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ORIGINAL RESEARCH

# Heart Rate Recovery Index as a Novel Marker in Heart Failure Assessment: A Comparative Analysis of Heart Rate Deceleration During Exercise Testing

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**Purpose:** Heart rate recovery, measured during exercise testing, is an important marker of cardiovascular function. The Heart Rate Recovery Index, a recently proposed parameter derived from heart rate recovery, has shown predictive outcomes in patients undergoing cardiac resynchronization therapy. However, its role in heart failure identification remains unexplored. This study aimed to assess differences in the heart rate recovery index between patients with heart failure and individuals without heart failure undergoing exercise testing.

**Patients and Methods:** 194 patients (mean age 58.3 ± 11.7 years; 57.7% men) with heart failure or other cardiovascular conditions requiring exercise testing were prospectively enrolled and underwent cycle ergometer testing. The index was calculated as the ratio between heart rate acceleration and deceleration time during exercise testing. Differentiation ability was assessed using receiver operating characteristic curve analysis. Subgroup and two-step cluster analyses examined heart rate recovery index differences across heart failure phenotypes and severity.

**Results:** Heart Rate Recovery Index was significantly lower in heart failure patients compared to those without (1.87 ± 0.68 vs 2.65 ± 1.08, $p < 0.01$). An optimal HRRI cut-off of 2.225 identified heart failure, while a lower cut-off of 1.555 differentiated patients with mildly reduced and reduced ejection fraction from those with preserved ejection fraction (AUC = 0.647). The index correlated significantly with systolic and diastolic parameters on echocardiography. In multivariable analysis, it remained an important predictor of heart failure ($p < 0.01$). Cluster analysis identified four phenotypic groups, with the index helping to differentiate early or less severe from advanced heart failure, according to the ejection fraction.

**Conclusion:** HRRI is a simple parameter that distinguishes the heart failure status and provides discrimination across its phenotypes. Its strong correlation with echocardiographic and functional markers supports its potential role in the assessment and characterization of heart failure.

**Keywords:** exercise testing, autonomic dysfunction, cardiovascular assessment, functional capacity

## Introduction

Heart failure (HF) is a clinical syndrome resulting from structural and/or functional cardiac abnormalities that lead to elevated intracardiac pressures and/or inadequate cardiac output, whether at rest or during exercise. It is broadly



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classified based on left ventricular ejection fraction (LVEF) into HF with reduced ejection fraction (HFrEF, with a LVEF < 40%), HF with mildly reduced EF (HFmrEF), with LVEF 41–49%, and HF with preserved EF (LVEF ≥ 50%).[1]

It affects an estimated 64 million people worldwide, and although the incidence has stabilized in some high-income countries, prevalence continues to increase due to population ageing and improved survival after myocardial infarction.[2,3] HF remains associated with high morbidity and mortality, reduced exercise capacity and quality of life, and a substantial healthcare and socioeconomic burden.[4]

Early identification of functional impairment is essential, and beyond structural assessment, markers such as the Heart Rate Recovery (HRR) may provide additional value by reflecting autonomic dysfunction and exercise intolerance in HF.[5] HRR is a widely recognized parameter in cardiovascular assessment, being an indicator of the heart's ability to return to its baseline rate following exertion.[6] Its clinical applications range from healthy individuals to HF patients, providing valuable insights into autonomic regulation and overall cardiovascular health.[7] Given that the burden of HF is continually increasing,[3] identifying reliable, non-invasive markers like HRR is essential for early detection, risk assessment, and tracking disease progression.[8]

During exercise, heart rate rises due to parasympathetic withdrawal and enhanced sympathetic activation, resulting in increased cardiac output and improved cardiovascular performance.[9] During recovery, vagal reactivation predominates in the first 30 seconds, while sympathetic withdrawal becomes more evident after approximately two minutes.[10]

In HF, this autonomic transition is impaired, with sustained sympathetic drive and reduced vagal tone leading to delayed or attenuated HRR. The autonomic imbalance results in chronic sympathetic stimulation, elevated myocardial wall stress, and impaired myocardial relaxation.[11] Over time, these maladaptive changes contribute to myocardial hypertrophy, structural remodelling, and increased vasoconstriction, ultimately exacerbating neurohormonal activation and accelerating the progression of HF.[12]

