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Research paper

Alterations of 8-iso-prostaglandin F2 alpha levels in heart failure patients with preserved and reduced ejection fraction- a case-control study

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Abstract

Introduction: Heart failure (HF) poses a global health challenge with decreased quality of life. HF can be HF with reduced ejection fraction (HFrEF) or preserved ejection fraction (HFpEF). Oxidative stress is implicated in the pathophysiology of heart failure. The study aimed to find the association of the oxidative biomarker 8-iso-prostaglandin F2 Alpha (8-iso-PGF2α) with the severity of heart failure.

Methods: The case-control study was conducted in the Departments of Cardiology and Biochemistry at Sri Ramachandra Institute of Higher Education and Research, India. The study involved 80 HF patients (HFpEF: n=40, HFrEF: n=40) aged between 30 and 75 years of both genders. Enzyme-Linked Immunosorbent Assay analyzed 8-iso-PGF2α. Institutional ethics committee approval was obtained. Statistical analysis was performed using SPSS software version 16. $P \leq 0.05$ was considered statistically significant.

Results: HFpEF was more prevalent in the 46-60 age group, whereas HFrEF was more common in the 61-75 age group. Among HFpEF and HFrEF, 8-iso-PGF2 □ levels were 910.07 ± 286.97 and 1185.02 ± 396.75 (p=0.001). 8-iso-PGF2□ showed correlation with NT-proBNP and echocardiography.

Conclusions: Elevated 8-iso-PGF2α levels suggested a potential link between oxidative stress and heart failure severity, contributing to our understanding of oxidative stress in heart failure.

Keywords: *Biomarkers; Cardiology; Heart Failure; Oxidative Stress; Stroke Volume.*

1. Introduction

Heart failure (HF) is a complex cardiovascular disorder resulting from the diminished capacity of the heart to pump blood to various parts of the body effectively. Its diagnosis and management pose a significant health challenge, with substantial morbidity, mortality, and healthcare costs [1]. Worldwide, the prevalence of HF cases amounted to 56.19 million, and several countries demonstrated an increasing trend from 1990 to 2019, especially in low-income ones [2]. HF is recognized as a worldwide pandemic, affecting around 64.3 million individuals globally in the year 2017, and it could increase further due to adverse lifestyle changes [3]. CVDs are the primary cause of death and disability in India; in 2017, they were responsible for 14.7% of disability-adjusted life years (DALYs) worldwide and 31.8% of all deaths [4]. According to projections from the World Health Organization (WHO), roughly 17.9 million people died from CVDs in 2019, accounting for 32% of all deaths globally [5].

HF has been classified according to left ventricular ejection fraction (LVEF), which includes heart failure with reduced ejection fraction (HFrEF), heart failure with mildly reduced or midrange ejection fraction (HFmrEF), and heart failure with preserved ejection fraction (HFpEF), classified based on specified LVEF thresholds of ≤40%, 41% to 49%, and ≥50%, respectively [6]. In South Asia, the NHFR (National Heart Failure Registry of India) presented that the most common classification was HFrEF (65%), followed by HFmrEF (22%) and HFpEF (13%) [7]. HF continues to represent a global public health concern; the prevalent HF cases amounted to 56.19 million individuals, and many countries have shown an increasing trend from 1990 to 2019, especially in low-income countries [8].

Oxidative stress causes damage to cellular components and contributes to disease progression, including heart failure [9]. Some risk factors of HF, such as hypertension, diabetes mellitus, and obesity, are shown to induce oxidative stress. Also, in myocardial hypertrophy,

parameters of the redox-sensitive signaling pathways, such as mitogen-activated protein kinases (MAPK) and transcription factors- nuclear factor-kappa beta (NF-κB) are activated [10], [11]. Factors contributing to oxidative stress in the heart are ischemia, ischemia-reperfusion injury, inflammation, auto-oxidation of catecholamines, and mitochondrial dysfunction [12]. Consequences of oxidative stress in the heart include apoptosis and fibrosis, leading to impaired cardiac function [11]. Understanding oxidative stress mechanisms is crucial for developing targeted therapies to mitigate its effects on the heart. Research and clinical practice in heart failure must prioritize the exploration of oxidative stress.

