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Original Article

Clinical Profile and Echocardiographic Predictors of Adverse Outcomes in Patients with HFPEF and Valvular Heart Disease.

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Abstract

Objective: To evaluate the clinical and echocardiographic profile of patients with heart failure with preserved ejection fraction (HFpEF) and valvular heart disease.

Methodology: We consecutively enrolled 230 patients with HFpEF and native valvular heart disease. We assessed baseline clinical, laboratory, and echocardiographic parameters, including left atrial reservoir strain. All participants were followed for 18 months for the first cardiovascular hospitalization or death. We performed Kaplan-Meier analysis and Cox proportional hazards regression to highlight the association between echocardiographic parameters and clinical outcomes.

Results: The mean age of participants was 67.4 ± 9.8 years, and 154 (67.0%) were female. The composite outcome was experienced by 97 (42.2%) patients during follow-up, including 81 (35.2%) cardiovascular hospitalizations and 16 (7.0%) deaths. Patients who experienced an event had significantly lower mean atrial reservoir strain than those without events (29.5 ± 10.0% vs. 34.3 ± 10.0%, p<0.001). After age adjustment, estimated glomerular filtration rate, atrial fibrillation, moderate valvular lesion count, and higher left atrial reservoir strain were associated with a lower hazard of the composite outcome (adjusted HR 0.969, 95% CI 0.947–0.991, p=0.006). High eGFR was independently associated with a lower hazard (adjusted HR 0.984, 95% CI 0.973–0.995, p=0.005).

Conclusion: There was an independent association of lower baseline left atrial reservoir strain with increased risk of cardiovascular hospitalization and death in patients with HFpEF and valvular heart disease.

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Introduction

Heart failure with preserved ejection fraction (HFpEF) is a clinical syndrome that is assessed using symptoms of heart failure (HF). Signs also include a left ventricular ejection fraction of at least 50% and elevated cardiac filling pressure at rest or during physical exertion.[1,2] The exercise capacity, symptom burden, and clinical course are variable among patients. The common comorbidities and clinical syndromes associated with HFpEF include hypertension, atrial fibrillation, renal dysfunction, and diabetes. These factors influence patient presentation and echocardiographic findings.[3,4] Clinical characteristics combined with echocardiographic readings help differentiate HFpEF from other unexplained dyspnoea.[5] However, after diagnosis, which findings at the initial examination are associated with the emergence of cardiovascular hospitalization or mortality becomes the most important question. This question is especially relevant when HFpEF coexists with native valvular heart disease. Abnormal cardiac loading may stem from a valve lesion, but it may also drive changes in chamber structure and function that affect HF. Mitral regurgitation in HFpEF patients is associated with higher left atrial dysfunction, damaged ventricular reserve, and pulmonary vascular disease.[6] During different stages of HFpEF, secondary tricuspid regurgitation has also been observed in patients with elevated filling pressures only during exercise.[7] It is safe to state that patients with the same grades of regurgitation may have different responses to physical exertion. Key descriptors include valve type and severity, but whether baseline chamber function is associated with outcomes after accounting for the burden of valvular disease is also important. The left atrium plays an important role in cardiac function by receiving pulmonary venous blood during ventricular systole. It also helps to maintain ventricular filling during diastole. Left atrial volume describes chamber enlargement. Reservoir strain measures the atrium's ability to stretch during ventricular systole. These measurements capture different aspects of atrial remodeling. In patients with HFpEF, greater left atrial stiffness has been associated with adverse outcomes.[8] Exercise echocardiography has also shown that patients with a limited increase in reservoir strain during exertion have poorer exercise capacity. These patients had a higher risk of subsequent heart failure events.[9] A meta-analysis involving patients with HFpEF identified several prognostic markers. These included lower left atrial reservoir strain, impaired left ventricular global longitudinal strain, and a lower ratio of tricuspid annular plane systolic excursion to pulmonary artery systolic pressure.[10] The relevant clinical question is whether strain is associated with adverse outcomes when differences in age, renal function, atrial rhythm, and burden of valvular lesion are considered. This study aimed to examine the clinical and echocardiographic profile of patients with HFpEF. It also assessed whether baseline left atrial reservoir strain was associated with time to the first occurrence of cardiovascular hospitalization or death from any cause.

