value	**0.48**	**-0.53**	**-0.63**	**1**											
	P-value	**0.009**	**0.003**	**<0.001**	**1**											
IVSd	*R*-value	**0.47**	**-0.51**	**-0.6**	**0.99**	**1**										
	P-value	**0.01**	**0.004**	**0.001**	**<0.001**	**1**										
LVPWs	*R*-value	**0.44**	**-0.49**	**-0.55**	**0.96**	**0.96**	**1**									
	P-value	**0.01**	**0.007**	**0.002**	**<0.001**	**<0.001**	**1**									
LVPWd	*R*-value	**0.42**	**-0.46**	**-0.53**	**0.96**	**0.97**	**0.99**	**1**								
	P-value	**0.02**	**0.01**	**0.003**	**<0.001**	**<0.001**	**<0.001**	**1**								
EDV	*R*-value	**-0.96**	**0.67**	**0.63**	**-0.45**	**-0.43**	**-0.41**	**-0.39**	**1**							
	P-value	**<0.001**	**<0.001**	**<0.001**	**0.01**	**0.01**	**0.02**	**0.03**	**1**							
ESV	*R*-value	**-0.95**	**0.61**	**0.62**	**-0.41**	**-0.41**	**-0.38**	**-0.37**	**0.93**	**1**						
	P-value	**<0.001**	**<0.001**	**<0.001**	**0.02**	**0.02**	**0.04**	**0.05**	**<0.001**	**1**						
SV	*R*-value	0.03	0.05	0.01	-0.12	-0.13	-0.19	-0.19	-0.07	-0.1	1					
	P-value	0.87	0.81	0.98	0.53	0.51	0.33	0.32	0.72	0.60	1					
FS	*R*-value	**0.92**	**-0.81**	**-0.75**	**0.45**	**0.46**	**0.41**	**0.39**	**-0.84**	**-0.82**	0.12	**1**				
	P-value	**<0.001**	**<0.001**	**<0.001**	**0.01**	**0.01**	**0.02**	**0.03**	**<0.001**	**<0.001**	0.52	**1**				
AO	*R*-value	-0.19	0.31	0.15	-0.05	-0.03	-0.09	-0.04	0.25	0.24	-0.07	-0.27	1			
	P-value	0.31	0.10	0.43	0.79	0.87	0.63	0.85	0.18	0.21	0.71	0.15	1			
LA	*R*-value	**-0.82**	**0.83**	**0.78**	**-0.52**	**-0.51**	**-0.49**	**-0.47**	**0.7**	**0.78**	0.03	**-0.79**	0.28	**1**		
	P-value	**<0.001**	**<0.001**	**<0.001**	**0.004**	**0.004**	**0.007**	**0.01**	**<0.001**	**<0.001**	0.85	<0.001	0.14	**1**		
E	*R*-value	-0.11	0.25	0.17	-0.15	-0.18	-0.14	-0.13	0.04	0.12	0.25	-0.04	0.09	0.27	**1**	
	P-value	0.57	0.19	0.36	0.42	0.35	0.47	0.49	0.81	0.54	0.19	0.81	0.65	0.15	**1**	
A	*R*-value	0.35	-0.18	-0.23	0.29	0.3	0.35	0.35	-0.32	**-0.43**	-0.11	0.24	-0.16	**-0.39**	-0.12	**1**
	P-value	0.06	0.36	0.23	0.13	0.11	0.06	0.06	0.09	**0.01**	0.55	0.20	0.40	**0.03**	0.55	**1**
E/A	*R*-value	**-0.38**	0.35	**0.37**	-0.31	-0.33	-0.35	-0.35	0.28	**0.44**	0.28	-0.24	0.07	**0.54**	**0.68**	**-0.74**
	P-value	**0.03**	0.06	**0.04**	0.09	0.07	0.06	0.06	0.13	**0.01**	0.14	0.21	0.73	**0.003**	**<0.001**	**<0.001**

LVIDd: Left ventricular internal diameter at end diastole, LVIDs: Left ventricular internal diameter at end systole, IVSs: Interventricular septum thickness in systole, IVSd: Interventricular septum thickness in diastole, LVPWs: Left ventricular posterior wall in systole, LVPWd: Left ventricular posterior wall in diastole, LVEDV: Left ventricular end diastolic volume, LVESV: Left ventricular end systolic volume

