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Research Article

Heart failure with preserved ejection fraction, clinical risk factors, biomarkers and predictors of adverse outcomes.

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Abstract: ***Background:*** HFpEF is a condition that is associated with significant morbidity and mortality. The discovery of clinical risk factors and biomarkers related to adverse outcome will better help to stratify and manage risk. The study objective was to assess clinical risk factors, biomarkers and echocardiographic parameters that are associated with adverse outcomes in patients with HFpEF. ***Methods:*** This is a prospective observational cohort study of 220 patients with HFpEF at a tertiary care hospital in Pakistan. Baseline demographic, clinical and laboratory data and echocardiographic parameters were evaluated. All-cause mortality or hospitalization for worsening HF were evaluated at 6-month follow-up. Multivariable Cox proportional hazards regression was used to identify independent predictors. ***Results:*** Adverse outcomes were seen in 55 patients (25.0%). Patients who were affected were significantly older ($p = 0.001$) and much more likely to be in an advanced NYHA functional class, atrial fibrillation and chronic kidney disease (all $p < 0.001$). NT-proBNP and high-sensitivity troponin levels were significantly raised (both $p < 0.001$). Advanced NYHA class (HR = 2.33), atrial fibrillation (HR = 2.09), increasing age (HR = 1.68 per decade), NT-proBNP (HR = 2.21) and high-sensitivity troponin (HR = 2.29) were all independent predictors. ***Conclusion:*** Clinical features and cardiac biomarker levels can offer important prognostic data in HFpEF, which can be used in daily practice for prognosticating and monitoring individual patients.

Keywords: Heart Failure with Preserved Ejection Fraction, NT-proBNP, cardiac Troponin, atrial fibrillation, risk factors, adverse outcomes.

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INTRODUCTION

Heart failure with preserved ejection fraction (HFpEF) is a growing cardiovascular syndrome with significant morbidity, re-hospitalisation, poor quality of life and mortality. It is responsible for about 50% of all heart failure cases in the world and it is rising due to population ageing and growing burden of cardiovascular and metabolic diseases. The symptoms and signs of heart failure are typical; a left ventricular ejection fraction (LVEF) of ≥50%, and objective measurement of raised cardiac filling pressures or structural and functional cardiac abnormalities. Although the EF is preserved, patients who develop the condition often feel short of breath on exertion, accumulate fluid in their bodies, and gradually lose their function. Early diagnosis, risk stratification and management are particularly difficult due to the heterogeneous pathophysiology and overlapping clinical manifestations [1,2].

Several cardiovascular and systemic risk factors (e.g., advanced age, hypertension, diabetes mellitus, obesity, coronary artery disease, atrial fibrillation, and chronic kidney disease) all play a role in the development and progression of HFpEF. These factors lead to myocardial stiffness, poor ventricular relaxation, endothelial dysfunction, systemic inflammation and raised ventricular filling pressures. Renal dysfunction and cardiovascular abnormalities add to the complexity of the clinical course and can predispose to worse clinical outcomes. Past studies have shown that HFpEF is a clinical syndrome with a variety of comorbidities that serve to worsen the disease and its prognosis, not a single condition of cardiac dysfunction. Hence, it is essential to identify the clinical risk factors that are associated with the disease and thus enable identification of high-risk patients and the ability to manage them individually [3,4].

Biomarkers in the circulation are increasingly important for the diagnosis, severity and prediction of cardiovascular complications of HFpEF. Biomarkers in the blood are becoming more important for diagnosing understanding the severity and predicting the problems that happen with HFpEF. The N-terminal -B-type natriuretic peptide (NT-proBNP) is a sign of stress on the heart muscle and high pressure inside the heart. The sensitivity cardiac troponin (hs-cTn) shows if the heart muscle is injured. This link with damage in the heart muscle and worse changes in the heart and worse health outcomes. Also the sensitivity C-reactive protein (hs-CRP) can give information about body-wide inflammation. The serum creatinine and estimated glomerular filtration rate can help show if the kidneys are not working properly and how that affects heart disease risk. Other health issues like obesity, atrial fibrillation and kidney problems can change how these biomarkers are understood. So using both methods biomarkers and clinical and echo tests) can give a better idea of how bad the disease is and how likely it is for bad things to happen than using either method alone [1,3].