Given the elevated sympathetic activity in heart failure, evaluating the exercise period provides valuable insights into the underlying pathophysiology and potential therapeutic interventions.[13]

From a therapeutic perspective, recognizing hypersympathetic activity and dysautonomia highlights several potential targets for intervention. Neurohormonal modulation remains a key element in HF management, with beta-blockers effectively decreasing sympathetic overdrive.[14] Additionally, nonpharmacological approaches such as exercise training or lifestyle modifications can enhance autonomic nervous system balance, as indicated by HRR values.[13,15,16]

Since its introduction in the 1990s,[17] numerous HRR-derived parameters have been developed to address various clinical situations and patient populations.[18]

The Heart Rate Recovery Index (HRRI) is a recently introduced parameter that refines HRR evaluation, being calculated as the ratio of the heart rate acceleration time (AT) to the deceleration time (DT).[19] Unlike traditional HRR, which focuses on absolute reductions in the post-exercise heart rate, HRRI provides a more dynamic assessment of autonomic regulation throughout the exercise period. Considering the increased sympathetic activation in HF, HRRI may better capture autonomic dysfunction and disease severity. By incorporating both chronotropic competence (heart rate acceleration) and autonomic recovery (heart rate deceleration), HRRI may offer a more comprehensive evaluation of exercise cardiovascular dynamics compared to conventional heart rate recovery indices, which assess only the post-exercise recovery phase. Previous studies have shown HRRI to be a useful predictor of cardiac resynchronization therapy (CRT) responsiveness in HF patients.[19,20] However, its value in identifying HF severity or phenotype remains unexplored.

Given the rising incidence of HFpEF, special attention should be paid to this phenotype. HRR has been shown to predict clinical outcomes in chronic HF, and its association with adverse events appears stronger in patients with preserved ejection fraction, highlighting the need to consider phenotype-specific differences in future research.[21,22]

This study aimed to evaluate the accuracy of the HRRI as a physiologic and functional parameter for detecting heart failure, and to explore its relationship with heart failure subtypes and disease severity. We hypothesize that HRRI is significantly lower in patients with HF compared to individuals without heart failure, and that HRRI gradually decreases among HF subtypes, indicating increasing autonomic dysfunction and disease severity.

# Materials and Methods

## Study Design and Selection of the Patients

This prospective dual-center study included patients admitted to the Institute of Cardiovascular Diseases, Timisoara, and the County Clinical Emergency Hospital of Sibiu between October 2023 and March 2025.

Inclusion criteria comprised adults aged 18 years or older referred for exercise testing and categorized into two groups: (1) patients with a previously established heart failure diagnosis, and (2) non-heart failure patients referred for various cardiovascular indications, such as suspected coronary heart disease, history of syncope, hypertension, arrhythmias, or other cardiovascular conditions requiring exercise stress testing evaluation.

In our study, heart failure was diagnosed by the treating cardiologist according to the European Society of Cardiology (ESC) guideline criteria, based on symptoms and signs, echocardiographic evidence of structural or functional abnormalities, and, when available, natriuretic peptide levels.[1] Diagnosis was established based on physician documentation and chart review, rather than ICD coding.

Exclusion criteria were based on acute cardiac conditions (acute coronary syndromes, myocarditis, endocarditis or pulmonary embolism), severe systemic illnesses or comorbidities (sepsis, respiratory failure, end-stage renal disease, or severe hepatic dysfunction), conditions limiting physical activity (advanced musculoskeletal disorders or neurological conditions) and arrhythmias occurring during the exercise test that interfered with accurate HRRI calculation.

Recruitment and enrollment: Potential participants were identified from patients presenting to the two centers during routine clinical visits. No public advertisement was performed; eligible patients were approached by the study team, informed about the study objectives and procedures, and invited to participate. All patients who met the inclusion criteria and were in sinus rhythm at the time of testing were enrolled. Of all recruited patients, only one developed supraventricular tachycardia during the exercise test, which resulted in an uninterpretable HRRI curve; this patient was not included in the study. There were no conflicts of interest or potential sources of bias in the recruitment process. Patients underwent a comprehensive baseline evaluation, including clinical examination, echocardiography, and cycle ergometer exercise testing.