Table 6: Comparisons among ECHO parameters of study participants

		TC	TGL	HDL	LDL	FPG	PPPG	HbA1c	hsCRP	NT-proBNP
TGL	*R*-value	**0.36**	1							
	P-value	**0.05**	1							
HDL	*R*-value	0.3	0.05	1						
	P-value	0.11	0.80	1						
LDL	*R*-value	**0.83**	0.3	0.1	1					
	P-value	**0.001**	0.06	0.61	1					
FPG	*R*-value	0.24	0.06	-0.18	0.34	1				
	P-value	0.20	0.73	0.34	0.07	1				
PPPG	*R*-value	0.32	0.12	-0.11	0.35	**0.96**	1			
	P-value	0.09	0.54	0.58	0.06	**<0.001**	1			
HbA1c	*R*-value	0.11	0.19	-0.26	0.2	**0.89**	**0.84**	1		
	P-value	0.55	0.31	0.18	0.29	**<0.001**	**<0.001**	1		
hsCRP	*R*-value	0.01	-0.08	-0.15	-0.11	0.26	0.27	0.26	1	
	P-value	0.99	0.68	0.44	0.56	0.17	0.15	0.17	1	
NTpoBNP	*R*-value	-0.13	0.08	-0.16	-0.26	0.31	**0.36**	0.35	0.33	1
	P-value	0.49	0.66	0.39	0.16	0.10	**0.05**	0.06	0.07	1
EF	*R*-value	-0.27	-0.27	0.07	0.03	**-0.39**	**-0.47**	**-0.48**	**-0.49**	**-0.59**
	P-value	0.15	0.16	0.72	0.86	**0.03**	**0.01**	**0.009**	**0.007**	**0.001**
LVIDd	*R*-value	0.09	0.22	0.04	-0.15	0.12	0.19	**0.37**	**0.39**	**0.42**
	P-value	0.65	0.26	0.81	0.44	0.52	0.31	**0.04**	**0.03**	**0.02**
LVIDs	*R*-value	0.09	0.24	0.03	-0.09	0.16	0.2	**0.4**	**0.4**	0.3
	P-value	0.64	0.21	0.88	0.63	0.39	0.29	**0.03**	**0.03**	0.11
IVSs	*R*-value	-0.27	0.02	0.09	-0.14	-0.26	-0.24	-0.27	**-0.41**	0.15
	P-value	0.15	0.93	0.65	0.46	0.16	0.21	0.15	**0.02**	0.42
IVSd	*R* value	-0.34	0.01	0.04	-0.21	-0.25	-0.24	-0.24	**-0.4**	0.16
	P-value	0.07	0.98	0.85	0.28	0.18	0.21	0.21	**0.03**	0.40
LVPWs	*R*-value	-0.3	-0.11	0.1	-0.2	-0.28	-0.26	-0.3	**-0.38**	0.18
	P-value	0.11	0.55	0.59	0.30	0.14	0.17	0.12	**0.04**	0.33
LVPWd	*R*-value	-0.33	-0.1	0.07	-0.24	-0.26	-0.24	-0.25	**-0.36**	0.19
	P-value	0.08	0.62	0.71	0.21	0.17	0.20	0.2	**0.05**	0.31
EDV	*R*-value	0.26	0.18	-0.16	-0.08	**0.45**	**0.52**	**0.51**	**0.54**	**0.59**
	P-value	0.17	0.34	0.40	0.67	**0.01**	**0.004**	**0.005**	**0.002**	**0.001**
ESV	*R*-value	0.34	0.28	-0.07	0.03	0.29	**0.38**	0.31	**0.55**	**0.58**
	P-value	0.07	0.14	0.70	0.99	0.13	**0.04**	0.10	**0.002**	**0.001**
SV	R-value	0.31	0.34	0.06	**0.37**	0.01	-0.03	0.1	-0.35	-0.32
	P-value	0.10	0.07	0.75	**0.04**	0.95	0.88	0.61	0.06	0.09
FS	*R*-value	-0.29	-0.18	-0.03	-0.03	**-0.45**	**-0.57**	**-0.5**	**-0.41**	**-0.61**
	P-value	0.13	0.35	0.87	0.88	**0.01**	**0.001**	**0.005**	**0.02**	**<0.001**
AO	*R*-value	0.15	0.3	-0.14	-0.03	0.02	0.15	0.1	0.25	0.22
	P-value	0.44	0.11	0.45	0.89	0.91	0.42	0.59	0.19	0.26