Patients with HFpEF often have problems like being admitted to the hospital because their heart failure is getting worse having heart problems or dying. The I-PRESERVE study showed that people with an almost normal left ventricular ejection fraction have a lot of health problems which can be hard to treat [4]. Recently the EMPEROR-Preserved study with 5,988 patients showed that empagliflozin helped reduce the chance of dying from heart problems or being admitted to the hospital for heart failure more than a dummy drug [5]. Similarly the DELIVER study with 6,263 patients who had mild to moderate heart failure, with normal or slightly lower ejection fraction showed that dapagliflozin helped reduce the chance of heart failure getting worse or dying from heart problems [6]. While these investigations have enhanced the therapeutic management, a correct identification of patients at high risk still remains crucial for the optimization of follow-up, selection of the intervention or of the preventive interventions and reduction of preventable hospitalizations.

Hypertension, diabetes mellitus, obesity and other cardiovascular risk factors are common and growing in Pakistan, which brings challenges for the management of HFpEF. In a hospital-based study from Lahore, 305 patients with heart failure showed that those with HFpEF were on average older, and more likely to have hypertension and diabetes, and to be obese, compared with those with reduced ejection fraction [7]. On the other hand, locally available data looking at the combined prognostic value of clinical risk factors, cardiac biomarkers and echo parameters is still sparse. Making it easy to identify easily accessible predictors of adverse outcomes can help to establish affordable risk stratification and aid in clinical decision making in resource limited healthcare environments. Hence, the present study sought to assess the clinical risk factors, laboratory biomarkers, and echocardiographic features for adverse outcomes in patients with HFpEF and identify independent predictors of all-cause mortality and heart-failure-related hospitalization over 12-months of follow-up.

MATERIALS AND METHODS

Study design and setting

This is a prospective observational cohort study which was carried out in the Department of Cardiology in a tertiary care teaching hospital during January - December 2025 in Pakistan. Consecutive recruitment of adult patients with confirmed diagnosis of heart failure with preserved ejection fraction (HFpEF) was performed in the cardiology inpatient and outpatient services. All patients were followed for 6 months from the enrolment to check for adverse clinical outcomes.

Sample size and sampling method

Patients aimed for a total of 220. We set the sample size by assuming that 25 % of patients would have adverse outcomes while we followed them. We also used a 95 % confidence level. Aimed for about 6 % absolute precision. We added a margin for patients who might be lost to follow-up. We chose a non-probability sampling method. This meant that every patient who was eligible and came to the clinic during the study period was invited to join until we reached the required number of patients.

Eligibility criteria

Patients who were 18 years of age or older and who showed symptoms or signs that suggested heart failure were considered. These patients also had a ventricular ejection fraction (LVEF) of at least 50 %. We diagnosed HFpEF according to standards. HFpEF diagnosis relied on the presence of symptoms or signs of heart failure, preserved LVEF and objective evidence of an increase in ventricular filling pressure or structural or functional heart abnormalities that matched diastolic dysfunction. Patients who had a documented LVEF of 40 % or less and whose LVEF later improved to 50 % or more were not counted as having HFpEF.

Patients who had a ST-elevation myocardial infarction at the time of presentation severe primary valvular heart disease that required intervention, complex congenital heart disease, severe primary pulmonary hypertension, active cancer with a limited life expectancy end-stage kidney disease that required dialysis or who could not finish follow-up were excluded.

Diagnosis

All patients had transthoracic echocardiography. A skilled cardiologist or trained echocardiographer performed the exam using standard two-dimensional, M-mode and Doppler techniques. We calculated LVEF preferably with the modified biplane Simpson method. An LVEF of 50 % or more was considered preserved.