Material and methods

This prospective observational cohort study was conducted in the Department of Cardiology, Pakistan Institute of Medical Sciences (PIMS), Islamabad, Pakistan, from January 2026 to June 2026. After obtaining institutional ethical approval, we recruited eligible adults consecutively. Each participant was provided with written informed consent. Inclusion required cardiologists to confirm heart failure with preserved ejection fraction (HFpEF). Diagnostic criteria included a left ventricular ejection fraction ≥50%, objective evidence of elevated filling pressures, diastolic dysfunction, and mild to moderate native valvular disease. Patients were excluded if they had a previous ejection fraction <40%, recent acute coronary syndrome, active endocarditis, prosthetic valves, infiltrative cardiomyopathy, or inadequate echocardiographic images. We calculated the sample size using a Cox regression approximation for a continuous predictor, informed by Freed et al. 11. Assuming a conservative hazard ratio of 1.43 per standard-deviation decrease in left atrial reservoir strain, two-sided α=0.05, 80% power, and predictor covariate R^2=0.20. The required events were 77. Using the anticipated event proportion of 115/308 (37.3%), the study evaluated 207 participants after upward rounding. After allowing for the 10% attrition, the recruitment target increased to 230. Baseline assessment included demographics, anthropometry, blood pressure, and heart rate. It also involved New York Heart Association functional class, comorbidities, smoking, previous heart failure admission, and medications. Laboratory measurements included hemoglobin, creatinine, sodium, and N-terminal pro-B-type natriuretic peptide. We calculated estimated glomerular filtration rate (eGFR) using the 2021 CKD-EPI creatinine equation. We performed transthoracic echocardiography after clinical stabilization using a Vivid E95 system (GE Vingmed Ultrasound, Horten, Norway). We calculated ejection fraction using the biplane Simpson method. We recorded chamber volumes, indexed measurements, diastolic velocities, right ventricular function, and estimated pulmonary pressures. We measured left atrial reservoir strain and left ventricular global longitudinal strain using EchoPAC software. We averaged measurements over three cardiac cycles in sinus rhythm and five suitable cycles in atrial fibrillation. We assessed valvular severity using integrated Doppler evaluation. We also recorded total and moderate lesion counts. We followed participants for up to 18 months through clinic visits, telephone contact, and hospital record review. The primary outcomes were first cardiovascular hospitalization and all-cause death. Cardiovascular hospitalization required an unplanned admission for a cardiovascular diagnosis. Event-free participants were censored at their last documented follow-up. Analysis used IBM SPSS Statistics version 26.0. We summarised continuous variables as mean±standard deviation and median with interquartile range. We presented categorical variables as frequencies and percentages. We used independent-samples t-tests (with Welch's correction where indicated), Mann-Whitney U tests, chi-square tests, or Fisher's exact test for comparisons. We compared Kaplan-Meier estimates using log-rank tests. We used reverse Kaplan-Meier analysis to estimate follow-up. We included strain as a continuous variable in Cox regression and adjusted for age, eGFR, atrial fibrillation, and moderate lesion count. Additional echocardiographic predictors were examined separately. We assessed proportional hazards and collinearity using covariate-by-log-time interactions and variance inflation factors. We reported hazard ratios with 95% confidence intervals. Two-sided $p<0.05$ indicated significance. Secondary analyses were exploratory.

RESULTS

The cohort included 230 patients with a mean age of 67.4 ± 9.8 years. Of all patients, 154 (67.0%) were women. The composite outcome occurred in 97 patients (42.2%). Out of these participants, 81(35.2%) experienced cardiovascular hospitalization as the first event, and 16 (7.0%) experienced death from any cause as the first event. The remaining 133 patients (57.8%) were censored at their last documented follow-up. Patients who had experienced an event were older and had a higher prevalence of atrial fibrillation and coronary artery disease than those without an event. These patients had lower estimated glomerular filtration rate (eGFR) and higher baseline NT-proBNP concentrations (Table I).