Table 6: Continued

		TC	TGL	HDL	LDL	FPG	PPPG	HbA1c	hsCRP	NT-proBNP
LA	*R*-value	0.23	0.26	0.1	-0.1	-0.05	0.07	0.09	0.35	**0.4**
	P-value	0.23	0.16	0.61	0.61	0.80	0.70	0.64	0.06	**0.03**
E	*R*-value	0.03	0.21	0.18	-0.1	**-0.44**	**-0.41**	**-0.37**	0.16	-0.13
	P-value	0.89	0.27	0.35	0.59	**0.01**	**0.03**	**0.05**	0.40	0.49
A	*R*-value	-0.13	-0.34	0.23	-0.05	-0.02	-0.04	-0.09	-0.34	-0.13
	P-value	0.50	0.06	0.23	0.79	0.90	0.84	0.65	0.07	0.50
E/A	*R*-value	0.11	**0.41**	-0.03	0.01	-0.27	-0.24	-0.15	**0.36**	0.05
	P-value	0.58	**0.02**	0.86	0.98	0.16	0.21	0.44	**0.05**	0.79

TGL: Triglycerides, HDL: High density lipoprotein, LDL: Low density lipoprotein, FPG: Fasting plasma glucose, PPPG: Postprandial plasma glucose, HbA1c: Glycated hemoglobin, hsCRP: High sensitivity C-reactive protein, NTpoBNP: High sensitivity C-reactive protein, EF: Ejection fraction, LVIDd: Left ventricular internal diameter at end diastole, IVSs: Interventricular septum thickness in systole, IVSd: Interventricular septum thickness in diastole, LVPWs: Left ventricular posterior wall in systole, LVPWd: Left ventricular posterior wall in diastole, EDV: End-diastolic volume, ESV: End-systolic volume, SV: Stroke volume, FS: Fractional shortening, AO: Aortic annulus, LA: Left atrial volume

In contrast, HFpEF management should prioritize controlling comorbid conditions such as hypertension and preserving renal function.

Study Limitation

The study was carried out during the COVID-19 pandemic. Only patients with HF were seeking medical advice from the hospital. Apparently healthy individuals who could serve as controls were not attending hospital. Hence the study did not consist of a control group. The cross-sectional design had limitations in assessing the outcomes. Further studies could be conducted as case-control or cohort studies, which could help identify better outcomes. Since this was a single centre study with a small sample size, and due to the study design, the findings are not generalizable. Other inflammatory markers, such as interleukin-6, tumor necrosis factor-alpha, total white blood cell count and differential count, could have provided further insights. A further study could be carried out as a multicentric study to increase validity, reliability, and generalizability.

CONCLUSION

In summary, the significant biochemical and metabolic differences between HFpEF and HFrEF patients highlight distinct underlying pathophysiological mechanisms. hsCRP and NT-proBNP were higher in HFrEF compared to HFpEF. Even though NT-proBNP performed well in ROC curve, correlation of hsCRP with ECHO variables with hsCRP was better than NT-proBNP. Recognizing these differences is crucial for enhancing diagnosis, treatment strategies, and prognosis in HF management. These findings underscore the necessity for personalized therapeutic interventions and the refinement of treatment protocols, ultimately aiming to improve patient outcomes.

Ethics

Ethics Committee Approval: Approval was obtained from the Ethics Committee of Sri Ramachandra Institute Of Higher Education And Research (approval number: IEC-NI/19/FEB/68/09, dated 10.11.2020).

Informed Consent: Written informed consent was obtained from all the study participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.T., J.C.A., K.J., S.S., Concept: S.T., J.C.A., K.J., S.S., Design: S.T., J.C.A., K.J., S.S., Data Collection or Processing: S.T., J.C.A., K.J., S.S., Analysis or Interpretation: S.T., J.C.A., K.J., S.S., Literature Search: S.T., J.C.A., K.J., S.S., Writing: S.T., J.C.A., K.J., S.S.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. D'Amato A, Prosperi S, Severino P, Myftari V, Labbro Francia A, Cestiè C, et al. Current approaches to worsening heart failure: Pathophysiological and molecular insights. Int J Mol Sci. 2024;25:1574.
2. Nguyen SV, Do TM, Tran TX, Nguyen TT, Pham DT. Prevalence, treatment, and 1-year outcomes of heart failure with mid-range ejection fraction. Biomedical Research and Therapy. 2022;9:5209-15.
3. Savarese G, Becher PM, Lund LH, Seferovic P, Rosano GMC, Coats AJS. Global burden of heart failure: A comprehensive and updated review of epidemiology. Cardiovasc Res. 2023;118:3272-87.