An isoprostane created by the non-enzymatic peroxidation of arachidonic acid in membrane phospholipids, the prostaglandin 8-iso-prostaglandin F2α (8-iso-PGF2α) can also be utilized as a marker of an increased rate of lipid peroxidation [13]. It influences blood vessel tone and potentially impacts blood pressure. It is also linked to inflammatory responses and oxidative stress, both critical factors in cardiovascular diseases (CVD) [14]. Therefore, measuring 8-iso-PGF2α levels may be a valuable tool in assessing the severity of oxidative stress in heart failure patients and help manage this condition. This study aimed to evaluate the levels of 8-iso-PGF2α in HFpEF and HFrEF patients.

2. Methods

Heart failure patients were recruited from the Department of Cardiology, and further analysis was conducted in the Department of Biochemistry at Sri Ramachandra Institute of Higher Education and Research, India. Institutional ethics committee approval was obtained (IEC-NI/19/FEB/68/09, dated 10.11.2020). Written informed consent was obtained from all the study participants.

2.1. Study design: case-control study

Study participants:

1) Heart failure with preserved ejection fraction (≥50%) n=40
2) Heart failure with reduced ejection fraction (≤49%) n=40

Inclusion criteria:

The study included participants aged between 30 and 75 of both genders who were diagnosed with heart failure based on the Framingham Heart Failure Diagnostic criteria.

Exclusion criteria:

- Individuals with a history of acute heart failure within the last 3 months or acute myocardial infarction within the last 6 weeks.
- Individuals with rheumatic heart disease, cardiomyopathy, and cardiac diseases other than HF
- Individuals with thyroid, lung, renal, or liver disorders; pregnant individuals; those with a history of cancer, systemic infectious diseases, or connective tissue disorders; and individuals currently using anticancer drugs, steroids, anabolic steroids, or oral contraceptive pills.

2.2. Sample collection and biomarker analysis

Blood samples were collected from the study participants, and serum was separated and stored at -80°C until analysis. The lipid profile was carried out using standard methods. 8-iso-PGF2 alpha and NT-proBNP were analyzed using the enzyme-linked immunosorbent assay (ELISA) technique. The study participants were subjected to the transthoracic 2D Doppler echocardiography using Phillips and GE Healthcare echocardiography, with patients lying supine in theleft lateral decubitus position.

2.3. Statistical analysis

Statistical analysis was performed using SPSS software version 16. The obtained data were subjected to the Kolmogorov-Smirnov test to check for normality of distribution. Continuous variables were expressed as mean and standard deviation, and the student t' t-test was used to compare the data between the groups. Categorical variables were expressed as frequency and percentage, and the Chi-squared test or Fisher's exact test was used to compare the data. $P \leq 0.05$ was considered statistically significant.

3. Results

The study consisted of 80 heart failure patients. The results obtained were displayed in five tables and three figures. Table 1 shows the demographic details of the study participants. The mean age of the participants in HFpEF and HFrEF was 51.78 and 64.85 years, respectively ($p<0.001$). In HFpEF, most patients were in the 46- to 60-year-old age group, whereas in HFrEF, they were in the 61- to 75-year-old age group, with a significant p-value of 0.02. The bar diagram also displays the age distribution of the study groups (Figure 1).

Table 1: Demographic Details of the Participants

Variables	Total (n=80)	HFpEF (n=40)	HFrEF (n=40)	p-value
Age (years)	58.11 (12.54)	51.78 (9.94)	64.85 (11.29)	<0.001**
Age distribution among participants (n/%) @				
<50	17 (21.25%)	13 (32.5%)	4 (10%)	
51-70	25 (31.25%)	17 (42.5%)	8 (20%)	0.02*
71-90	38 (47.5%)	10 (25%)	28 (70%)	
Gender distribution among participants (n/%) @				
Female	24 (30%)	15 (37.5%)	9 (22.5%)	0.14
Male	56 (70%)	25 (62.5%)	31 (77.5%)	
NYHA (n) #$	I-37, II-3, III-20, IV-20	I-37, II-3	III-20, IV-20	<0.001**

NYHA: New York Heart Association classification.