Table I. Baseline clinical characteristics by occurrence of cardiovascular hospitalization or all-cause death

Characteristic	Overall (n=230)	No event (n=133)	Event (n=97)	p-value
Age, years	67.4 ± 9.8	65.9 ± 9.5	69.4 ± 10.0	0.007
Female sex	154 (67.0)	90 (67.7)	64 (66.0)	0.788
Body mass index, kg/m²	31.0 ± 5.5	31.0 ± 5.6	31.1 ± 5.4	0.919
Systolic blood pressure, mmHg	137.1 ± 13.8	136.1 ± 14.7	138.5 ± 12.5	0.183
Diastolic blood pressure, mmHg	75.0 ± 9.0	74.7 ± 9.2	75.3 ± 8.8	0.635
NYHA functional class				0.123
I	11 (4.8)	8 (6.0)	3 (3.1)	
II	103 (44.8)	63 (47.4)	40 (41.2)	
III	113 (49.1)	62 (46.6)	51 (52.6)	
IV	3 (1.3)	0 (0.0)	3 (3.1)	
Hypertension	178 (77.4)	97 (72.9)	81 (83.5)	0.058
Diabetes mellitus	85 (37.0)	53 (39.8)	32 (33.0)	0.287
Atrial fibrillation	62 (27.0)	27 (20.3)	35 (36.1)	0.008
Coronary artery disease	63 (27.4)	29 (21.8)	34 (35.1)	0.026
Dyslipidaemia	127 (55.2)	71 (53.4)	56 (57.7)	0.513
Current smoking	14 (6.1)	11 (8.3)	3 (3.1)	0.105
Previous heart failure admission	65 (28.3)	37 (27.8)	28 (28.9)	0.862
Creatinine, mg/dL	1.22 (0.94–1.50)	1.10 (0.89–1.41)	1.34 (1.02–1.56)	0.001
eGFR, mL/min/1.73 m²	54.60 (39.88–73.15)	60.35 (44.93–81.63)	48.40 (37.10–60.20)	<0.001
NT-proBNP, pg/mL	936 (539–1471)	816 (515–1393)	1129 (604–1649)	0.037
Loop diuretic	207 (90.0)	119 (89.5)	88 (90.7)	0.755
SGLT2 inhibitor	116 (50.4)	65 (48.9)	51 (52.6)	0.579
Beta-blocker	162 (70.4)	86 (64.7)	76 (78.4)	0.025
ACEI, ARB or ARNI	164 (71.3)	96 (72.2)	68 (70.1)	0.731
Mineralocorticoid receptor antagonist	86 (37.4)	48 (36.1)	38 (39.2)	0.633

Mean left atrial reservoir strain was 4.81 percentage points lower in patients with an event than in those without (95% CI 2.18–7.43, p<0.001). Patients with an event also had a larger left atrial volume index and right atrial area. No statistical difference in left ventricular ejection fraction was observed between groups. Moderate mitral regurgitation was the most frequent moderate valve lesion, followed by tricuspid regurgitation. At least one moderate lesion was present in 100 patients (43.5%). The distribution of moderate lesion counts did not differ significantly by outcome (p=0.690, Table II).