4. Hu SS, Kong LZ, Gao RL, Zhu ML, Wang W, Wang YJ, et al. Outline of the report on cardiovascular disease in China, 2010. Biomed Environ Sci. 2012;25:251-6.
5. Lam CSP. Heart failure in Southeast Asia: facts and numbers. ESC Heart Fail. 2015;2:46-9.
6. Shoman H, Ellahham S. The role of biomarkers in the diagnosis and management of heart failure. J Cardiol Cardiovasc Surg. 2017;4:1-4.
7. Harikrishnan S, Oomman A, Jadhav UM, Raghuraman B, Mohanan PP, Tiwaskar M, et al. Heart failure with preserved ejection fraction: Management guidelines (From Heart Failure Association of India, Endorsed by Association of Physicians of India). J Assoc Physicians India. 2022;70:11-2.
8. Chaturvedi V, Parakh N, Seth S, Bhargava B, Ramakrishnan S, Roy A, et al. Heart failure in India: The INDUS (India Ukieri Study) study. J Pract Cardiovasc Sci. 2016;2:28-35.
9. Son MK, Park JJ, Lim NK, Kim WH, Choi DJ. Impact of atrial fibrillation in patients with heart failure and reduced, mid-range or preserved ejection fraction. Heart. 2020;106:1160-8.
10. van der Horst IC, Voors AA, van Veldhuisen DJ. Treatment of heart failure with ACE inhibitors and beta-blockers: What is next? Aldosterone receptor antagonists? Clin Res Cardiol. 2007;96:193-5.
11. Osman R, L'Allier PL, Elgharib N, Tardif JC. Critical appraisal of C-reactive protein throughout the spectrum of cardiovascular disease. Vasc Health Risk Manag. 2006;2:221-37.
12. Ferreira JP, Claggett BL, Liu J, Sharma A, Desai AS, Anand IS, et al. High-sensitivity C-reactive protein in heart failure with preserved ejection fraction: Findings from TOPCAT. Int J Cardiol. 2024;402:131818.
13. Birrell H, Isles C, Fersia O, Anwar M, Mondoa C, McFadyen A. Assessment of the diagnostic value of NT-proBNP in heart failure with preserved ejection fraction. Br J Cardiol. 2024;31:002.
14. Lakhani I, Leung KSK, Tse G, Lee APW. Novel mechanisms in heart failure with preserved, midrange, and reduced ejection fraction. Front Physiol. 2019;10:874.
15. van den Berg MP, Mulder BA, Klaassen SHC, Maass AH, van Veldhuisen DJ, van der Meer P, et al. Heart failure with preserved ejection fraction, atrial fibrillation, and the role of senile amyloidosis. European Heart Journal. 2019;40:1287-93.
16. Arul JC, Raja Beem SS, Parthasarathy M, Kuppusamy MK, Rajamani K, Silambanan S. Association of microRNA-210-3p with NT-proBNP, sST2, and Galectin-3 in heart failure patients with preserved and reduced ejection fraction: A cross-sectional study. PLoS One. 2025;20:e0320365.
17. Schwinger RHG. Pathophysiology of heart failure. Cardiovasc Diagn Ther. 2021;11:263-76.
18. Wang H, Cai J. The role of microRNAs in heart failure. Biochim Biophys Acta Mol Basis Dis. 2017;1863:2019-30.
19. Sreeniwas Kumar A, Sinha N. Cardiovascular disease in India: A 360 degree overview. Med J Armed Forces India. 2020;76:1-3.
20. Li H, Hastings MH, Rhee J, Trager LE, Roh JD, Rosenzweig A. Targeting age-related pathways in heart failure. Circ Res. 2020;126:533-51.
21. Harikrishnan S, Sanjay G, Agarwal A, Kumar NP, Kumar KK, Bahuleyan CG, et al. One-year mortality outcomes and hospital readmissions of patients admitted with acute heart failure: data from the Trivandrum heart failure registry in kerala, India. Am Heart J. 2017;189:193-9.
22. Dokainish H. Global mortality variations in patients with heart failure: Results from the international congestive heart failure (INTER-CHF) prospective cohort study. Lancet Glob Health. 2017;5:e665-e672.