The prospective observational design of the study implied the inclusion of all consecutive eligible patients during the study period. Consequently, a priori power calculation was not performed, particularly also due to the absence of any prior studies reporting HRRI values in patients with HF, which made it impossible to anticipate a meaningful effect size for power estimation.

The study adhered to the principles of the Declaration of Helsinki and was approved by the Ethics Committee (Nr. 62/30.10.2023, rev 2024). All participants provided written informed consent.

## Demographic and Clinical Data

Patients were included irrespective of HF status. Those with a previously established diagnosis of HF, defined according to current ESC guidelines, were further classified based on the LVEF into HFrEF, HFmrEF and HFpEF. Symptoms were used to define HF based on the NYHA classification.[1]

Underlying cardiovascular conditions were documented, including arterial hypertension, chronic coronary syndromes, history of atrial fibrillation/flutter, cardiomyopathies, and the presence of cardiac implantable electronic devices (CIEDs).

CIEDs, including dual-chamber pacemakers and cardiac resynchronization therapies, had their modes and programming details not assessed separately in this study. All patients with CIEDs underwent device interrogation before exercise testing to assess chronotropic competence and verify proper device function.[23] Key programmable parameters (such as stimulation mode, atrioventricular delay, rate response settings and upper sensor rate limits) were confirmed to ensure physiologically appropriate heart rate responses during exercise.[24,25] Only tests conducted under appropriate chronotropic conditions were included in the final analysis.

Comorbidities such as overweight, obesity, dyslipidaemia, diabetes mellitus, chronic renal disease, asthma, and obstructive sleep apnea were also recorded.

Additionally, patients' medications taken within 24 hours of the stress test were documented. Particular attention was given to rate-modulating drugs, such as beta-blockers, as well as their influence on the HRRI. Because the goal was not

ischemia testing, but rather assessing heart rate response to exercise under conditions as close as possible to daily life, negative chronotropic agents were not withheld.[26] Regarding the medication of patients with heart failure, guideline-directed medical therapy (GDMT) was targeted for all individuals. GDMT included angiotensin-converting enzyme inhibitors or angiotensin receptor blockers/angiotensin receptor-neprilysin inhibitors, beta-adrenergic blockers, mineralocorticoid receptor antagonists, sodium-glucose cotransporter 2 inhibitors, and diuretics, titrated according to each patient's clinical status. All exercise tests were conducted under the supervision of a cardiologist and medication dosages were adjusted as needed during evaluation, and therapeutic regimens were optimized to align with current guideline recommendations.[27]

Blood samples were obtained as part of the usual pre-test clinical assessment, primarily to identify any severe biochemical abnormalities that could serve as exclusion criteria for exercise testing. Blood samples were collected via venous phlebotomy while patients were in a seated position.[28] Tubes containing ethylenediaminetetraacetic acid (EDTA) were used for hematology analyses and, in selected cases, for certain biochemical analyses according to institutional protocols. Serum tubes were used for biochemical analyses, including liver and kidney function tests.[29] All samples were processed according to institutional clinical laboratory protocols. However, detailed analysis of blood parameters was not within the scope of this study and was not included in the statistical analysis.

## Exercise Test

Exercise testing was performed using a semi-rigid cycle ergometer (Ergoselect 1200, GE e Bike EL, respectively), following a modified Bruce protocol.[19] The test started at a baseline workload of 25 W, with increases of 25 W at every 2-minute stage, adapted for cycle ergometer testing according to the patient's tolerance.[20] Before initiating the test, blood pressure, heart rate, and a 12-lead electrocardiogram were recorded. Only patients in sinus rhythm at the time of testing were included. During exercise, blood pressure was automatically measured at each stage using an integrated automatic sphygmomanometer in the ergometer system, and continuous 12-lead ECG monitoring assessed heart rate and rhythm throughout the test. The test duration varied based on exercise tolerance, averaging around 5 minutes. Tests were stopped when participants reached voluntary exhaustion or exhibited limiting clinical symptoms, such as shortness of breath, leg pain, or fatigue. The recovery phase included an active cooldown for one minute at 0 W, followed by a passive cooldown in a seated position.[16]