Evidence that patients had elevated left filling pressure or diastolic dysfunction included any of the following: an average E/e' ratio higher than 9, a left atrial volume index above 34 mL/m² for patients in sinus rhythm a left ventricular mass index of at least 115 g/m² for men or 95 g/m² for women a tricuspid regurgitation velocity above 2.8 m/s a pulmonary artery systolic pressure above 35 mmHg or an elevated natriuretic peptide concentration. For patients, with fibrillation we used higher natriuretic peptide and left atrial volume thresholds that are recommended for this group during diagnosis.

Clinical assessment and risk factors

At the start of the study basic personal and health details were written down on a form. The information included age, sex, body mass index (BMI) whether the person smoked, blood pressure (both bottom numbers) resting heart rate how long heart failure symptoms had been present New York Heart Association (NYHA) functional class and if the person had been hospitalized before for heart failure.

Other major health risks recorded were blood pressure, diabetes, obesity, high cholesterol, heart disease, irregular heartbeat (atrial fibrillation) kidney problems, past heart attack and a history of stroke.

High blood pressure was noted if the person had been diagnosed before was taking medicine for it or had office blood pressure readings of 140/90 mmHg or higher on repeat checks. Diabetes was confirmed if there was a diagnosis, treatment for diabetes fasting blood sugar of 126 mg/dL or above or HbA1c of 6.5% or more. Obesity was defined as BMI of 30 kg/m² or higher following the World Health Organization standard. Anemia was identified when hemoglobin was than 13 g/dL in men or less than 12 g/dL in women. Kidney disease was recorded if it had been noted before or if estimated glomerular filtration rate (eGFR) was below 60 mL/min/1.73 m² for least three months. Atrial fibrillation was found by looking at medical records or through a 12-lead electrocardiogram.

Laboratory and biomarker assessment

Blood samples were taken from each person at the beginning using standard methods. To keep things for local hospitals in Pakistan only tests commonly available in big city hospitals were chosen. These included N- pro-B-type natriuretic peptide (NT-proBNP) high-sensitivity cardiac troponin I or T high-sensitivity C-reactive protein (hs-CRP) serum creatinine, blood urea nitrogen, serum sodium, serum potassium, hemoglobin, fasting blood glucose, HbA1c and lipid profile. The main heart-related marker was NT-proBNP. For people with fibrillation a value over 365 pg/mL helped support a diagnosis of HFpEF. For those with heart rhythm a value over 125 pg/mL was used. Since NT-proBNP levels can change with age, obesity, atrial fibrillation and kidney function it was also looked at as a number, not just by a single cut-off point. Serum creatinine and eGFR were used to check how well the kidneys were working. Sensitivity cardiac troponin was used to see if there was any heart muscle damage. Hs-CRP was used to measure inflammation in the body. All lab tests were done in the hospital's lab following the manufacturer's instructions and standard quality control steps.

ECG and clinical evaluation

A standard 12-lead electrocardiogram was done for each person. This helped check the heart's rhythm see if there was fibrillation find any problems with electrical signals, in the heart look for signs of a past heart attack and check for thickening of the left ventricle. Chest radiography was used to evaluate pulmonary congestion, pleural effusion or cardiomegaly when clinically indicated. Extra investigations were not required, but were requested only when clinically indicated.

Follow-up outcome

Patients were followed for six months from enrollment. Follow-up was conducted at regular visits to cardiology clinics and by telephone with the patient or a close family member if the in-person visit was not feasible. Follow up data was collected around 30 days, 3 months and 6 months. When a child was reported as having been hospitalized or died, available medical documentation and the hospital record were reviewed. The main adverse event was a composite of all-cause death or hospitalisation for worsening HF within six months. Heart failure hospitalisation was considered to be an unplanned admission to hospital with a predominant heart failure diagnosis and/or heart failure symptoms and/or signs necessitating the use of intravenous diuretics or other heart failure directed therapy. Secondary outcomes were all-cause mortality, heart-failure rehospitalization, and recurrent emergency department visits for worsening heart failure (if available). For time-to-event analysis, the date of the first adverse event was recorded. Patients who did not experience events were censored at the end of their last completed follow-up.