Expressed as mean and SD, @ expressed frequency and percentage, # expressed as frequency

Student' t'test used; @ Chi-square test was used. $ Fisher exact test was used P value: * significant, ** highly significant

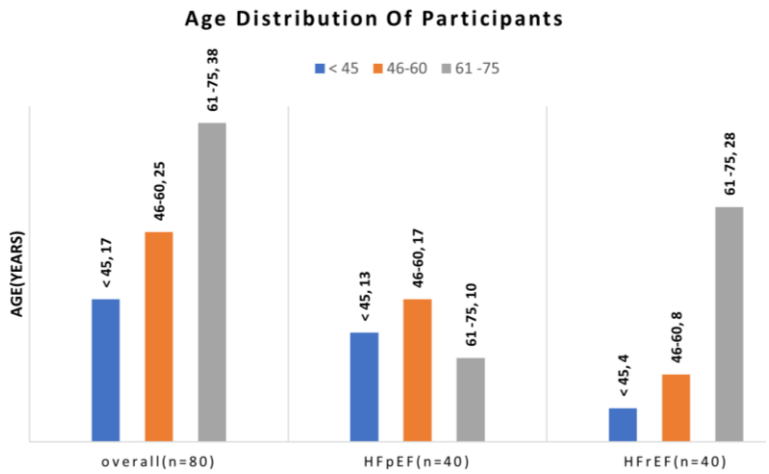

Fig. 1: Bar Diagram Shows the Age Distribution Among the Study Groups.

Around 62% and 77% were males in HFpEF and HFrEF respectively which was statistically insignificant. (p=0.14). The bar diagram also displays the gender distribution of study groups (Figure 2).

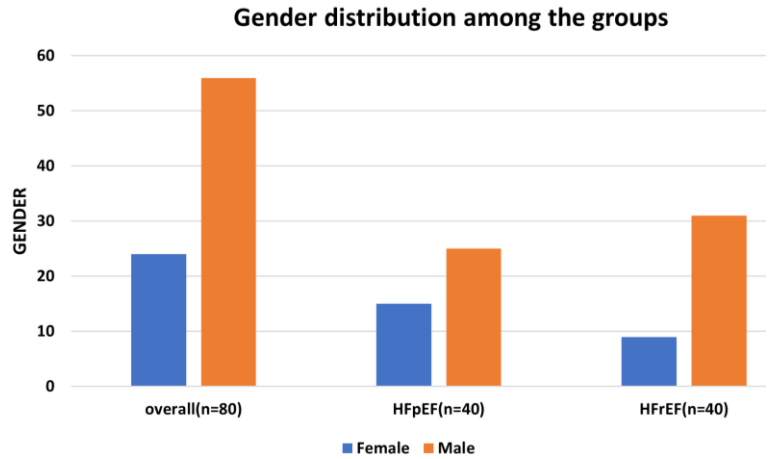

Fig. 2: Gender Distribution Among HFpEF and HFrEF.

Aortic root diameter (Ao), left atrial volume (LA volume), fractional shortening (%FS), left ventricular diastolic (LVIDd) and systolic (LVIDs) cavity diameters, left diastolic and systolic ventricular posterior wall (LVPWd and LVPWs) diameters, diastolic interventricular septum diameter (IVSd), systolic interventricular septum diameter (IVSs), left ventricular mass (LV mass), left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic (LVESV) volume, ejections fraction (EF), and stroke volume (SV) were all measured at the level of the left ventricle and aortic valve. All the ECHO variables showed statistically significant differences between the groups, as shown in Table 2.

Table 2: Echocardiography Findings in the Study Participants

Variables	Total (n=80)	HFpEF (n=40)	HFrEF (n=40)	p-value
EF (%)	48.84 (14.25)	61.53 (2.12)	36.15 (8.68)	<0.001**
LVIDs (cm)	49.58 (5.9)	44.83 (1.62)	52.43 (5.70)	<0.001**
LVIDd (cm)	37.75 (6.08)	33.0 (2.89)	40.60 (5.72)	<0.001**
IVSs (cm)	10.23 (2.72)	12.50 (1.62)	8.87 (2.32)	<0.001**
IVSd (cm)	11.35 (2.69	13.56 (1.65)	10.03 (2.31)	<0.001**
LVPWs (cm)	11.45 (2.43)	12.62 (2.0)	10.27 (2.48)	<0.001**
LVPWd (cm)	12.48 (2.43)	13.62 (2.0)	11.35 (2.31)	<0.001**
LVESV (mL)	107.65 (25.75)	91.08 (4.54)	124.23 (27.54)	<0.001**
LVEDV (mL)	58.15 (25.1)	35.80 (4.89)	80.50 (20.96)	<0.001**
SV (mL)	49.93 (7.83)	51.98 (5.53)	47.88(9.22)	<0.01*
FS (%)	24.47 (7.03)	30.65 (1.0)	18.85 (5.27)	<0.001**
AO (mm)	29.28 (1.79)	28.83 (1.24)	29.73 (2.14)	0.02*
LA (mL)	35.91 (6.21)	32.78 (5.78)	39.05 (6.61)	<0.001**
E-wave velocity (m/s)	0.77 (0.67)	0.71 (0.18)	0.83 (0.24)	0.01*
A-wave velocity (m/s)	0.67 (0.21)	0.76 (0.16)	0.59 (0.22)	<0.001**
E/A ratio	1.33 (0.78)	0.97 (0.33)	1.69 (0.92)	<0.001**