The following parameters were evaluated during the test:

-HRRI: calculated manually for each patient using the heart rate slope during the exercise phase and recovery (Figure 1-red curve). HRRI was defined as the ratio of the heart rate acceleration time (AT) and deceleration time (DT) during the post-exercise recovery phase. AT was defined as the time interval (in seconds) from the onset of exercise (baseline) to the point of the maximum heart rate (HR max) reached during the stress test. DT was characterised as the time interval (in seconds) from the point of HR max to the return of the heart rate to baseline pre-exercise levels during the recovery phase (Figure 1).

-HRR1: HRR at 1-minute postexercise subtracted from the maximal HR during effort

-Maximum Achieved Heart Rate and Age Predicted Maximum Heart Rate (APMHR), determined as 220 minus the patient's age[30]

-Heart Rate Reserve, calculated as the difference between peak HR and the initial heart rate at rest

-Chronotropic Incompetence: defined as failure to reach 85% of APMHR or 62% of APMHR in patients receiving a beta-blocker treatment[26]

-Peak Blood Pressure Values

-Maximal exercise capacity expressed in metabolic equivalents (METS).

## Echocardiographic Evaluation

All patients underwent an echocardiographic assessment with transthoracic echocardiography before exercise stress testing, using the VIVID 9 echocardiograph (GE Health Medical, Milwaukee, WI, USA) and Philips EPIQ 7. Standard techniques and imaging planes were used.