Table II. Baseline echocardiographic and valvular characteristics by occurrence of the composite outcome

Characteristic	Overall (n=230)	No event (n=133)	Event (n=97)	p-value
Left ventricular ejection fraction, %	61.4 ± 5.2	61.6 ± 5.5	61.1 ± 4.7	0.471
Left ventricular mass index, g/m²	112.4 ± 22.2	110.9 ± 21.8	114.5 ± 22.7	0.222
Left atrial reservoir strain, %	32.3 ± 10.2	34.3 ± 10.0	29.5 ± 10.0	<0.001
Left atrial volume index, mL/m²	42.80 (34.80–49.75)	40.65 (33.05–47.28)	44.30 (37.93–52.75)	0.007
Left ventricular global longitudinal strain, %	−17.1 ± 3.0	−17.1 ± 2.9	−17.0 ± 3.2	0.857
E/e′ ratio	14.33 (12.14–16.78)	14.52 (12.28–16.89)	13.97 (11.76–16.17)	0.329
Right atrial area, cm²	19.4 ± 3.7	19.0 ± 3.3	20.1 ± 4.0	0.031
TAPSE, mm	20.2 ± 3.3	20.4 ± 3.4	19.9 ± 3.1	0.26
Right ventricular fractional area change, %	43.8 ± 5.6	43.9 ± 5.4	43.8 ± 6.0	0.896
PASP, mmHg	38.25 (31.65–46.18)	36.70 (30.50–45.58)	39.30 (32.45–47.23)	0.129
Moderate mitral regurgitation	60 (26.1)	35 (26.3)	25 (25.8)	—
Moderate tricuspid regurgitation	41 (17.8)	20 (15.0)	21 (21.6)	—
Moderate aortic regurgitation	7 (3.0)	4 (3.0)	3 (3.1)	—
Moderate aortic stenosis	6 (2.6)	3 (2.3)	3 (3.1)	—
Number of moderate valve lesions				0.69
None	130 (56.5)	77 (57.9)	53 (54.6)	
One	87 (37.8)	50 (37.6)	37 (38.1)	
Two	12 (5.2)	6 (4.5)	6 (6.2)	
Three	1 (0.4)	0 (0.0)	1 (1.0)	

Median event-free survival was not reached in the overall cohort. Patients with atrial fibrillation had a median event-free survival of 453 days. The median was not reached in patients without the condition (log-rank p = 0.005). Events occurred in 56 of 115 patients (48.7%) with reservoir strain below the cohort median of 32.8% and in 41 of 115 (35.7%) at or above the median. Event-free survival did not differ significantly between these groups (log-rank p=0.063). Event-free survival also did not differ significantly by sex (p=0.497) or NYHA class I–II versus III–IV (p=0.219). All 230 patients were included in the primary Cox model. After adjustment for age, eGFR, atrial fibrillation, and moderate valve lesion count, each 1-percentage-point increase in left atrial reservoir strain was associated with a lower hazard of the composite outcome (adjusted HR 0.969, 95% CI 0.947–0.991, p=0.006). Higher eGFR was also associated with a lower hazard (Table III). In exploratory models, left atrial volume index and right atrial area were associated with the outcome before adjustment. The association was not statistically significant after adjustment.

Table III. Cox regression analyses of time to first cardiovascular hospitalization or all-cause death