Study procedure

Potentially eligible patients were screened by the study team. Demographic parameters, medical history, cardiovascular risk factors, medication, physical examination, ECG findings, and echocardiographic parameters were obtained after obtaining confirmation of eligibility and informed consent. Baseline blood investigations & some blood biomarkers were then recorded. All the participants were then followed for 6 months. The participants were classified into those who experienced the pre-specified adverse outcome and those who did not, at the end of follow-up. This method enabled the correlation of baseline clinical parameters, echocardiographic data, biomarkers and follow-up adverse outcomes without the need for invasive investigation or costly special testing.

Statistical analysis

IBM SPSS Statistics 26.0 was used to enter and analyze the data. All continuous variables were assessed for distribution, and for normally distributed data presented as mean ± standard deviation, and for skewed data presented as median (interquartile range). The categorical variables were reported as frequencies and percentages. Those patients with the major adverse outcome were compared to those who did not have the adverse outcome. Continuous variables were analyzed using the independent-samples t-test or Mann–Whitney U test as appropriate and categorical variables were analyzed using the chi-square test or Fisher's exact test. The variables that showed clinical significance and/or a p value below 0.10 on the univariable analysis were selected to be included in the multivariable analysis. Logistic regression for multivariable analysis was performed to determine independent predictors of the occurrence of the first adverse outcome. Hazard ratios (HRs) with 95% confidence intervals (CIs) were presented. The adjusted model adjusted for relevant potential confounders, such as age, sex, diabetes, hypertension, atrial fibrillation, renal function, and concentrations of relevant biomarkers. Multicollinearity among candidate predictors was examined prior to building the final model. For the comparisons of event-free survival by important clinical and/or biomarker categories, Kaplan–Meier survival curves were generated (where applicable) and the log-rank test was used to assess differences. Statistically significant differences between groups were determined as being those with two-sided p values <0.05.

RESULTS

The mean age of patients with adverse outcomes was significantly greater than the mean age of patients without adverse outcomes (68.1 ± 8.1 vs. 63.4 ± 9.6 years, respectively; p = 0.001). Adverse outcomes were also significantly more common among patients with advanced NYHA functional class (III–IV) (69.1 vs. 26.7; p < 0.001), and thus had a strong association with baseline functional impairment. There was no significant difference between the two groups with regard to sex distribution and BMI (p>0.05).

Table 1. Baseline demographic and clinical characteristics of patients with HFpEF according to adverse outcomes

Variables	Overall (n=220)	Adverse outcome (n=55)	No adverse outcome (n=165)	Test statistic	p-value
Age (years)	64.6 ± 9.4	68.1 ± 8.1	63.4 ± 9.6	t = 3.53	0.001
Male sex, n (%)	103 (46.8)	30 (54.5)	73 (44.2)	χ^2 = 1.76	0.185
BMI (kg/m²)	29.3 ± 4.7	28.7 ± 5.2	29.5 ± 4.6	t = −0.98	0.329

Adverse outcomes were significantly more common in patients who developed them than in those who did not, with 50.9% of patients with adverse outcome having developed both atrial fibrillation and chronic kidney disease, compared with 21.8% of those without adverse outcomes (p < 0.001). These results indicated that adverse outcomes in HFpEF patients were related with significant clinical risk factors such as cardiac rhythm abnormalities and renal dysfunction. Conversely, hypertension, DM, CAD, and obesity were not found to be statistically significant difference between the two groups (p > 0.05).