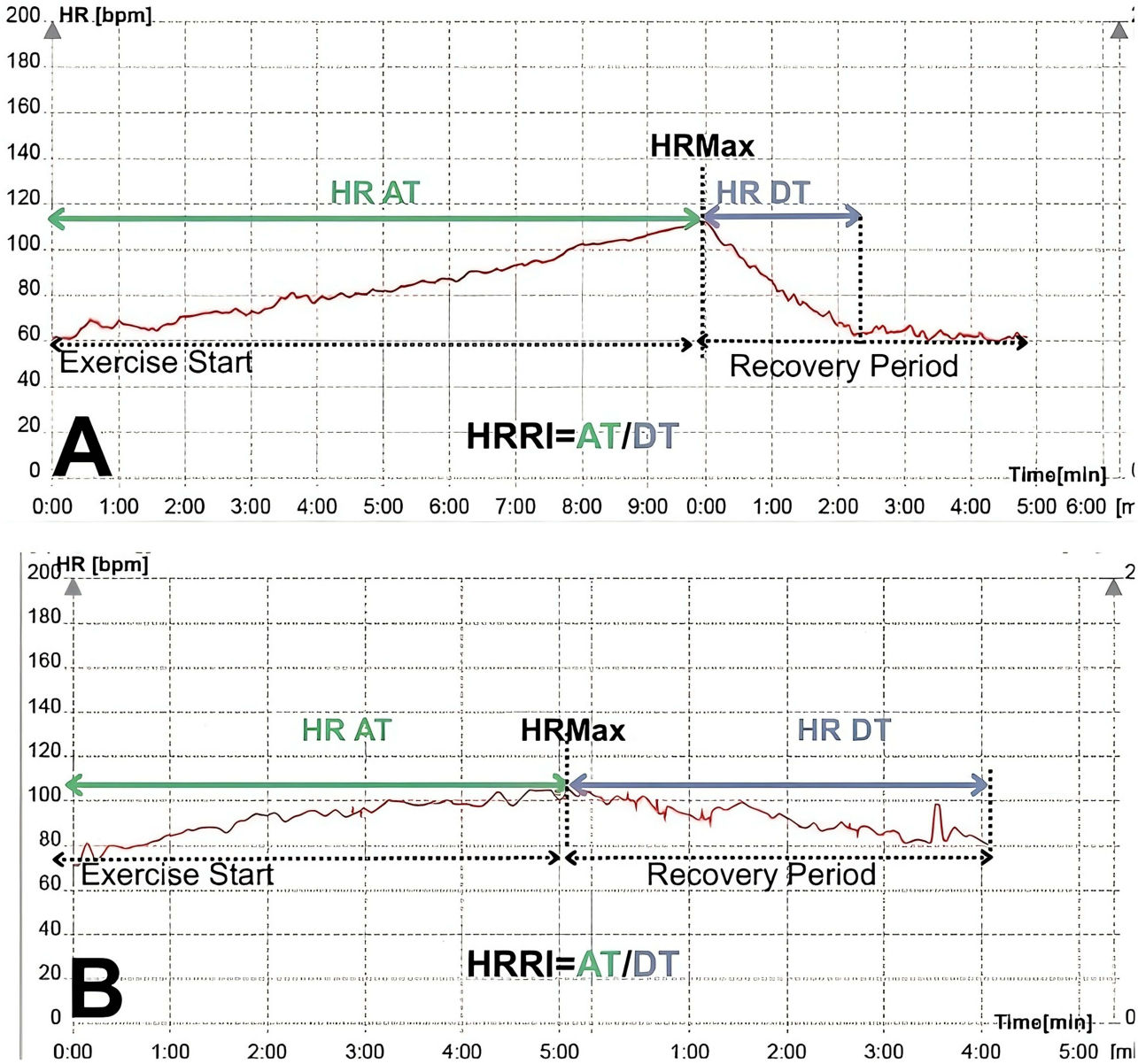


**Figure 1** Graphical representation of the Heart Rate Recovery Index (HRRI). Acceleration time (AT)/Deceleration time (DT). HR Max Maximal Heart rate; BPM Beats per Minute; Min = Minutes. (**A**) HRRI curve of a healthy patient; HRRI=AT/DT= 571.2s/132s=4.32. (**B**) HRRI curve of a patient with Heart Failure with reduced Ejection Fraction (HFrEF); HRRI=AT/DT=312/220s=1.41.

Left ventricular size was assessed by measuring the end-diastolic diameter (LVEDD). The presence of left ventricular hypertrophy (LVH) was determined based on the interventricular septum and posterior wall diameter.[31] Global left ventricular function was evaluated by calculating the ejection fraction (LVEF) using the modified Simpson's method.

Longitudinal systolic function was determined through Mitral Annular Plane Systolic Excursion (MAPSE) and myocardial systolic velocity (S wave on Tissue Doppler imaging) on the septal wall.

Diastolic function was assessed based on diastolic filling patterns, including E and A waves, the E/A ratio, and the E/e' ratio.

Left atrial assessment included measurements of diameter, area, and volume. The left atrium was measured at its maximum size, right before the mitral valve opening, to capture the largest possible size. The left atrial volume index (LAVI) was calculated for all patients by indexing LA volume to body surface area. In the apical four-chamber view,


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a trapezoidal shape of the left atrium (LA) was identified when the basal LA diameter (LAb) was greater than the mid-transversal diameter (LAt), indicating a wider base relative to the mid-portion.[32]

Mitral regurgitation and other valvular diseases were categorized as mild, moderate, or severe according to the recommendations of the European Association of Cardiovascular Imaging.[33] Systolic pulmonary artery pressure (sPAP) was estimated using the maximal tricuspid regurgitation velocity, inferior vena cava diameter, and its inspiratory collapse.

## Statistical Analysis

### Bivariate Analysis

Categorical variables were described using frequencies and percentages, whereas continuous variables were described by their means, standard deviations, minimum and maximum values, interquartile ranges, and 95% confidence intervals. The distribution of continuous variables was assessed for normality using the Kolmogorov–Smirnov or Shapiro–Wilk tests. For group comparisons, the Chi-square or Fisher's exact tests were applied to categorical variables. Continuous variables were compared using the independent samples *t*-test when normally distributed, or the Mann–Whitney *U*-test in the absence of normality. When comparing continuous variables across more than two categories, one-way analysis of variance (ANOVA) was used for normally distributed data, and the Kruskal–Wallis test was applied when the assumption of normality was not met.

A significance threshold of $\alpha = 0.05$ was used for all bivariate analyses and for determining eligibility for inclusion in logistic regression models and the two-step cluster analysis.

Data visualization and analysis were performed using Microsoft Excel® and SPSS® version 21.0.0.0.

