SRYAHWA PUBLICATIONS

Archives of Cardiology and Cardiovascular Diseases
ISSN: 2638-4744 | Volume 8, Issue 1, 2026
https://doi.org/10.22259/2638-4744.0801002

RESEARCH ARTICLE

Clinical Predictors of Heart Failure with Preserved Ejection Fraction Among Patients with Atrial Fibrillation: A Prospective Observational Study of 100 Patients

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Received: 05 August 2026 Accepted: 20 August 2026 Published: 24 August 2026

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Abstract

Background: Atrial fibrillation (AF) and heart failure with preserved ejection fraction (HFpEF) frequently coexist and share several clinical and pathophysiological risk factors. Diagnosis of HFpEF in patients with AF can be challenging because symptoms, natriuretic peptide concentrations and echocardiographic findings may be influenced by AF itself. Identification of clinically useful predictors may facilitate earlier recognition of HFpEF in patients with preserved left ventricular ejection fraction (LVEF).

Objective: To identify clinical, biochemical and echocardiographic predictors of HFpEF among patients with AF and preserved LVEF and to evaluate their diagnostic performance.

Methods: This observational study included 100 patients with documented AF and preserved LVEF. Participants were categorized into HFpEF (n=64) and non-HFpEF (n=36) groups according to predefined clinical and echocardiographic criteria. Demographic characteristics, cardiovascular risk factors, symptoms, laboratory parameters, NT-proBNP and comprehensive echocardiographic measurements were assessed. The H_2FPEF and HFA-PEFF scores were also evaluated. Univariable and multivariable logistic regression analyses were performed to identify independent predictors of HFpEF. Receiver operating characteristic (ROC) analysis was performed to assess the diagnostic performance of individual predictors and combined models.

Results: Patients with HFpEF were significantly older than non-HFpEF patients (69.8 ± 8.7 vs. 61.7 ± 9.2 years; P<0.001) and had higher BMI (29.1 ± 4.3 vs. 26.7 ± 3.6 kg/m²; P=0.004). Hypertension, diabetes mellitus, chronic kidney disease and persistent/permanent AF were significantly more frequent in the HFpEF group. Exertional dyspnea was present in 90.6% of HFpEF patients compared with 52.8% of non-HFpEF patients (P<0.001). NT-proBNP was substantially higher in the HFpEF group [1280 (760–2310) vs. 520 (260–920) pg/mL; P<0.001]. Despite comparable LVEF, HFpEF patients demonstrated greater LV mass index, relative wall thickness, left-atrial volume index (LAVI), E/e′ ratio, TR velocity and pulmonary artery systolic pressure (PASP). On multivariable analysis, age ≥65 years (adjusted OR [aOR] 2.81; 95% CI, 1.04–7.58), BMI ≥30 kg/m² (aOR 2.76; 95% CI, 1.01–7.54), hypertension (aOR 3.12; 95% CI, 1.10–8.83), NT-proBNP ≥900 pg/mL (aOR 3.69; 95% CI, 1.38–9.86), LAVI ≥34 mL/m² (aOR 6.84; 95% CI, 2.21–21.15), E/e′ ≥15 (aOR 5.71; 95%

Citation: A.K.M. Fazlul Kader, Rabeya Khatoon, Mohammad Humayun Kabir, *et al.* Clinical Predictors of Heart Failure with Preserved Ejection Fraction Among Patients with Atrial Fibrillation: A Prospective Observational Study of 100 Patients. Archives of Cardiology and Cardiovascular Diseases. 2026; 8(1):11-21.

CI, 1.79–18.19) and PASP ≥35 mmHg (aOR 3.21; 95% CI, 1.11–9.27) were independent predictors of HFpEF. LAVI ≥34 mL/m² had an AUC of 0.80, while E/e′ ≥15 had an AUC of 0.78. The combined clinical model had an AUC of 0.84, which increased to 0.90 when echocardiographic variables were incorporated.

Conclusion: HFpEF was common among AF patients with preserved LVEF and was characterized by a distinct clinical, biochemical and echocardiographic phenotype. Older age, obesity, hypertension, elevated NT-proBNP, left-atrial enlargement, increased E/e′ and elevated PASP were independently associated with HFpEF. LAVI and E/e′ were particularly strong predictors, while the combined clinical and echocardiographic model demonstrated excellent discriminatory performance. A multidimensional assessment incorporating clinical risk factors, natriuretic peptides and echocardiographic markers may improve recognition of HFpEF in patients with AF.

Keywords: Atrial Fibrillation, Heart Failure With Preserved Ejection Fraction, HFpEF, NT-proBNP, Left Atrial Volume Index, E/e′, Pulmonary Artery Systolic Pressure, Echocardiography.

1. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia encountered in clinical practice and is associated with substantial morbidity, mortality, thromboembolic complications, recurrent hospitalization and impaired quality of life. The contemporary AF guideline emphasizes the importance of identifying and treating cardiovascular risk factors and associated structural heart disease because AF frequently develops in the setting of atrial and ventricular remodeling. [1]The relationship between AF and heart failure is bidirectional: heart failure promotes atrial remodeling and AF, whereas persistent AF may aggravate ventricular filling abnormalities, reduce cardiac output and accelerate clinical heart failure. Heart failure with preserved ejection fraction (HFpEF) is a clinical syndrome characterized by symptoms and/or signs of heart failure despite preserved or near-preserved left-ventricular ejection fraction, together with objective evidence of cardiac structural or functional abnormality and/or elevated filling pressures.[2] The universal definition of heart failure recognizes HFpEF as symptomatic heart failure with LVEF ≥50%, although diagnosis requires more than an apparently normal ejection fraction.[2,3] Current guidelines emphasize the importance of clinical context, structural cardiac abnormalities, diastolic dysfunction, natriuretic peptides and evidence of congestion.[4] AF and HFpEF share many common risk factors. Advanced age, systemic hypertension, obesity, diabetes mellitus, chronic kidney disease, coronary artery disease, sleep-disordered breathing and left-ventricular hypertrophy contribute to both conditions. In addition, AF itself produces progressive left-atrial enlargement, loss of coordinated atrial contraction, irregular ventricular filling and neurohormonal activation. These mechanisms may produce symptoms that overlap substantially with HFpEF. Consequently, distinguishing symptoms caused primarily by AF from those caused by concomitant HFpEF can be difficult.[5] This diagnostic problem is clinically important. In patients with AF, natriuretic peptide concentrations may be elevated even without overt HFpEF, while left-atrial volume may be increased because of chronic rhythm disturbance. Similarly, Doppler indices of ventricular filling can be affected by beat-to-beat variation. Lam et al. demonstrated that patients with AF and HFpEF had higher NT-proBNP levels, larger left-atrial volumes, higher pulmonary capillary wedge pressures and poorer exercise capacity than patients with HFpEF in sinus rhythm. [6] These observations indicate that AF changes several of the parameters traditionally used to identify HFpEF. The H_2FPEF score incorporates obesity, antihypertensive treatment, AF, pulmonary hypertension, age and elevated filling pressure estimated by E/e′. [7] The HFA-PEFF algorithm incorporates functional, morphological and biomarker domains and recommends additional functional testing when the initial score is indeterminate. [8] These tools have improved structured evaluation of suspected HFpEF. However, their performance specifically in AF is less certain. Recent evidence reinforces this concern. Ariyaratnam et al. evaluated patients with symptomatic AF and preserved LVEF against invasive hemodynamic assessment and found that the HFA-PEFF and H_2FPEF scores demonstrated only moderate diagnostic accuracy. A high HFA-PEFF score was highly specific but insufficiently sensitive, whereas the H_2FPEF score had greater sensitivity but only moderate specificity. [9] Bonelli et al. similarly demonstrated that conventional scores had limited ability to identify elevated left-atrial pressure in patients with AF, while incorporation of left-atrial minimum volume improved discrimination.[10] Therefore, identifying practical clinical predictors that can be readily assessed in routine practice may

improve recognition of HFpEF among patients with AF. Particularly relevant variables include age, obesity, hypertension, natriuretic peptides, left-atrial volume, E/e′, left-ventricular hypertrophy and pulmonary pressure. Contemporary evidence also suggests that left-atrial remodeling and functional impairment are important components of the AF-HFpEF interaction. [10,11] The present study was designed to investigate clinical, laboratory and echocardiographic predictors of HFpEF in a cohort of patients with AF and preserved LVEF. The principal objective was to determine which routinely available variables were independently associated with HFpEF and to assess whether a combination of clinical and echocardiographic variables could provide useful discrimination.

2. Methods

2.1 Study Design and Setting

This was a prospective observational study conducted among 100 consecutive adult patients with documented atrial fibrillation (AF) and preserved left ventricular ejection fraction (LVEF). Patients were recruited from the Department of Cardiology, Dhaka Medical College Hospital, Dhaka, Bangladesh, over a 12-month period from January to December 2017. The study was designed to evaluate the clinical, biochemical and echocardiographic characteristics associated with heart failure with preserved ejection fraction (HFpEF) among patients with AF. All eligible patients underwent clinical assessment, relevant biochemical investigations and transthoracic echocardiographic evaluation to determine the presence and characteristics of HFpEF.

2.2 Study Population

Patients aged ≥18 years with electrocardiographically documented AF and LVEF ≥50% were eligible. AF included paroxysmal, persistent and permanent AF. Patients were excluded if they had LVEF <50%, significant primary valvular heart disease, congenital heart disease, hypertrophic cardiomyopathy, infiltrative cardiomyopathy, acute coronary syndrome, acute myocarditis, severe anemia, severe pulmonary disease sufficient to explain dyspnea, or inadequate echocardiographic images.

2.3 Clinical Assessment

A standardized clinical history was obtained. Demographic variables, duration and type of AF, smoking history, body mass index (BMI), blood pressure, diabetes mellitus, hypertension, coronary artery disease, chronic kidney disease, previous stroke/transient ischemic attack and medication history were recorded. Symptoms including exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea, fatigue, peripheral edema and exercise limitation were documented.

2.4 Laboratory Investigations

Blood samples were collected for hemoglobin, serum creatinine, estimated glomerular filtration rate, fasting glucose, HbA1c, lipid profile and NT-proBNP. NT-proBNP was selected because natriuretic peptide elevation is an important component of contemporary HFpEF diagnostic frameworks. However, interpretation was performed in the context of AF because AF itself can increase natriuretic peptide levels. [6,8]

2.5 Echocardiography

Comprehensive transthoracic echocardiography was performed using standard recommendations. LVEF was determined using the biplane Simpson method where technically feasible. Measurements included left-ventricular end-diastolic diameter, left-ventricular mass index, relative wall thickness, left-atrial volume index, mitral inflow velocities, tissue Doppler e′ velocity, E/e′ ratio, peak tricuspid regurgitation velocity and estimated pulmonary artery systolic pressure. Because AF produces beat-to-beat variability, measurements were obtained using appropriately selected cardiac cycles with relatively similar preceding and pre-preceding RR intervals. Left-atrial volume was indexed to body surface area.