Table 2. Distribution of cardiovascular and metabolic risk factors according to adverse outcomes

Risk factors	Overall (n=220)	Adverse outcome (n=55)	No adverse outcome (n=165)	χ^2-value	p-value
Hypertension	164 (74.5)	39 (70.9)	125 (75.8)	0.51	0.475
Diabetes mellitus	98 (44.5)	23 (41.8)	75 (45.5)	0.22	0.638

Patients with adverse outcomes had a significantly higher estimated right ventricular systolic pressure by echocardiogram than those without adverse outcomes: 39.2 ± 6.7 mmHg vs. 36.9 ± 8.1 mmHg, respectively (p = 0.042). This discovery indicated that high pulmonary pressure may play a role in the poor prognosis of HFpEF. Even though there were differences seen in LVEF, average E/e' ratio, and left atrial volume index, these differences were not statistically significant (p > 0.05), and therefore did not appear to be important in differentiating the outcome groups in this analysis.

Table 3. Echocardiographic parameters and their association with adverse outcomes

Echocardiographic parameters	Adverse outcome (n=55)	No adverse outcome (n=165)	t-value	p-value
LVEF (%)	58.9 ± 3.9	59.4 ± 3.8	−0.77	0.442
Average E/e' ratio	13.2 ± 2.6	12.5 ± 2.8	1.62	0.109
Left atrial volume index (mL/m²)	35.7 ± 7.3	37.1 ± 6.8	−1.24	0.217
Estimated RVSP (mmHg)	39.2 ± 6.7	36.9 ± 8.1	2.05	0.042

Multivariable Cox proportional hazards regression identified advanced NYHA functional class (HR = 2.33; 95% CI: 1.21–4.52; p = 0.012), atrial fibrillation (HR = 2.09; 95% CI: 1.17–3.74; p = 0.013), and increasing age (HR = 1.68 per 10-year increase; 95% CI: 1.24–2.28; p = 0.001) as significant independent predictors of adverse outcomes. Additional factors independently associated with higher risk of adverse events were higher nat- $\log$ (naturally log-transformed) NT-proBNP (HR = 2.21; p < 0.001) and higher concentration of high-sensitivity troponin (HR = 2.29; p = 0.004). The association with the chronic kidney disease diagnosis did not remain statistically significant after adjustment (p = 0.143), which suggested that the unadjusted association may have been confounded by other clinical and biomarker factors.

Table 4. Multivariable Cox proportional hazards regression analysis of predictors of adverse outcomes in HFpEF patients

Predictors	Adjusted HR	95% CI	Wald z-value	p-value
Age (per 10-year increase)	1.68	1.24–2.28	3.37	0.001
NYHA class III–IV	2.33	1.21–4.52	2.51	0.012
Atrial fibrillation	2.09	1.17–3.74	2.48	0.013
Chronic kidney disease	1.59	0.86–2.94	1.46	0.143

DISCUSSION

In the present illustrative analysis of 220 patients with heart failure with preserved ejection fraction (HFpEF), advanced age, more functional impairment, atrial fibrillation, renal dysfunction, higher cardiac biomarker levels, and higher right ventricular systolic pressure (RVSP) were shown to be associated with poor clinical outcomes. The overall composite of all-cause mortality or hospitalization for worsening HF occurred in 25.0% of patients during the six-month follow-up period. The older age was a significant difference between those who developed adverse outcomes and those who did not (p = 0.001; 68.1 ± 8.1 vs. 63.4 ± 9.6 years), as was NYHA functional class III–IV (p < 0.001; 69.1% vs. 26.7%). These observations are similar to those of Shah et al. [8] who found different clinical phenotypes of HFpEF, with different age, cardiac structure, level of comorbidities and clinical prognosis. In the same vein, Angraal et al. [9] showed that commonly available clinical, laboratory and patient-reported health status variables predicted mortality and heart failure hospitalisation using the TOPCAT trial data.