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

Expressed as mean and SD, # expressed as median and interquartile range. Student' t'test used; P value: * significant, ** highly significant

Among HFpEF and HFrEF, 8-iso-PGF2 α levels were 910.07 ± 286.97 and 1185.02 ± 396.75 pg/mL, with a statistically significant p-value of 0.001 shown in Table 3. Figure 3 provides information on 8-iso-prostaglandin F2 alpha and shows mean values with 95% confidence interval among the groups, HFpEF (n=40) and HFrEF (n=40). NT-proBNP levels were 279.07 ± 93.33 and 521.09 ± 151.59 pg/mL in HFpEF and HFrEF, respectively, which was statistically significant (P<0.001). None of the variables in the lipid profile showed a statistically significant difference between the groups. (Table 3).

Table 3: Biomarker Levels in HFpEF and HFrEF Patients

Variables	Total (n=80)	HFpEF (n=40)	HFrEF (n=40)	p-value
TC (mg/dL)	200.11 (43.07)	200.30 (40.94)	199.93 (45.62)	0.96
TGL (mg/dL)	150.69 (63.95)	153.58 (66.15)	147.80 (62.38)	0.68
HDL (mg/dL)	41.73 (10.94)	42.25 (9.94)	41.20 (11.96)	0.67
LDL (mg/dL)	125.81 (38.04)	133.78 (31.69)	117.85 (42.40)	0.06
8-iso-PGF2 α (pg/mL)	1047.54 (370.81)	910.07 (286.97)	1185.02 (396.75)	0.001**
NT-proBNP (pg/mL)	400.08 (174.56)	279.07 (93.33)	521.09 (151.59)	<0.001**

TC: total cholesterol, TGL: triglyceride, HDL: high-density lipoprotein, LDL: low-density lipoprotein, 8-iso-PGF2 α: 8-iso-prostaglandin F2 alpha, NT-proBNP: N-terminal-pro Brain Natriuretic Peptide
Expressed in mean and SD; Student's t was used; P value: *-significant; **- highly significant

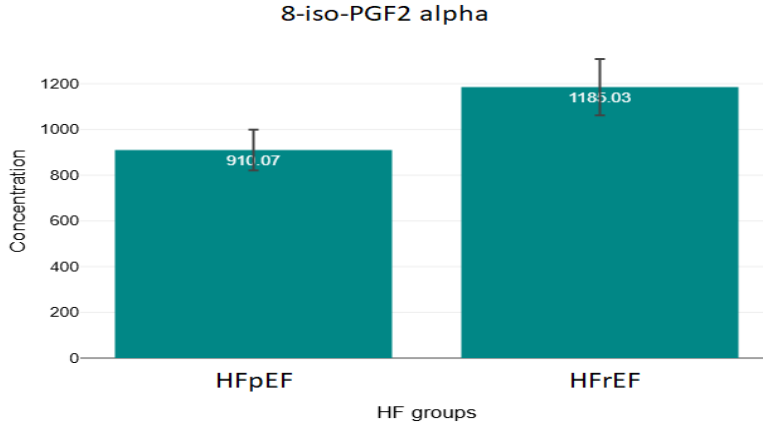

Fig. 3: 8-Iso-Prostaglandin F2 Alpha Levels Among the Groups.

8-iso-PGF2 alpha correlated with NT-proBNP, EF, left ventricular internal diameter (systole and diastole), end systolic volume, and fractional shortening. NT-proBNP showed correlations with all the echocardiography parameters. Among the variables of echocardiography, most of the variables showed correlations. (Table 4).