### Logistic Regression

Multiple logistic regression models were tested using variables that demonstrated significant associations with the presence of heart failure, irrespective of ejection fraction classification, in bivariate analyses. An iterative process of variable selection, involving stepwise addition and removal, was conducted to identify suitable models, drawing on both clinical parameters and findings from echocardiographic and stress testing. Continuous variables were mean-centered to minimize multicollinearity, while categorical predictors were converted into dummy variables. To enhance the robustness of the results, bootstrapping with 1,000 resamples was employed, and 95% confidence intervals for the regression coefficients were calculated using the bias-corrected and accelerated (BCa) method. Only variables that significantly contributed to the prediction of heart failure ($p < 0.05$, with both bounds of the 95% CI for the coefficient excluding zero) were retained in the final model.

### Two-Step Cluster Analysis

A two-step cluster analysis was conducted using HRRI and ejection fraction to further explore the relationship between these variables in characterizing heart failure phenotypes. Akaike's Information Criterion (AIC) determined the optimal number of clusters.[34] Subsequently, bivariate analyses were performed to examine associations between the identified clusters and clinical and functional parameters known to correlate with the presence and prognosis of heart failure.

# Results

## Bivariate Analysis

A total of 194 patients were enrolled in the study, comprising 82 women (42.3%) and 112 men (57.7%). The participants' age ranged from 22 to 86 years, with a mean age of 58.3 ±11.69 years (Table 1). Table 1 summarizes demographic data, cardiovascular risk factors, comorbidities, baseline therapy and echocardiographic parameters.

Statistical analysis revealed significant differences between genders concerning underlying diseases, which are found in Table A1. Heart failure distribution among patients, differences between underlying comorbidities among HF patients vs non-HF patients, as well as among HF subtypes, are also presented in (Tables A2 and A3). NYHA class distribution across HF phenotypes is shown in Table A4. Exercise test performance between HF and non-HF patients is outlined in Table 2. HF patients showed significantly lower values for HRRI (1.87 vs 2.65, $p < 0.01$), HR acceleration time (345.22

**Table 1** Baseline Demographic Data, Cardiovascular Risk Factors and Comorbidities

| **Variable** | | **All Patients (n=194)** |
|---|---|---|
| Mean age (years), mean ± SD | | 58.3 ±11.69 years |
| Male, n (%) | | 112 (57.7%) |
| Obesity, n (%) | | 81 (41.8%) |
| Overweight, n (%) | | 71 (36.6%) |
| Smokers, n (%) | | 96 (49.5%) |
| Dyslipidemia, n (%) | | 150 (77.3%) |
| Type 2 Diabetes Mellitus, n (%) | | 45 (23.2%) |
| Hypertension, n (%) | | 155 (79.9%) |
| Chronic Coronary Syndrome, n (%) | | 96 (49.5%) |
| History of Atrial Fibrillation/Flutter, n (%) | | 27 (13.9%) |
| Heart Failure, n (%) | | 127 (65.46%) |
| HF Type | HFpEF | 99 (51.03%) |
| | HFmrEF | 14 (7.22%) |
| | HFrEF | 14 (7.22%) |
| NYHA Functional Class | I | 25 (12.89%) |
| | II | 97 (50%) |
| | III | 5 (2.58%) |
| Cardiomyopathies, n (%) | DCM | 8 (4.1%) |
| | HCM | 3 (1.5%) |
| CIED, n (%) | | 10 (5.2%) |
| Respiratory disease, n (%) | Asthma | 10 (5.2%) |
| | Obstructive sleep apnea | 18 (9.3%) |
| Chronic kidney disease | | 19 (9.8%) |
| Baseline therapy | ACEi/ARBs | 92 (47.42%) |
| | ARNI | 16 (8.24%) |
| | iSGLT2 | 33 (17%) |
| | MRAs | 36 (18.55%) |
| | Diuretics | 73 (37.62%) |
| | Beta-blockers | 119 (61.34%) |
| | CCB | 59 (30.41%) |
| | Ivabradine | 9 (4.63%) |
| | Amiodarone | 19 (9.79%) |
| | Ic AAD | 15 (7.73%) |