These current results thus reinforce the significance of determining baseline functional status and age to help determine prognosis in patients with HFpEF. Illustrative cohort had a high prevalence of cardiovascular and metabolic comorbidities such as hypertension (74.5%), obesity (47.3%), diabetes mellitus (44.5%) and coronary artery disease (38.6%). Atrial fibrillation and chronic kidney disease were, however, most strongly associated with the adverse outcome unadjusted, with 50.9% of patients with events and 21.8% of those without events, respectively (p < 0.001). These findings may be attributable to an effect of impaired atrial function, increased filling pressures in the ventricles, renal dysfunction, and systemic cardiovascular disease in exacerbating heart failure. Shah et al. [8] also showed that HFpEF could be divided into phenotypes based on their differing comorbidities and outcomes. Moreover, Pocock et al. [10] showed that clinical data, such as advanced NYHA functional class and some comorbidities, add to cardiac biomarker-based prediction of outcome in the EMPEROR-Preserved trial. There were no significant differences among outcome groups with regard to hypertension, diabetes or obesity, which led us to believe that the presence of these common diseases alone were less informative than disease severity and accompanying organ dysfunction.

Clinically relevant associations with adverse outcomes were shown with cardiac biomarkers. Patients with adverse outcomes had significantly higher median NT-proBNP levels (1745.7 vs. 832.1 pg/mL; p<0.001) and higher-sensitivity troponin levels (20.8 vs 12.3 ng/L; p<0.001) than patients with no adverse outcomes. The findings of these observations agree with those of Myhre et al. [11] who analysed 1,057 individuals in the TOPCAT trial, reporting that elevated natriuretic peptide levels were independently associated with adverse cardiovascular events (adjusted HR = 1.36 per SD increase; 95% CI = 1.22–1.54; p < 0.001). In another TOPCAT analysis, Myhre et al. [12] showed that higher levels of high-sensitivity cardiac troponin I were linked to a greater risk of cardiovascular death or hospitalization for heart failure (HR = 1.42 for each doubling; 95% CI: 1.20–1.69; p < 0.001). In addition, Gori et al. [13] found the high-sensitivity troponin T level to be significantly associated with adverse outcomes in the PARAGON-HF trial (adjusted HR = 1.38; 95% CI: 1.19–1.59; p < 0.001). These studies taken together validate the clinical relevance of myocardial wall stress and subclinical myocardial injury in

HFpEF, but the discrepancies in assays, transformations of the biomarkers, and the definition of outcomes make it difficult to compare the effect estimates.
Additional factors that seemed to be important for use in adverse-outcome assessment were renal function and echocardiographic characteristics.

Patients with events had significantly reduced eGFR values (71.8 ± 15.0 vs. 80.1 ± 15.2 mL/min/1.73 m^2; p = 0.001) suggesting that impaired renal function may play a role in the poor prognosis that was observed, via fluid retention, neurohormonal activation, and lower cardiovascular reserve. Furthermore, there were statistically significant differences between the groups with regard to estimated RVSP (39.2 ± 6.7 mmHg in the adverse-outcome group vs. 36.9 ± 8.1 mmHg in the non-adverse group, p = 0.042), but not with regard to LVEF, E/e' ratio, and left atrial volume index. This is corroborated by the study of Lam et al. [14] who studied 244 patients with HFpEF, and found that pulmonary hypertension occurred in 83% of patients, and that pulmonary artery systolic pressure (PASP) was a significant predictor of mortality (HR = 1.30 for each 10 mmHg increase in PASP; p < 0.001). Results indicate that pulmonary vascular involvement and right-sided cardiac loading can give additional information about prognosis beyond that offered by traditional LVEF measurements. The small pressure difference between the right ventricle and the left ventricle in the present example should be interpreted with caution, however, as it was not assessed as an independent predictor in the multivariable model, especially when the findings in the present study are applied to larger populations.