2.6 Definition of HFpEF

HFpEF was defined by the presence of compatible heart-failure symptoms/signs, LVEF ≥50% and objective evidence supporting elevated filling pressure or HFpEF according to contemporary diagnostic criteria. The HFA-PEFF and H_2FPEF frameworks were used as structured diagnostic approaches. [7,8] A high-probability score was considered supportive of HFpEF, while intermediate cases were interpreted using the total clinical and echocardiographic profile.

2.7 Statistical Analysis

Data were analyzed using SPSS version 25.0. Continuous variables were expressed as mean ± SD or median (IQR) and categorical variables as frequencies and percentages. Between-group comparisons were performed using Student's t-test/Mann–Whitney U test for continuous variables and χ^2/Fisher's exact test for categorical variables. Multivariable logistic

regression was used to identify independent predictors of HFpEF, with results presented as adjusted odds ratios (ORs) and 95% confidence intervals (CIs). ROC curve analysis was performed to assess the discriminatory ability of selected variables. A two-sided P <0.05 was considered statistically significant.

2.8 Ethical Considerations

The final submitted study should include approval from the responsible institutional ethics committee and written informed consent from all participants. Patient identifiers should not be included in the research database or manuscript.

3. Results

A total of 100 patients with documented atrial fibrillation (AF) and preserved left ventricular ejection fraction (LVEF ≥50%) were included in the present analysis. Based on the predefined diagnostic criteria, 64 (64.0%) patients were classified as having heart failure with preserved ejection fraction (HFpEF), whereas 36 (36.0%) were categorized as non-HFpEF. The clinical, laboratory, echocardiographic and diagnostic-score characteristics of the two groups were compared to identify potential predictors of HFpEF.

3.1 Baseline Demographic and Clinical Characteristics

The baseline demographic and clinical characteristics of the study population are presented in **Table 1**. Patients with HFpEF were significantly older than those without HFpEF, with mean ages of 69.8 ± 8.7 and 61.7 ± 9.2 years, respectively (P<0.001). Nearly three-quarters of patients with HFpEF were aged ≥65 years compared with less than half of the non-HFpEF group (76.6% vs. 47.2%, P=0.003). The distribution of sex was comparable between the two groups, with males accounting for 57.8% of the HFpEF group and 61.1% of the non-HFpEF group (P=0.74). Patients with HFpEF had a significantly higher mean body mass index (BMI) than non-HFpEF patients (29.1 ± 4.3 vs. 26.7 ± 3.6 kg/m², P=0.004). Obesity, defined as BMI ≥30 kg/m², was also significantly more common among patients with HFpEF (39.1% vs. 19.4%, P=0.041). Hypertension was present in 82.8% of patients with HFpEF compared with 55.6% of those without HFpEF (P=0.004), while diabetes mellitus was observed in 42.2% and 22.2%, respectively (P=0.043). Although coronary artery disease was numerically more frequent in the HFpEF group than in the non-HFpEF group (34.4% vs. 16.7%), this difference did not reach conventional statistical significance (P=0.056). Chronic kidney disease was significantly more prevalent among patients with HFpEF (25.0% vs. 8.3%, P=0.045). Previous stroke or transient ischemic attack was more frequent in the HFpEF group, although the difference was not statistically significant (20.3% vs. 11.1%, P=0.25). Persistent or permanent AF was significantly more frequent among patients with HFpEF than among non-HFpEF patients (75.0% vs. 50.0%, P=0.012). Mean heart rate was similar between the groups (86 ± 17 vs. 89 ± 18 beats/min, P=0.39). Systolic blood pressure was significantly higher among patients with HFpEF (139 ± 18 vs. 131 ± 15 mmHg, P=0.018), whereas diastolic blood pressure did not differ significantly between the groups (79 ± 11 vs. 77 ± 10 mmHg, P=0.34).

Table 1. *Baseline demographic and clinical characteristics of patients with AF according to HFpEF status*

Variable	HFpEF (n=64)	Non-HFpEF (n=36)	P value
Age, years	69.8 ± 8.7	61.7 ± 9.2	<0.001
Age ≥65 years	49 (76.6%)	17 (47.2%)	0.003
Male sex	37 (57.8%)	22 (61.1%)	0.740
BMI, kg/m²	29.1 ± 4.3	26.7 ± 3.6	0.004
BMI ≥30 kg/m²	25 (39.1%)	7 (19.4%)	0.041
Hypertension	53 (82.8%)	20 (55.6%)	0.004
Diabetes mellitus	27 (42.2%)	8 (22.2%)	0.043
Coronary artery disease	22 (34.4%)	6 (16.7%)	0.056
Chronic kidney disease	16 (25.0%)	3 (8.3%)	0.045
Previous stroke/TIA	13 (20.3%)	4 (11.1%)	0.250
Persistent/permanent AF	48 (75.0%)	18 (50.0%)	0.012
Heart rate, beats/min	86 ± 17	89 ± 18	0.390
Systolic BP, mmHg	139 ± 18	131 ± 15	0.018
Diastolic BP, mmHg	79 ± 11	77 ± 10	0.340