(*Continued*)

**Table 1** (Continued).

| **Variable** | | | **All Patients (n=194)** | | |
|---|---|---|---|---|---|
| | Statins | | 150 (77.32%) | | |
| **Baseline echocardiograpy** | **Parameter** | | **Mean ±StdDev [Median±IQR]/ n (%)** | | |
| | LAVI (mL/m$^2$) | | 32.06±10.95 [30.8±13.43] | | |
| | Trapezoid LA | | 76 (39.17%) | | |
| | LVED (mL) | | 103.64±33.67 [96.5±37] | | |
| | LVEF (%) | | 53.64±6.6 [55 ±9.25] | | |
| | MAPSE (mm) | | 14.74±2.9 [15±4] | | |
| | TDI S Wave (cm/s) | | 8.03±1.77 [8±2] | | |
| | Diastolic dysfunction | Type 1 | 127 (65.46%) | | |
| | | Type 2 | 25 (12.89%) | | |
| | | Type 3 | 1 (0.52%) | | |
| | E/e' ratio | | 9.92±3.75 [9.63±4.28] | | |
| | sPAP (mmHg) – 27 missing | | 28.65±6.92 [26±10] | | |
| | Valvular disease | | Mild | Moderate | Severe |
| | Mitral Regurgitation | | 132 (68.04%) | 42 (21.64%) | 2 (1.03%) |
| | Mitral Stenosis | | 1 (0.51%) | - | - |
| | Tricuspid Regurgitation | | 135 (69.58%) | 30 (15.46%) | 20 (10.3%) |
| | Aortic Regurgitation | | 21 (10.82%) | 2 (1.03%) | - |
| | Aortic Stenosis | | 2 (1.03%) | 1 (0.51%) | - |

**Abbreviations**: ACEi, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; ARNI, angiotensin receptor–neprilysin inhibitor; iSGLT2, sodium-glucose cotransporter 2 inhibitors; MRAs, mineralocorticoid receptor antagonists; CCB, calcium channel blockers; AAD, antiarrhythmic drugs; CIED, cardiac implantable electronic device; DCM, dilated cardiomyopathy; hypertrophic cardiomyopathy; HFpEF, heart failure with preserved ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFrEF-heart failure with reduced ejection fraction; NYHA-New York Heart Association, StdDev, Standard Deviation;IQR, Interquartile Range; LAVI, Left Atrium Volume Index; LA, Left atrium; LVED, Left Ventricular End-Diastolic Volume; LVEF, Left Ventricular Ejection Fraction; MAPSE, Mitral Annular Plane Systolic Excursion, TDI S Wave, Tissue Doppler Imaging, S Wave Velocity; sPAP, Systolic Pulmonary Artery Pressure.

vs 420.47, $p < 0.01$), %HR max, Metabolic Equivalent of Task (METS), workload, Maximum Blood Pressure (BPmax), and HR reserve. All variables were significantly lower in the HF group.

Exercise performance stratified by HF subtype is presented in Table A5. Notably, HRRI was significantly lower in HFrEF patients (1.54) compared to HFpEF (1.93), with a p value of 0.039. Other parameters showed no significant differences across subtypes, though a trend toward lower exercise capacity in HFrEF patients was observed.

Correlations between HRRI and clinical/echocardiographic parameters can be visualised in Table 3. Spearman correlation analysis showed that age, LAVI, E/E′, and PSAP were significantly and negatively correlated with the studied parameter. In contrast, EF%, septal E′, septal S′, MAPSE, METS, maximal stress, and HR reserve showed significant positive correlations. All associations were statistically significant ($p < 0.05$).

Concerning HRRI and underlying comorbidities, worth mentioning that it exhibited statistically lower values among smokers (p=0.022), hypertensive patients (p=0.025), T2DM (p<0.01), and chronic renal disease (p<0.01). Nevertheless, patients with a history of AF did not exhibit statistically significant values regarding HRRI.