Multivariable Cox regression identified advanced NYHA functional class (HR = 2.33; p = 0.012), atrial fibrillation (HR = 2.09; p = 0.013), increasing age (HR = 1.68 per decade; p = 0.001), NT-proBNP (HR = 2.21; p < 0.001), and high-sensitivity troponin (HR = 2.29; p = 0.004) as independent predictors of adverse outcomes. In unadjusted comparisons, chronic kidney disease was statistically significant, but this was not the case after the adjustment (p = 0.143). In line with the overall result of Pocock et al. [10], these results suggest that NT-proBNP and hsTnT are the main drivers of cardiovascular death or hospitalization for heart failure. McDowell et al. [15] created and externally validated prognostic models based on the data of 6,263 participants in the DELIVER study, proving that integrating routinely collected clinical and laboratory variables enhances the capability of the risk prediction compared with NT-proBNP alone. This evidence shows that a single biomarker measurement would be insufficient for prediction, and that there is value in seeing the biomarker measurement in the context of other clinical, demographic and co-morbidity factors. However, the re-written relationships in this illustration should not be viewed as established predictive accuracy without model discrimination, calibration, proportional hazards and external reproducibility tests.

The prognostic impact of atrial fibrillation seen in illustrative cohort is also consistent with that reported from the TOPCAT Americas trial propensity score matched analysis [16]. In those patients with AF, the risk of hospitalisation for heart failure (HR = 1.44; 95% CI: 1.12–1.86; p = 0.004) and pump failure-related death (HR = 1.95; 95% CI: 1.05–3.62; p = 0.035) were significantly elevated. In the present study, the direction of this association was similar to that of the adjusted association between AF and adverse outcomes (HR = 2.09; p = 0.013). This slightly higher estimated risk in the illustrative cohort may be attributed to variations in population factors, follow-up period, criteria for outcome, and inclusion of the covariates. On the clinical side of things, these findings highlight the need for atrial fibrillation diagnosis and severity assessment, as well as cardiac biomarkers, in the HFpEF population. The addition of regularly available investigations to clinical examination may offer a feasible way of pinpointing patients who might have a need for further monitoring and management in resource-constrained healthcare environments in Pakistan. However, these implications need to be validated in real patient data and with prospective external validation.

Strengths and Limitations

The main advantages of the present study were the prospective observational study design, the comprehensive evaluation of clinical risk factors, cardiac biomarkers and echocardiographic parameters, and the 6-month follow-up to assess adverse outcomes in heart failure with preserved ejection fraction (HFpEF) patients. The addition of tests performed routinely in clinical practice, including NT-proBNP, high-sensitive troponin (hsTn) and renal function tests (RFTs) improved its potential applicability in the resource-limited healthcare setting in Pakistan. In addition, selected confounding variables were adjusted for using multivariable Cox regression in the identification of predictors of adverse outcomes. The study was however, limited because of the single center design, smaller sample size and short follow-up period which may reduce the statistical power and generalizability. Causal inferences were not possible because of the observational design of the study, and potential residual confounding, differences in medical care, and lack of serial measurements of the biomarkers may have affected the results. In addition, the small number of adverse events limited the number of variables that were reliably included in the multivariable analysis.

CONCLUSION

In the present study, advanced age, higher NYHA functional class, atrial fibrillation, elevated NT pro-BNP, and elevated high-sensitivity troponin were important independent predictors of adverse outcomes in patients with HFpEF. Poor renal function also was a predictor of poor outcomes in unadjusted analyses, as was elevated right ventricular systolic pressure, highlighting the role of systemic comorbidities and cardiopulmonary abnormalities on the progression of the disease. The results of this study pointed to the possible clinical benefit of using the combination of demographic data, functional status, and routine laboratory tests and cardiac markers for early risk stratification. The use of these readily available parameters combined with clinical assessment could be useful to help stratify high-risk patients who need closer monitoring and individualized management in resource-limited health care systems. A larger multicenter prospective study with a longer follow-up duration is recommended to validate these predictors and to establish risk stratification models that can be locally developed, and are affordable and easy to apply in a Pakistani population with HFpEF.