Variable and increment	Unadjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Primary multivariable model				
Left atrial reservoir strain, per percentage point	—	—	0.969 (0.947–0.991)	0.006
Age, per year	—	—	1.000 (0.975–1.027)	0.975
eGFR, per mL/min/1.73 m²	—	—	0.984 (0.973–0.995)	0.005
Atrial fibrillation, present versus absent	—	—	1.133 (0.681–1.884)	0.631
Moderate valve-lesion count, per lesion	—	—	1.081 (0.769–1.521)	0.652
Exploratory echocardiographic models				
LV ejection fraction, per percentage point	0.986 (0.950–1.024)	0.466	0.986 (0.948–1.026)	0.496
LV end-diastolic volume, per mL	1.003 (0.993–1.013)	0.597	1.002 (0.992–1.013)	0.652
LV end-systolic volume, per mL	1.010 (0.989–1.032)	0.346	1.009 (0.987–1.032)	0.418
LV mass index, per g/m²	1.006 (0.997–1.015)	0.196	1.005 (0.996–1.014)	0.279
Left atrial volume index, per mL/m²	1.026 (1.007–1.045)	0.008	1.012 (0.991–1.034)	0.269
Septal e′, per cm/s	1.001 (0.861–1.164)	0.986	1.006 (0.862–1.174)	0.938
Lateral e′, per cm/s	1.035 (0.915–1.170)	0.586	1.062 (0.937–1.203)	0.346
Mitral E velocity, per cm/s	0.999 (0.992–1.006)	0.72	0.999 (0.992–1.006)	0.823
E/e′ ratio, per unit	0.977 (0.922–1.034)	0.414	0.975 (0.919–1.034)	0.397
LV global longitudinal strain, per percentage point	1.009 (0.944–1.079)	0.786	1.003 (0.937–1.073)	0.93
TAPSE, per mm	0.964 (0.908–1.023)	0.23	0.957 (0.899–1.019)	0.173
Right ventricular fractional area change, per percentage point	1.003 (0.967–1.041)	0.854	0.992 (0.956–1.030)	0.678
Tricuspid regurgitation velocity, per m/s	1.104 (0.671–1.816)	0.696	1.035 (0.616–1.740)	0.896
PASP, per mmHg	1.010 (0.991–1.029)	0.317	1.007 (0.988–1.028)	0.464
TAPSE/PASP ratio, per mm/mmHg	0.409 (0.137–1.219)	0.109	0.445 (0.145–1.363)	0.156
Right atrial area, per cm²	1.065 (1.010–1.124)	0.02	1.038 (0.975–1.104)	0.244

DISCUSSION

Lower baseline left atrial reservoir strain was associated with earlier cardiovascular hospitalization or death in this cohort of 230 patients with heart failure with HFpEF and valvular disease. The mean strain was 29.5% in patients with an event and 34.3% in patients without an event. There was a difference of 4.81 percentage points (95% CI, 2.18 - 7.43). After age adjustment, each 1% increase in strain was associated with a 3.1% lower hazard of age, renal function, AF, and valve lesion count. Of the first 97 events, cardiovascular hospitalization accounted for 81. The principal findings describe susceptibility to hospitalization.Zhu et al. 12 reported a similar association between peak left atrial strain and HF hospitalization or death (adjusted HR 0.88, 95% CI 0.81–0.95), comparable to 0.969 (95% CI 0.947–0.991) in the current study. The association remained persistent even after adjustment for left atrial volume index and ventricular strain, compared with the current study's model, which addressed renal function, rhythm, and valve burden. Ovchinnikov et al. observed events in 133 of 274 hypertensive patients with HFpEF in sinus rhythm (49%) over a 4.3-year study period.[13] Their study found that reservoir strain distinguished outcomes better than atrial volume. In the current study, left atrial volume index was similarly associated with events before adjustment (HR 1.026 per mL/m²) and after adjustment, where it was estimated to be unity (HR 1.012, 95% CI 0.991–1.034). Although events occurred in 48.7% of patients with strain at or below 32.8% and 35.7% in the current study, the log-rank comparison remained inconclusive (p=0.063). Katahira et al. found poor event-free survival with impaired atrial and ventricular strains.[14] They used magnetic resonance median values of 13.8% and 12.2%, respectively. Lee et al. used an atrial strain threshold of 18% in 1,184 patients and found higher five-year mortality in the group with impairment of both chambers (adjusted HR 1.660, p=0.026).[15] Another study by Backhaus et al. examined atrial compliance during rest and exercise.[16] They recorded 23 cardiovascular hospitalization events among 68 participants. Transferring any single threshold to the current study's patients is limited by differences in imaging modes, loading conditions, and endpoints.Moderate mitral regurgitation occurred in 26.1% of patients and tricuspid regurgitation in 17.8%, but only 13 patients in the current study had two or more lesions. The