Table 4: Correlation Among the Biomarkers and Echocardiography

		8-iso-PGF2α	NT-proBNP	EF%	LVIDd	LVIDs	IVSs	IVSd	LVPWd	LVPWs	EDV	ESV	SV	FS	Ao	LA	E	A
NT-proBNP	r	0.32	1															
	p	0.004																
EF%	r	0.38	-0.67	1														
	p	0.007	<0.001															
LVIDd	r	0.27	0.53	-0.76	1													
	p	0.01	<0.001	<0.001														
LVIDs	r	0.24	0.56	-0.71	0.87	1												
	p	0.02	<0.001	<0.001	<0.001													
IVSs	r	0.19	-0.35	0.56	-0.57	-0.61	1											
	p	0.1	0.001	<0.001	<0.001	<0.001												
IVSd	r	0.19	-0.36	0.55	-0.58	-0.63	0.99	1										
	p	0.09	0.001	<0.001	<0.001	<0.001	<0.001											
LVPWd	r	0.2	-0.38	0.57	-0.56	-0.6	0.97	0.97	1									
	p	0.08	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001										
LVPWs	r	0.21	-0.39	0.58	-0.58	-0.62	0.97	0.98	0.99	1								
	p	0.06	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001									

EDV	r p	-0.15 0.18	0.45 <0.001	-0.7 <0.001	0.48 <0.001	0.47 <0.001	-0.32 0.004	-0.31 0.005	-0.33 0.002	-0.34 0.002	1						
ESV	r p	0.32 0.004	0.63 <0.001	-0.92 <0.001	0.71 <0.001	0.69 <0.001	-0.47 <0.001	-0.47 <0.001	-0.48 <0.001	-0.49 <0.001	0.74 <0.001	1					
SV	r p	0.03 0.75	-0.27 0.01	0.28 0.01	-0.2 0.08	-0.15 0.19	0.07 0.54	0.05 0.63	0.09 0.43	0.08 0.48	-0.08 0.46	-0.3 0.007	1				
FS	r p	0.31 0.006	-0.65 <0.001	0.96 <0.001	-0.78 <0.001	-0.73 <0.001	0.58 <0.001	0.58 <0.001	0.6 <0.001	0.61 <0.001	-0.63 <0.001	-0.84 <0.001	0.3 0.007	1			
Ao	r p	0.06 0.57	0.23 0.04	-0.22 0.05	0.14 0.22	0.1 0.39	-0.12 0.29	-0.1 0.37	-0.11 0.31	-0.11 0.34	0.19 0.08	0.25 0.02	-0.11 0.318	-0.24 0.03	1		
LA	r p	-0.07 0.54	0.43 <0.001	-0.62 <0.001	0.63 <0.001	0.56 <0.001	-0.37 0.001	-0.38 0.001	-0.36 0.001	-0.37 0.001	0.38 0.001	0.58 <0.001	-0.24 0.03	-0.61 <0.001	0.33 0.002	1	
E	r p	-0.13 0.23	0.21 0.05	-0.31 0.005	0.23 0.04	0.25 0.02	-0.25 0.02	-0.26 0.02	-0.23 0.03	-0.24 0.03	0.29 0.01	0.23 0.04	0.04 0.73	-0.3 0.007	0.22 0.05	0.46 <0.001	1
A	r p	0.03 0.81	-0.43 <0.001	0.46 <0.001	-0.45 <0.001	-0.45 <0.001	0.59 <0.001	0.58 <0.001	0.58 <0.001	0.58 <0.001	-0.44 <0.001	-0.43 <0.001	0.21 0.06	0.45 <0.001	-0.27 0.01	-0.45 <0.001	-0.28 0.01
E/A	r p	-0.08 0.48	0.41 <0.001	-0.51 <0.001	0.45 <0.001	0.46 <0.001	-0.54 <0.001	-0.53 <0.001	-0.52 <0.001	-0.51 <0.001	0.46 <0.001	0.46 <0.001	-0.19 0.09	-0.5 <0.001	0.31 0.005	0.59 <0.001	0.72 <0.001

Neither 8-iso-PGF2 alpha nor NT-proBNP showed correlations with lipid profile. Total cholesterol and LDL cholesterol showed statistically significant differences among the lipid profiles. (Table 5).