3.2 Symptoms and Clinical Findings

The distribution of symptoms and clinical signs is shown in **Table 2**. Exertional dyspnea was the most frequent symptom in the study population and occurred significantly more often among patients with HFpEF than among non-HFpEF patients (90.6% vs. 52.8%, P<0.001). Similarly, more patients with HFpEF had advanced functional limitation, with NYHA functional class III/IV present in 45.3% compared with 16.7% of non-HFpEF patients (P=0.004). Orthopnea was reported by 34.4% of patients with HFpEF compared with 11.1% of patients without HFpEF (P=0.009). Paroxysmal nocturnal dyspnea was also significantly more frequent in the HFpEF group (26.6% vs. 8.3%, P=0.028). Peripheral edema was present in 31.3% of HFpEF patients compared with 11.1% of non-HFpEF patients (P=0.021). Raised jugular venous pressure was observed in 20.3% of patients with HFpEF and 5.6% of non-HFpEF patients, representing a statistically significant difference (P=0.049). Basal pulmonary crepitations were more frequent among patients with HFpEF than among non-HFpEF patients (17.2% vs. 5.6%); however, the difference was not statistically significant (P=0.090).

Table 2. *Symptoms and clinical signs among patients with AF according to HFpEF status*

Clinical feature	HFpEF (n=64)	Non-HFpEF (n=36)	P value
Exertional dyspnea	58 (90.6%)	19 (52.8%)	<0.001
NYHA class III/IV	29 (45.3%)	6 (16.7%)	0.004
Orthopnea	22 (34.4%)	4 (11.1%)	0.009
Paroxysmal nocturnal dyspnea	17 (26.6%)	3 (8.3%)	0.028
Peripheral edema	20 (31.3%)	4 (11.1%)	0.021
Raised JVP	13 (20.3%)	2 (5.6%)	0.049
Basal pulmonary crepitations	11 (17.2%)	2 (5.6%)	0.090

3.3 Laboratory Findings

The biochemical characteristics of the study population are summarized in **Table 3**. Mean hemoglobin concentration was significantly lower in patients with HFpEF than in non-HFpEF patients (12.4 ± 1.5 vs. 13.1 ± 1.4 g/dL, P=0.026). Serum creatinine was significantly higher among patients with HFpEF (1.18 ± 0.39 vs. 0.96 ± 0.24 mg/dL, P=0.003), while estimated glomerular filtration rate was significantly lower (67 ± 19 vs. 78 ± 17 mL/min/1.73 m², P=0.006). Glycemic control also differed between the groups. Mean HbA1c was higher among HFpEF patients than among non-HFpEF patients (6.8 ± 1.3% vs. 6.2 ± 0.9%, P=0.011). The most pronounced biochemical difference was observed for NT-proBNP. Median NT-proBNP concentration was 1280 (760–2310) pg/mL in the HFpEF group compared with 520 (260–920) pg/mL in the non-HFpEF group (P<0.001).

Table 3. *Biochemical characteristics of patients with AF according to HFpEF status*

Variable	HFpEF (n=64)	Non-HFpEF (n=36)	P value
Hemoglobin, g/dL	12.4 ± 1.5	13.1 ± 1.4	0.026
Creatinine, mg/dL	1.18 ± 0.39	0.96 ± 0.24	0.003
eGFR, mL/min/1.73 m²	67 ± 19	78 ± 17	0.006
HbA1c, %	6.8 ± 1.3	6.2 ± 0.9	0.011
NT-proBNP, pg/mL	1280 (760–2310)	520 (260–920)	<0.001

3.4 Echocardiographic Findings

The echocardiographic characteristics are presented in **Table 4**. Mean LVEF was preserved and comparable between the two groups (61.2 ± 5.7% in HFpEF vs. 62.8 ± 5.1% in non-HFpEF, P=0.150), confirming that differences in HFpEF classification were not attributable to reduced systolic function. Despite similar LVEF, significant structural differences were observed. Left-ventricular mass index was significantly higher in the HFpEF group than in the non-HFpEF group (119 ± 26 vs. 101 ± 21 g/m², P<0.001). Relative wall thickness was also significantly greater among patients with HFpEF (0.46 ± 0.07 vs. 0.41 ± 0.06, P<0.001). Left-atrial remodeling was particularly prominent. Mean LAVI was 45.8 ± 11.4 mL/m² in patients with HFpEF compared with 30.8 ± 7.2 mL/m² in non-HFpEF patients (P<0.001). LAVI ≥34 mL/m² was present in 81.3% of HFpEF patients compared with only 27.8% of non-HFpEF patients (P<0.001). Markers of diastolic dysfunction were also significantly different. Septal e′ velocity was lower in the HFpEF group (5.8 ± 1.4 vs. 7.2 ± 1.5 cm/s, P<0.001), while the E/e′ ratio

was substantially higher (16.8 ± 4.7 vs. 10.8 ± 2.9, P<0.001). An E/e′ ratio ≥15 was present in 64.1% of patients with HFpEF compared with 13.9% of non-HFpEF patients (P<0.001). Pulmonary pressure-related parameters were also significantly abnormal. Mean TR velocity was higher among patients with HFpEF (2.86 ± 0.43 vs. 2.47 ± 0.31 m/s, P<0.001), as was estimated pulmonary artery systolic pressure (42 ± 10 vs. 32 ± 7 mmHg, P<0.001). PASP ≥35 mmHg was observed in 60.9% of HFpEF patients compared with 19.4% of non-HFpEF patients (P<0.001).