adjusted HR per additional lesion was 1.081 (95% CI 0.769–1.521). Jiang et al. reported a 1-year mortality of 15.8% in grades 3-4+ mitral regurgitation.[17] Compared with grade 0- 2+ disease, the findings were (HR 1.54, 95% CI 1.22–1.95). An adverse prognosis with isolated tricuspid regurgitation was also found in a study by Adamo et al., with a patient classification using the valve involved.[18] Counting moderate lesions across valves raises a different question and can obscure associations with individual lesions.Associations were less consistent with other measures of cardiac function. The adjusted HR for left ventricular global longitudinal strain in the current study was 1.003 (95% CI 0.937–1.073) compared to a study by Minamisawa et al. where they reported an adjusted HR of 1.06 per percentage point (95% CI 1.02–1.11) in 790 Paragon-HF patients.[19] Lu et al. in their study found at least two abnormal right ventricular measurements on higher risk of HF, hospitalisation and mortality (HR 2.07, 95% CI 1.15–3.73).[20] The current study focused on individual measurements separately. Therefore, we cannot determine whether a combined right ventricular assessment provides prognostic benefit.In the current study, renal function was associated with outcomes, with a median eGFR of 48.42 compared with 60.35 mL/min/1.73 m^2 in patients with and without cardiovascular events. The DELIVER study showed that 49% of the 6,262 participants had an eGFR below 60 mL/min/1.73 m^2.[21] Another study by Lassen et al. reported a rate ratio of 3.06 (95% CI 2.33–4.03) for HF hospitalizations and death in patients with three cardiovascular, renal, and metabolic comorbidities compared to HF alone.[22] A study by Kocaman et al. found that log-transformed NT-proBNP predicted 30-day mortality (adjusted OR 3.05, 95% CI 1.52–6.13).[23] The participants in the current study also had higher median NT-proBNP in events (1,129 versus 816 pg/mL). However, the current study did not examine the independence of this factor.The major limitation is potential residual confounding. This is due to an imbalance in NT-proBNP and coronary artery disease between the outcome groups. This makes it difficult to isolate the true cause of the difference in results. Another limitation is the composite endpoint, which groups multiple outcomes. Furthermore, the high number of exploratory comparisons may increase the risk of false positives due to chance. The absence of an independent validation cohort limits the generalizability of the current study's results.

Conclusion

The study shows that in patients with HFpEF with valvular heart disease, lower baseline left atrial reservoir strain was associated with a higher risk of first cardiovascular hospitalization and mortality after adjustment for age, renal function, atrial fibrillation, and valve lesion count. Lower estimated glomerular filtration rate was also independently associated with this outcome. Left atrial reservoir strain as a prognostic marker in this population requires further evaluation.

Ethical approval

The Institutional Review Board (IRB) of the Pakistan Institute of Medical Sciences (PIMS), Islamabad, Pakistan, approved this study under Reference No. **PIMS/IRB/2025/07/487.** We obtained informed verbal consent from all participating patients or their legally authorized representatives, in accordance with institutional ethical guidelines and standard protocols for observational trauma studies conducted in emergency settings.

Informed Consent

We obtained written informed consent from all participants before enrolment. We informed participants and their parents or legal guardians about the study objectives, procedures, and the voluntary nature of participation. Participation was entirely voluntary.

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Conflict of Interest

The authors declare no competing interests or conflicts of interest related to this study.

Authors' Contributions

Sangeen Khan Wazir: Contributed to conceptualization, study design, data collection, interpretation of findings, manuscript drafting, critical revision, and final approval. He also accepts accountability for all aspects of the work.

Muneeb Ullah Khan, Sarah Hameed, Asadullah Khan: Contributed to study design, data collection, data curation, literature review, data interpretation, manuscript revision, and final approval. He also accepts accountability for all aspects of the work.

Mujahid Hameed Gillani and Muhammad Azadar Abbas
Contributed to conceptualization, study supervision, clinical assessment, interpretation of findings, and critical revision of the manuscript for important intellectual content. She also approved the final version and accepts accountability for all aspects of the work.

All authors: Reviewed and approved the final version of the manuscript and agreed to be accountable for all aspects of the work in accordance with the **ICMJE** authorship criteria.

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