Table 5: Correlations Among the Biomarkers and Lipid Profile

		8-iso-PGF2α	NT-proBNP	TC	TGL	HDL
NT-proBNP	r p	0.32 0.004				
TC	r p	0.06 0.59	0.02 0.86	1		
TGL	r p	0.16 0.14	-0.07 0.52	0.39 <0.001	1	
HDL	r p	-0.01 0.91	0.04 0.74	0.55 <0.001	0.14 0.21	1
LDL	r p	0.13 0.24	-0.08 0.47	0.75 <0.001	0.3 0.006	0.38 0.001

4. Discussion

Heart failure (HF) is a complex clinical syndrome with distinct phenotypes, often classified based on ejection fraction. Cardiovascular disease (CVD) is emerging as the primary cause of illness and mortality in India. HF impacts 8-10 million individuals in the country, with an estimated annual mortality rate of approximately 0.1–0.16 million [15]. According to the World Health Organization (WHO), India contributes significantly to global CVD deaths, particularly among the younger population, accounting for one-fifth of such fatalities [16]. The Global Burden of Disease (GBD) study found that India has a higher age-standardized CVD mortality rate of 272 per 100,000 population compared to the global average of 235 [17]. The mortality linked to coronary artery disease in Asians is 20–50% higher compared to other population groups [18].

In the present study, the mean age of the participants in HFpEF and HFrEF was 51.78 and 64.85 years, respectively ($p<0.001$). In individuals under 45 years and 46-60 years, there was a higher prevalence of HFpEF than HFrEF. This indicated that HFpEF was prevalent among younger and middle-aged participants. In the 61-75 age group, there was a higher prevalence of HFrEF (70%) than HFpEF (25%). There was a statistically significant difference between the three age groups, HFpEF and HFrEF ($p=0.02$). (Table 1, Figure 1) This suggested that HFrEF was more common in older people than HFpEF. HFpEF patients with less than 65 years display adverse cardiac remodeling almost the same as that of their older counterparts, and those with poor outcomes. Older patients are predisposed to the development of HF because

of age-related changes in the heart. It is characterized by oxidative stress, mitochondrial damage, ventricular-vascular stiffness, and peripheral abnormalities in the vasculature and skeletal muscle [19]. These results underscore the significance of age as a pivotal factor in comprehending the prevalence dynamics of HFpEF and HFrEF.

In the present study, among the overall study population, 30% (n=24) were females and 70% (n=56) were males. Among HFpEF, 37.5% (n=15) were females and 62.5% (n=25) were males, whereas among HFrEF, 22.5% (n=9) were females and 77.5% (n=31) were males. There was no statistically significant difference among the groups regarding gender (p=0.14). (Table 1, Figure 2) HF is primarily a disease involving the male gender, because coronary risk factors are more common in males than females. However, the scenario changes with advancing age, and the incidence appears to be the same or higher among men [20]. Usually, HFpEF is more prevalent in women, whereas HFrEF is more prevalent in men. Women with HF survive longer than men and have a lower risk of sudden death. Ischemia is the most prominent cause in men, whereas hypertension and diabetes contribute to HF in women [20]. Women with HF have a greater stiffness of the smaller left ventricle and a higher EF than men. Higher stiffness of women's hearts could be due to increased fibrosis at old age. In younger women, estrogen reduces collagen production in female cardiac fibroblasts but stimulates it in males. Lipid and energy metabolism is better maintained in female than male stressed hearts. More research on sex differences in the pathophysiology and therapy of HF is needed [20]. Thus, understanding of the pathophysiological mechanisms of HF in both sexes should be improved, and the inclusion of more women in clinical trials should be encouraged.

The understanding of the relationship between oxidative stress and ventricular remodeling remains limited. A plausible hypothesis involves the influence of mechanical factors, wherein overstretching of the myocardium has been shown to enhance the generation of reactive oxygen species (ROS), leading to increased expression of Fas and induction of apoptosis. Fas, also known as CD95 or APO-1, is a cell surface protein that acts as a death receptor, triggering programmed cell death or apoptosis when activated by its ligand, FasL. Increased expression of Fas plays a role in various physiological and pathological processes [21]. This cascade may result in rarefaction and slippage of myocytes, intensifying ventricular dilatation [22]. There is an association between pericardial levels of 8-iso prostaglandin F2 alpha (8-iso-PGF2α) and the functional severity of heart failure, highlighting its correlation with ventricular dilatation [23].