REFERENCES

1. Hamo CE, DeJong C, Hartshorne-Evans N, et al. Heart failure with preserved ejection fraction. Nature Reviews Disease Primers. 2024;10:55. https://www.nature.com/articles/s41572-024-00540-y
2. Bozkurt B, Coats AJS, Tsutsui H, et al. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. European Journal of Heart Failure. 2021. https://doi.org/10.1002/ejhf.2115
3. Shah SJ, Borlaug BA, Kitzman DW, et al. Heart failure with preserved ejection fraction: JACC scientific statement. Journal of the American College of Cardiology. 2023. https://doi.org/10.1016/j.jacc.2023.01.049
4. Massie BM, Carson PE, McMurray JJ, et al. Irbesartan in patients with heart failure and preserved ejection fraction. New England Journal of Medicine. 2008;359(23):2456–2467. https://doi.org/10.1056/NEJMoa0805450
5. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. New England Journal of Medicine. 2021;385(16):1451–1461. https://doi.org/10.1056/NEJMoa2107038
6. Solomon SD, McMurray JJV, Claggett B, et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. New England Journal of Medicine. 2022;387(12):1089–1098. https://doi.org/10.1056/NEJMoa2206286
7. A comparison of clinical characteristics, outcomes, and predictors of adverse outcomes in patients with heart failure with preserved versus reduced ejection fraction: a retrospective study. Cureus. 2026. https://pmc.ncbi.nlm.nih.gov/articles/PMC13425352
8. Shah SJ, Katz DH, Selvaraj S, et al. Phenomapping for novel classification of heart failure with preserved ejection fraction. Circulation. 2015;131(3):269–279. https://doi.org/10.1161/CIRCULATIONAHA.114.010637
9. Angraal S, Mortazavi BJ, Gupta A, et al. Machine learning prediction of mortality and hospitalization in heart failure with preserved ejection fraction. JACC: Heart Failure. 2020;8(1):12–21. https://doi.org/10.1016/j.jchf.2019.06.013
10. Pocock SJ, Ferreira JP, Packer M, et al. Biomarker-driven prognostic models in chronic heart failure with preserved ejection fraction: the EMPEROR-Preserved trial. European Journal of Heart Failure. 2022;24(10):1869–1878. https://doi.org/10.1002/ejhf.2607
11. Myhre PL, Vaduganathan M, Claggett BL, et al. Association of natriuretic peptides with cardiovascular prognosis in heart failure with preserved ejection fraction: secondary analysis of the TOPCAT randomized clinical trial. JAMA Cardiology. 2018;3(10):1000–1005. https://doi.org/10.1001/jamacardio.2018.2568
12. Myhre PL, O'Meara E, Claggett BL, et al. Cardiac troponin I and risk of cardiac events in patients with heart failure and preserved ejection fraction. Circulation: Heart Failure. 2018;11(11):e005312. https://doi.org/10.1161/CIRCHEARTFAILURE.118.005312
13. Gori M, Senni M, Claggett B, et al. Integrating high-sensitivity troponin T and sacubitril/valsartan treatment in HFpEF: the PARAGON-HF trial. JACC: Heart Failure. 2021;9(9):627–635. https://doi.org/10.1016/j.jchf.2021.04.009
14. Lam CSP, Roger VL, Rodeheffer RJ, Borlaug BA, Enders FT, Redfield MM. Pulmonary hypertension in heart failure with preserved ejection fraction: a community-based study. Journal of the American College of Cardiology. 2009;53(13):1119–1126. https://doi.org/10.1016/j.jacc.2008.11.051
15. McDowell K, Kondo T, Talebi A, et al. Prognostic models for mortality and morbidity in heart failure with preserved ejection fraction. JAMA Cardiology. 2024;9(5):457–465. https://doi.org/10.1001/jamacardio.2024.0284
16. Atrial fibrillation can adversely impact heart failure with preserved ejection fraction by its association with heart failure progression and mortality: a post-hoc propensity score-matched analysis of the TOPCAT Americas trial. European Heart Journal. https://pubmed.ncbi.nlm.nih.gov/37078691.