23. Adams KF Jr, Fonarow GC, Emerman CL, LeJemtel TH, Costanzo MR, Abraham WT, et al. Characteristics and outcomes of patients hospitalized for heart failure in the United States: Rationale, design, and preliminary observations from the first 100,000 cases in the acute decompensated heart failure national registry (ADHERE) Am Heart J. 2005;149:209-16.
24. Regitz-Zagrosek V. Sex and gender differences in heart failure. Int J Heart Fail. 2020;2:157-81.
25. Maddox TM, Januzzi JL Jr, Allen LA, Breathett K, Butler J, Davis LL, et al. 2021 Update to the 2017 ACC expert consensus decision pathway for optimization of heart failure treatment: Answers to 10 pivotal issues about heart failure with reduced ejection fraction: A report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2021;77:772-810.
26. Palau P, Bertomeu-González V, Sanchis J, Soler M, de la Espriella R, Domínguez E, et al. Differential prognostic impact of type 2 diabetes mellitus in women and men with heart failure with preserved ejection fraction. Rev Esp Cardiol (Engl Ed). 2020;73:463-70.
27. Capotosto L, Massoni F, De Sio S, Ricci S, Vitarelli A. Early diagnosis of cardiovascular diseases in workers: Role of standard and advanced echocardiography. Biomed Res Int. 2018;2018:7354691.
28. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2015;16:233-70.
29. Kohashi K, Nakagomi A, Saiki Y, Morisawa T, Kosugi M, Kusama Y, et al. Effects of eicosapentaenoic acid on the levels of inflammatory markers, cardiac function and long-term prognosis in chronic heart failure patients with dyslipidemia. J Atheroscler Thromb. 2014;21:712-29.
30. Bayeva M, Sawicki KT, Ardehali H. Taking diabetes to heart--deregulation of myocardial lipid metabolism in diabetic cardiomyopathy. J Am Heart Assoc. 2013;2:e000433.
31. Mishra S, Kass DA. Cellular and molecular pathobiology of heart failure with preserved ejection fraction. Nat Rev Cardiol. 2021;18:400-23.
32. Simmonds SJ, Cuijpers I, Heymans S, Jones EAV. Cellular and molecular differences between HFpEF and HFrEF: A step ahead in an improved pathological understanding. Cells. 2020;9:242.
33. Kazory A. Emergence of blood urea nitrogen as a biomarker of neurohormonal activation in heart failure. Am J Cardiol. 2010;106:694-700.
34. Sîrbu O, Floria M, Dascalita P, Stoica A, Adascalitei P, Sorodoc V, et al. Anemia in heart failure-from guidelines to controversies and challenges. Anatolian journal of cardiology. 2018;20:52.
35. Murphy SP, Kakkar R, McCarthy CP, Januzzi JL Jr. Inflammation in heart failure: JACC state-of-the-art review. J Am Coll Cardiol. 2020;75:1324-40.
36. Pellicori P, Zhang J, Cuthbert J, Urbinati A, Shah P, Kazmi S, et al. High-sensitivity C-reactive protein in chronic heart failure: Patient characteristics, phenotypes, and mode of death. Cardiovasc Res. 2020;116:91-100.
37. Zhang L, He G, Huo X, Tian A, Ji R, Pu B, et al. Long-term cumulative high-sensitivity C-Reactive protein and mortality among patients with acute heart failure. J Am Heart Assoc. 2023;12:e029386.
38. Al Miraj AK, Hossain MK, Ajmai M, Ullah MA. The role of NT-proBNP in the diagnosis of diastolic heart failure and its correlation with echocardiography. BJMAS. 2023;4:54-63.
39. Santas E, Villar S, Palau P, Llàcer P, de la Espriella R, Miñana G, et al. High-sensitivity C-reactive protein and risk of clinical outcomes in patients with acute heart failure. Sci Rep. 2024;14:21672.