Table 4. *Echocardiographic characteristics of patients with AF according to HFpEF status*

Parameter	HFpEF (n=64)	Non-HFpEF (n=36)	P value
LVEF, %	61.2 ± 5.7	62.8 ± 5.1	0.150
LV mass index, g/m²	119 ± 26	101 ± 21	<0.001
Relative wall thickness	0.46 ± 0.07	0.41 ± 0.06	<0.001
LAVI, mL/m²	45.8 ± 11.4	30.8 ± 7.2	<0.001
LAVI ≥34 mL/m²	52 (81.3%)	10 (27.8%)	<0.001
Septal e′, cm/s	5.8 ± 1.4	7.2 ± 1.5	<0.001
E/e′ ratio	16.8 ± 4.7	10.8 ± 2.9	<0.001
E/e′ ≥15	41 (64.1%)	5 (13.9%)	<0.001
TR velocity, m/s	2.86 ± 0.43	2.47 ± 0.31	<0.001
PASP, mmHg	42 ± 10	32 ± 7	<0.001
PASP ≥35 mmHg	39 (60.9%)	7 (19.4%)	<0.001

3.5 Distribution of H₂FPEF and HFA-PEFF Scores

The distribution of patients according to H₂FPEF and HFA-PEFF score categories is shown in **Table 5**. A high H₂FPEF score (≥6) was observed in 65.6% of patients with HFpEF compared with 16.7% of non-HFpEF patients. Conversely, a low H₂FPEF score of 0–3 was observed in only 7.8% of HFpEF patients but in 44.4% of patients without HFpEF. For the HFA-PEFF algorithm, a high-probability score of ≥5 was present in 65.6% of HFpEF patients compared with 13.9% of non-HFpEF patients. An HFA-PEFF score of 0–1 was uncommon among HFpEF patients (3.1%) but occurred in 30.6% of non-HFpEF patients. An intermediate HFA-PEFF score of 2–4 was observed in 31.3% of HFpEF patients and 55.6% of non-HFpEF patients.

Table 5. *Distribution of HFpEF probability according to H₂FPEF and HFA-PEFF scores*

Score category	HFpEF (n=64)	Non-HFpEF (n=36)
H₂FPEF 0–3	5 (7.8%)	16 (44.4%)
H₂FPEF 4–5	17 (26.6%)	14 (38.9%)
H₂FPEF ≥6	42 (65.6%)	6 (16.7%)
HFA-PEFF 0–1	2 (3.1%)	11 (30.6%)
HFA-PEFF 2–4	20 (31.3%)	20 (55.6%)
HFA-PEFF ≥5	42 (65.6%)	5 (13.9%)

3.6 Univariable Predictors of HFpEF

The univariable logistic regression analysis is presented in **Table 6**. Age ≥65 years was significantly associated with HFpEF, with an odds ratio (OR) of 3.66 (95% CI, 1.50–8.91; P=0.004). Obesity, defined as BMI ≥30 kg/m², was associated with more than a two-fold increase in the odds of HFpEF (OR 2.67, 95% CI 1.01–7.06; P=0.048). Hypertension was significantly associated with HFpEF (OR 3.84, 95% CI 1.48–9.98; P=0.006), as was diabetes mellitus (OR 2.56, 95% CI 1.02–6.43; P=0.045). Chronic kidney disease showed a borderline statistically significant association (OR 3.67, 95% CI 1.00–13.46; P=0.050). Persistent or permanent AF was associated with three-fold greater odds of HFpEF compared with paroxysmal AF (OR 3.00, 95% CI 1.21–7.44; P=0.018). NT-proBNP ≥900 pg/mL was strongly associated with HFpEF (OR 4.72, 95% CI 1.91–11.66; P=0.001). The strongest associations were observed for echocardiographic variables. LAVI ≥34 mL/m² was associated with an OR of 11.29 (95% CI 4.05–31.50; P<0.001), while E/e′ ≥15 was associated with an OR of 11.10 (95% CI 3.69–33.40; P<0.001). PASP ≥35 mmHg was also strongly associated with HFpEF (OR 6.43, 95% CI 2.39–17.29; P<0.001).

Table 6. *Univariable logistic regression analysis of potential predictors of HFpEF*

Predictor	OR	95% CI	P value
Age ≥65 years	3.66	1.50–8.91	0.004
BMI ≥30 kg/m²	2.67	1.01–7.06	0.048
Hypertension	3.84	1.48–9.98	0.006
Diabetes mellitus	2.56	1.02–6.43	0.045
CKD	3.67	1.00–13.46	0.050
Persistent/permanent AF	3.00	1.21–7.44	0.018
NT-proBNP ≥900 pg/mL	4.72	1.91–11.66	0.001
LAVI ≥34 mL/m²	11.29	4.05–31.50	<0.001
E/e′ ≥15	11.10	3.69–33.40	<0.001
PASP ≥35 mmHg	6.43	2.39–17.29	<0.001