The pathogenesis of heart failure and left ventricular (LV) hypertrophy has been linked to increased ROS generation. In pressure overload LV hypertrophy, NADPH oxidase, which is expressed in the cardiomyocyte, is a significant source of ROS production. It might cause pathophysiological alterations such as redox-sensitive kinase activation and heart failure progression [24]. In the present study, the mean level of 8-iso-PGF2α for the entire study population was 1047.54 ± 370.81 pg/mL, while the mean levels were 910.07 ± 286.97 and 1185.02 ± 396.75 in HFpEF and HFrEF, respectively (p=0.001). (Table 3, Figure 3) Plasma 8-iso-PGF2α levels are elevated in patients with acute myocardial infarction (AMI). The levels of 8-iso-PGF2α are elevated in patients with heart failure, indicating increased oxidative stress in the myocardium. This marker is associated with the activation of inflammatory pathways, endothelial dysfunction, and apoptotic cell death, all of which contribute to the pathophysiology of the progression of heart failure [25]. These findings suggest that 8-iso-PGF2α may serve as a potential marker indicating the progression from asymptomatic to symptomatic heart failure and the gradual impairment of cardiac function [23].

ROS have been linked to the oxidation of low-density lipoproteins (LDL), producing oxidized LDL (ox-LDL), which are eliminated from the bloodstream by attaching to scavenger receptors on the surface of macrophages. Through the NF-κB pathway, this triggers an inflammatory response and controls the production of foam cells. Ox-LDLs trigger endothelial cell death and caspase activation [26]. In hypertension, diabetes mellitus, and obesity, inflammatory chemokines, including IL-6, IL-1β, TNF-α, and IL-17, are produced by chronic inflammation and encourage oxidative stress. They also attract macrophages, T, and B lymphocytes, which produce ROS and vascular fibrotic remodeling [27].

NT-proBNP levels were 279.07 ± 93.33 and 521.09 ± 151.59 pg/mL in HFpEF and HFrEF, respectively, which was statistically significant (P<0.001). None of the variables in the lipid profile showed a statistically significant difference between the groups. (Table 3) It has become increasingly clear that the diagnosis of heart failure cannot be made solely based on clinical signs and symptoms; instead, an HF diagnosis can be made using indicators that indicate hemodynamic circumstances, such as high natriuretic peptide (NP) levels. Particular attention should be paid to HFpEF and mildly reduced HF EF, as NPs' diagnostic utility is more constrained in these conditions than in HFrEF [28]. 8-iso-PGF2 alpha correlated with NT-proBNP, EF, left ventricular internal diameter (systole and diastole), end systolic volume, and fractional shortening. NT-proBNP showed correlations with all the echocardiography parameters. Among the variables of echocardiography, most of the variables showed correlations. (Table 4) NT-proBNP is a primary biomarker for diagnosing and monitoring heart failure, while 8-iso-PGF2α reflects the role of oxidative stress in the disease. NT-proBNP and ECHO provide information about the heart's functional status and structural abnormalities, while 8-iso-PGF2 alpha can provide insights into the role of oxidative stress in the disease process. Studies have shown that 8-iso-PGF2α levels correlate with echocardiographic findings of ventricular dilatation, a common feature of heart failure [29]. The ability to measure 8-iso-PGF2α levels may offer a non-invasive way to monitor heart failure and potentially predict the risk of cardiovascular events.

Diastolic function and NT-proBNP are significantly correlated. NT-proBNP levels rise as diastolic dysfunction gets severe. Compared to HFrEF, NT-proBNP levels are lower in HFpEF. Elderly people and those over 60 are more likely to have grade 1 impairment. This would be regarded as typical if no additional signs of diastolic dysfunction existed. Because the apex of the LV has lower pressures than the base, the early diastolic phase (E) of ventricular filling is more prominent in younger patients than the late phase (A). Collagen builds up in the myocardium as we age, mainly affecting the early diastolic phase (E), in response, filling increases in the late phase (A), reversing the E/A pattern [30].

Neither 8-iso-PGF2 alpha nor NT-proBNP showed correlations with lipid profile. Total cholesterol and LDL cholesterol showed statistically significant differences among the lipid profiles. (Table 5) Studies have explored the relationship between 8-iso-PGF2α and lipid profiles, with some indicating a link between oxidative stress and dyslipidemia. One study found that urinary 8-iso-PGF2α was correlated with HDL cholesterol levels in patients with coronary heart disease [31]. The potential link between 8-iso-PGF2α, NT-proBNP, lipid profiles, and heart failure suggests that measuring 8-iso-PGF2α may help in risk stratification and early detection of heart failure.