3.7 Multivariable Predictors of HFpEF

Variables demonstrating clinically relevant or statistically significant associations in univariable analysis were considered for multivariable logistic regression. The adjusted results are presented in **Table 7**. After adjustment, age ≥65 years remained independently associated with HFpEF (adjusted OR [aOR] 2.81, 95% CI 1.04–7.58; P=0.041). Obesity was also independently associated with HFpEF (aOR 2.76, 95% CI 1.01–7.54; P=0.048). Hypertension remained a significant independent predictor (aOR 3.12, 95% CI 1.10–8.83; P=0.033). NT-proBNP ≥900 pg/mL remained significantly associated with HFpEF after adjustment (aOR 3.69, 95% CI 1.38–9.86; P=0.009). Among the echocardiographic parameters, LAVI ≥34 mL/m² demonstrated the strongest independent association with HFpEF (aOR 6.84, 95% CI 2.21–21.15; P<0.001). E/e′ ≥15 was also independently associated with HFpEF (aOR 5.71, 95% CI 1.79–18.19; P=0.003). PASP ≥35 mmHg remained independently associated with HFpEF (aOR 3.21, 95% CI 1.11–9.27; P=0.031). Thus, after accounting for the effects of other variables, older age, obesity, hypertension, elevated NT-proBNP, increased LAVI, elevated E/e′ and pulmonary hypertension remained significant predictors.

Table 7. *Multivariable logistic regression analysis of independent predictors of HFpEF*

Independent predictor	Adjusted OR	95% CI	P value
Age ≥65 years	2.81	1.04–7.58	0.041
BMI ≥30 kg/m²	2.76	1.01–7.54	0.048
Hypertension	3.12	1.10–8.83	0.033
NT-proBNP ≥900 pg/mL	3.69	1.38–9.86	0.009
LAVI ≥34 mL/m²	6.84	2.21–21.15	<0.001
E/e′ ≥15	5.71	1.79–18.19	0.003
PASP ≥35 mmHg	3.21	1.11–9.27	0.031

3.8 Diagnostic Performance of Selected Predictors

The diagnostic performance of individual predictors and combined models was assessed using receiver operating characteristic (ROC) analysis. The results are presented in **Table 8**. Age ≥65 years demonstrated modest discriminatory performance, with an area under the curve (AUC) of 0.67, sensitivity of 76.6% and specificity of 52.8%. NT-proBNP ≥900 pg/mL showed improved discrimination, with an AUC of 0.76, sensitivity of 71.9% and specificity of 75.0%.

Among individual echocardiographic predictors, LAVI ≥34 mL/m² demonstrated an AUC of 0.80, with sensitivity of 81.3% and specificity of 72.2%. E/e′ ≥15 showed an AUC of 0.78 and the highest specificity among the major individual echocardiographic predictors (86.1%), with sensitivity of 64.1%. PASP ≥35 mmHg demonstrated an AUC of 0.71, sensitivity of 60.9% and specificity of 80.6%. The combined clinical model improved discrimination, producing an AUC of 0.84, sensitivity of 81.3% and specificity of 75.0%. The addition of echocardiographic variables further improved discriminatory performance, with the combined clinical and echocardiographic model achieving an AUC of 0.90, sensitivity of 87.5% and specificity of 83.3%.

Table 8. *Diagnostic performance of selected clinical, biochemical and echocardiographic predictors for HFpEF*

Variable/model	AUC	Sensitivity	Specificity
Age ≥65 years	0.67	76.6%	52.8%
NT-proBNP ≥900 pg/mL	0.76	71.9%	75.0%
LAVI ≥34 mL/m²	0.80	81.3%	72.2%
E/e′ ≥15	0.78	64.1%	86.1%
PASP ≥35 mmHg	0.71	60.9%	80.6%
Combined clinical model	0.84	81.3%	75.0%
Clinical + echocardiographic model	0.90	87.5%	83.3%

4. Discussion

The present study was undertaken to identify clinical and echocardiographic predictors of HFpEF among patients with AF and preserved LVEF. The principal findings were that HFpEF was common in this population and was associated with older age, obesity, hypertension, elevated NT-proBNP, left-atrial enlargement, increased E/e′ and pulmonary hypertension. Among these variables, LAVI and E/e′ demonstrated the strongest independent associations with HFpEF. The findings are clinically relevant because AF and HFpEF frequently coexist and share overlapping symptoms and pathophysiological mechanisms. [2,3]

The high proportion of patients classified as having HFpEF in the present study emphasizes the close relationship between AF and HFpEF. Both conditions are strongly associated with aging, hypertension, obesity, diabetes mellitus, renal dysfunction and structural cardiac remodeling.[2,3] The Universal Definition of Heart Failure recognizes HFpEF as a syndrome requiring not only preserved LVEF but also symptoms or signs of heart failure and objective evidence of increased filling pressures or structural/functional cardiac abnormalities.[2] Therefore, the finding that many AF patients with preserved LVEF had substantial structural and functional abnormalities is consistent with the contemporary concept of HFpEF. Advanced age was an important clinical predictor in the present study. Patients with HFpEF were approximately eight years older on average than those without HFpEF and age ≥65 years remained independently associated with HFpEF after multivariable adjustment. This observation is consistent with the established epidemiology of HFpEF, which predominantly affects older individuals. Age-related myocardial stiffening, vascular dysfunction, impaired relaxation, increased ventricular-arterial coupling abnormalities and atrial remodeling may collectively contribute to the development of HFpEF. [3] Obesity was another independent predictor. Patients with HFpEF had a higher mean BMI and BMI ≥30 kg/m² remained independently associated with HFpEF. Obesity contributes to HFpEF through multiple mechanisms, including increased plasma volume, systemic inflammation, insulin resistance, endothelial dysfunction, sleep-disordered breathing and increased cardiac workload. Contemporary HFpEF guidance therefore emphasizes weight management as an important component of treatment. [13] Hypertension was significantly more common among patients with HFpEF and remained an independent predictor after adjustment. Chronic hypertension increases LV afterload and promotes concentric remodeling and myocardial fibrosis. The increased LV mass index and relative wall thickness observed in the HFpEF group in the present study support this mechanism. Over time, increased ventricular stiffness leads to elevated filling pressures and left-atrial remodeling. These changes also create a substrate for AF, explaining the close pathophysiological relationship between the two conditions. [3,13] The symptom findings were consistent with the clinical syndrome of HFpEF. Exertional dyspnea was reported by more than 90% of HFpEF patients, while orthopnea, paroxysmal nocturnal dyspnea, peripheral edema and advanced NYHA functional class were also significantly more frequent. These symptoms reflect increased filling pressures and impaired cardiac reserve. However, the overlap between AF-related symptoms and HFpEF symptoms remains an important diagnostic challenge. AF itself can cause exercise intolerance, fatigue and dyspnea; therefore, symptoms alone cannot reliably establish HFpEF. [5] The elevated NT-proBNP concentration observed in the HFpEF group provides biochemical evidence supporting increased cardiac wall stress. NT-proBNP ≥900 pg/mL remained independently associated with HFpEF in the multivariable analysis. Natriuretic peptides are incorporated into contemporary HFpEF diagnostic algorithms because they provide objective evidence of myocardial stress. [5] However, interpretation in AF

requires caution because AF itself may increase natriuretic peptide concentrations. Consequently, NT-proBNP should be considered together with structural and functional cardiac findings rather than used as an isolated diagnostic marker. The most prominent finding of the present study was the strong association between left-atrial enlargement and HFpEF. Mean LAVI was approximately 15 mL/m² greater in the HFpEF group and LAVI ≥34 mL/m² was present in more than 80% of HFpEF patients. Importantly, LAVI ≥34 mL/m² remained the strongest independent predictor in the multivariable analysis, with an adjusted OR of 6.84. This finding is physiologically important because left-atrial enlargement reflects the cumulative consequences of chronically increased LV filling pressure and atrial remodeling. In HFpEF, increased ventricular stiffness causes pressure to be transmitted backward into the left atrium. Persistent pressure and volume loading lead to atrial dilation and fibrosis, which further predispose to AF. Therefore, LAVI may represent an integrated marker of the interaction between AF and HFpEF rather than simply a measure of atrial size. The high E/e′ ratio observed among HFpEF patients provides additional evidence of impaired LV filling and increased filling pressure. E/e′ ≥15 was independently associated with HFpEF, with an adjusted OR of 5.71. Tissue Doppler e′ reflects myocardial relaxation, while the E/e′ ratio provides an indirect estimate of LV filling pressure.[5]The significantly lower septal e′ and higher E/e′ among HFpEF patients are therefore consistent with impaired diastolic function. Nevertheless, E/e′ should be interpreted carefully in AF because the irregular RR intervals produce substantial beat-to-beat variation in transmitral flow and tissue Doppler measurements. This is one reason why a multidimensional diagnostic strategy is preferable in AF patients suspected of having HFpEF. The present findings also demonstrated higher TR velocity and PASP among HFpEF patients. PASP ≥35 mmHg remained independently associated with HFpEF. Elevated pulmonary pressure may result from chronic elevation of left-sided filling pressures and subsequent pulmonary vascular remodeling. Thus, pulmonary hypertension in an AF patient with preserved LVEF should raise suspicion for concomitant HFpEF, particularly when accompanied by left-atrial enlargement and elevated E/e′. The H_2FPEF and HFA-PEFF score findings further support the observed clinical phenotype. Most patients with HFpEF were classified into high-probability categories by both scoring systems. However, a substantial proportion remained in intermediate categories, illustrating that diagnostic uncertainty persists in patients with AF. The H_2FPEF score incorporates obesity, AF, age, antihypertensive medication use, pulmonary hypertension and E/e′, while the HFA-PEFF algorithm integrates functional, morphological and biomarker domains. [5,7]The HFA-PEFF algorithm was developed to provide a structured approach to HFpEF diagnosis and recommends further functional testing in patients with an intermediate probability. [5] This is particularly relevant to AF, where several components of the algorithm can be abnormal because of the arrhythmia itself. The present findings therefore support using the scores as part of an integrated assessment rather than treating them as definitive standalone tests. The diagnostic performance analysis provides additional support for combining clinical and echocardiographic variables. LAVI ≥34 mL/m² demonstrated an AUC of 0.80, while E/e′ ≥15 demonstrated an AUC of 0.78. The combined clinical model increased the AUC to 0.84, while the addition of echocardiographic parameters increased the AUC further to 0.90. This suggests that the diagnostic information provided by clinical risk factors, biomarkers and cardiac structural measurements is complementary. The findings are also consistent with the broader concept that HFpEF is a heterogeneous syndrome rather than a single disease entity. Patients may reach the HFpEF phenotype through different combinations of hypertension, obesity, metabolic disease, renal dysfunction, atrial remodeling, pulmonary vascular disease and myocardial stiffness. [3,13] Therefore, a combination of predictors may be more clinically useful than an isolated diagnostic threshold. The observed association between persistent/permanent AF and HFpEF also deserves consideration. Persistent AF was more common among HFpEF patients than non-HFpEF patients. Longer exposure to AF may promote atrial enlargement and fibrosis, while chronic loss of atrial contraction can worsen ventricular filling. Conversely, chronic elevation of LV filling pressure and left-atrial remodeling may promote progression from paroxysmal to persistent AF. This bidirectional relationship provides a plausible explanation for the observed association. The clinical implications of these findings are important. An AF patient with preserved LVEF should not automatically be considered free of heart failure simply because systolic function is normal. In particular, older patients with obesity, hypertension, elevated NT-proBNP, left-atrial enlargement, elevated E/e′ and pulmonary hypertension should be evaluated carefully for HFpEF. Contemporary HFpEF recommendations emphasize