While the elevated levels of 8-iso-PGF2α suggest a connection between oxidative stress and HFrEF, it is imperative to acknowledge that this association does not establish causation. Further in-depth research is indispensable to unravel the specific cellular and molecular mechanisms through which oxidative stress contributes to the development and progression of HFrEF. This may entail a thorough investigation into the impact of ROS on key signaling pathways, cellular structures, and overall cardiac function. The present study contributes to the accumulating evidence underscoring the role of oxidative stress in the pathophysiology of heart failure. A multi-marker approach natriuretic peptide, oxidative marker, inflammatory marker, and echocardiography, could be the potential application of these biomarkers in the diagnosis and prognosis of heart failure and thus can offer personalized management.

5. Limitations

The study did not include healthy individuals, so baseline levels of 8-iso-PGF2α could not be established. Since the sample size was small and this was a single-centre study, the findings obtained were not generalizable. Further research will be conducted as a multi-centric study, with the inclusion of apparently healthy individuals as a control group would provide the baseline for the variables studied. Inclusion of a control group would help in arriving at the cut-off level of 8-iso-PGF2 alpha. Further inclusion of oxidized LDL would help in finding its correlation with 8-iso-PGF2 alpha. Future research as a case-control or cohort study, could enhance the credibility of the marker.

6. Conclusions

Our study underscores the age and gender-specific prevalence of HFpEF and HFrEF, highlighting the significance of oxidative stress, specifically elevated levels of 8-iso-PGF2α, particularly in HFrEF. The findings suggested a potential link between oxidative stress and the pathophysiology of HFrEF, but more research is needed for conclusive evidence and a deeper understanding of the underlying mechanisms. This study provides a valuable starting point for researchers investigating the complex interplay between oxidative stress and heart failure.

Ethics approval and consent to participate:

Institutional ethics committee approval was obtained (IEC-NI/19/FEB/68/09, dated 10.11.2020). Written informed consent was obtained from all the study participants.

Competing interests: The authors declare that they have no competing interests.

Availability of data and material: The authors confirm that the data supporting the findings of this study are available within the article. Raw data were generated at the location of research, Sri Ramachandra Institute of Higher Education and Research, Chennai, India. Derived data supporting the findings of this study are available from the corresponding author, Dr Santhi Silambanan, on request. No supplementary material is available with this research, The data will be available with the corresponding author for five years from the time of publication.

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List of abbreviations

HF	-Heart failure
HFrEF	- Heart failure with reduced ejection fraction
HFpEF	- Heart failure with preserved ejection fraction
8-iso-PGF2α	-8-iso-prostaglandin F2 alpha
ROS	- Reactive oxygen species
AMI	- Acute myocardial infarction
NYHA	- New York Heart Association
WHO	-World Health Organization
CVD	-Cardiovascular disease
ELISA	-Enzyme-Linked Immunosorbent Assay
GBD	-Global Burden of Disease
NADPH	-Nicotinamide adenine dinuclotide phosphate hydrogen
NP	-Natriuretic peptide
NT-proBP	-N-terminal pro brain natriuretic peptide
DALY	-disability-adjusted life years
HFmrEF	-heart failure mid-range ejection fraction
LVEF	-left ventricular ejection fraction
MAPK	-mitogen-activated protein kinases
NF-κB	-nuclear factor-kappa beta
Ox-LDL	-oxidized low-density lipoprotein
HDL	-high-density lipoprotein
TGL	-triacylglycerol
ECHO	- echocardiography
Ao	-Aortic root diameter
LA	-left atriam
FS	-fractional shortening
LVIDd	-left ventricular diastolic cavity diameter
LVIDs	-left ventricular systolic cavity diameter
LVPWd	-left ventricular posterior wall diameter in diastole
LVPWs	-left ventricular posterior wall diameter in systole
IVSd	-diastolic interventricular septum diameter
IVSs	-systolic interventricular septum diameter (IVSs
LVEDV	-left ventricular end-diastolic volume

LVESV -left ventricular end-systolic volume
SV -stroke volume

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