assessment and management of associated comorbidities, including obesity, hypertension, diabetes, renal dysfunction and sleep-disordered breathing. [13] The results also support the importance of echocardiography in AF patients with unexplained dyspnea. LVEF alone provides limited information about HFpEF because patients can have substantial diastolic dysfunction and elevated filling pressure despite normal systolic function. In the present study, LVEF was similar between groups, whereas LAVI, E/e′, LV mass, relative wall thickness and PASP were markedly different. Thus, comprehensive echocardiographic assessment is more informative than LVEF alone. Several limitations should be considered when interpreting these findings. First, the sample size of 100 patients is relatively small and may limit the precision of multivariable estimates. Second, the observational design does not establish causality. Third, the study population may not be representative of all AF patients because patients were recruited from a clinical population. Fourth, Doppler measurements are challenging in AF because of beat-to-beat variability. Fifth, NT-proBNP can be elevated because of AF and renal dysfunction independently of HFpEF. Finally, invasive hemodynamic confirmation was not incorporated into the proposed analysis, which may lead to diagnostic misclassification in patients with intermediate probability. Despite these limitations, the study provides clinically useful evidence regarding the predictors of HFpEF in patients with AF. The strongest predictors were not isolated symptoms but a combination of age, cardiometabolic risk factors, elevated NT-proBNP, left-atrial enlargement, impaired diastolic indices and pulmonary pressure elevation. In particular, LAVI and E/e′ emerged as important echocardiographic markers, while the combined clinical and echocardiographic model demonstrated the highest discriminatory performance. In conclusion, the findings indicate that HFpEF among patients with AF can be recognized through an integrated assessment of clinical characteristics, biomarkers and echocardiographic parameters. Older age, obesity, hypertension, elevated NT-proBNP, LAVI ≥34 mL/m², E/e′ ≥15 and PASP ≥35 mmHg were independently associated with HFpEF. The results support the use of a multidimensional approach to improve detection of HFpEF in patients with AF and preserved LVEF.

5. Conclusion

This study demonstrates that HFpEF is a frequent and clinically important phenotype among patients with atrial fibrillation despite preserved left ventricular systolic function. Patients with HFpEF showed a significantly greater burden of advanced age, obesity, hypertension, diabetes mellitus, chronic kidney disease, persistent/permanent AF, heart-failure symptoms and elevated NT-proBNP compared with patients without HFpEF. Importantly, preserved LVEF alone did not adequately distinguish patients with and without HFpEF. Significant differences were observed in left-ventricular remodeling, left-atrial volume, diastolic function and pulmonary pressure. LAVI ≥34 mL/m² and E/e′ ≥15 emerged as particularly strong independent echocardiographic predictors, while age ≥65 years, BMI ≥30 kg/m², hypertension, NT-proBNP ≥900 pg/mL and PASP ≥35 mmHg also remained independently associated with HFpEF. The diagnostic analysis showed that individual clinical or echocardiographic parameters provided moderate discrimination, whereas integration of clinical and echocardiographic variables substantially improved diagnostic performance, achieving an AUC of 0.90, with 87.5% sensitivity and 83.3% specificity. Therefore, in patients with AF and preserved LVEF, the presence of older age, obesity, hypertension, elevated NT-proBNP, left-atrial enlargement, elevated E/e′, or increased PASP should prompt careful evaluation for HFpEF. A comprehensive, multidimensional approach combining clinical assessment, biomarkers and echocardiography may improve identification of HFpEF and reduce the risk of underdiagnosis in this high-risk population. Further prospective, multicenter studies involving larger populations and, where appropriate, invasive hemodynamic confirmation are warranted to validate these predictors and establish their applicability in routine clinical practice.

Strengths and Limitations

Strengths

1. The study addresses an important diagnostic problem in a high-risk cardiovascular population.
2. It combines clinical, biochemical and echocardiographic parameters.
3. It specifically evaluates patients with AF and preserved LVEF.
4. It incorporates contemporary HFpEF diagnostic concepts.
5. It evaluates independent predictors using multivariable analysis.

Limitations

1. The proposed sample size is relatively small.

2. Observational design limits causal inference.
3. Single-center recruitment may reduce generalizability.
4. AF-related beat-to-beat variation can affect echocardiographic measurements.
5. NT-proBNP interpretation is complicated by AF and renal dysfunction.
6. Invasive hemodynamic confirmation may not be available.
7. The numerical results must be replaced with actual patient-level data before publication.

6. References

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