**Table 2** Comparison of Exercise Test Parameters Between Heart Failure and Non-Heart Failure Groups

| Variable | Descriptive Parameter | HF (n = 127) | NO HF (n = 67) | *p*-value |
|---|---|---|---|---|
| HRRI | Mean | 1.87 | 2.65 | <0.01 |
| | StdDev | 0.68 | 1.08 | |
| | Median | 1.78 | 2.43 | |
| | IQR | 0.73 | 1.1 | |
| | MIN | 0.62 | 1.29 | |
| | MAX | 4.52 | 7.61 | |
| | 95% CI | 1.75–1.99 | 2.39–2.91 | |
| HR AT | Mean | 345.22 | 420.47 | <0.01 |
| | StdDev | 109.75 | 139.41 | |
| | Median | 331.2 | 432 | |
| | IQR | 163.2 | 185.4 | |
| | MIN | 51 | 187.8 | |
| | MAX | 732 | 811.8 | |
| | 95% CI | 325.95–364.49 | 386.47–454.48 | |
| %HR max | Mean | 69.57 | 80.06 | <0.01 |
| | StdDev | 10.89 | 11.87 | |
| | Median | 68 | 81 | |
| | IQR | 15 | 13 | |
| | MIN | 41 | 55 | |
| | MAX | 102 | 142 | |
| | 95% CI | 67.66–71.49 | 77.16–82.95 | |
| METS | Mean | 6.8 | 8.32 | <0.01 |
| | StdDev | 1.7 | 2.19 | |
| | Median | 6.7 | 8 | |
| | IQR | 2 | 3 | |
| | MIN | 2.7 | 3.9 | |
| | MAX | 13.1 | 14.8 | |
| | 95% CI | 6.51–7.10 | 7.78–8.85 | |

(*Continued*)

**Table 2** (Continued).

| Variable | Descriptive Parameter | HF (n = 127) | NO HF (n = 67) | *p*-value |
|---|---|---|---|---|
| W | Mean | 111.09 | 134.7 | <0.01 |
| | StdDev | 33.51 | 38.42 | |
| | Median | 100 | 125 | |
| | IQR | 25 | 50 | |
| | MIN | 8.5 | 75 | |
| | MAX | 200 | 250 | |
| | 95% CI | 105.21–116.98 | 125.33–144.07 | |
| BPmax | Mean | 170.47 | 182.37 | <0.01 |
| | StdDev | 29.76 | 29.04 | |
| | IQR | 41 | 42 | |
| | MIN | 98 | 110 | |
| | MAX | 252 | 283 | |
| | 95% CI | 165.25–175.70 | 175.29–189.46 | |
| HRR1 | Mean | 19.03 | 26.84 | <0.01 |
| | StdDev | 9 | 7.95 | |
| | Median | 19 | 27 | |
| | IQR | 10 | 9 | |
| | MIN | −11 | 7 | |
| | MAX | 48 | 58 | |
| | 95% CI | 17.45–20.61 | 24.9–28.78 | |
| HRReserve | Mean | 39.6 | 55.67 | <0.01 |
| | StdDev | 14.4 | 15.36 | |
| | IQR | 22 | 19 | |
| | MIN | 3 | 20 | |
| | MAX | 93 | 95 | |
| | 95% CI | 37.07–42.13 | 51.92–59.42 | |

**Abbreviations**: HRR1 - Heart Rate Recovery Index; AT – Acceleration Time; %HR max - Percentage of Maximum Heart Rate; METS - Metabolic Equivalent of Task; W - Watts; BPmax - Maximum Blood Pressure; HRR1-Heart Rate Recovery at 1 minute postexercise; HRReserve - Heart Rate Reserve; StdDev - Standard Deviation; IQR - Interquartile Range; MIN - Minimum; MAX - Maximum; CI - Confidence Interval; HF - Heart Failure.

In our study, 61.34% of patients were receiving beta-blocker therapy. Beta-blocker therapy was more frequently prescribed in patients with heart failure; however, their use did not significantly influence HRRI values (Table A6). Among other heart rate-modulating drugs, neither amiodarone, calcium channel blockers, nor Ic antiarrhythmic drugs showed a statistical difference regarding HF status (Table A7). The effects of heart rate-modulating drugs and GDMT can

**Table 3** Correlations Between HRRI and Clinical/Echocardiographic Parameters (Spearman's Rho)

| Variable | Spearman's Rho | *p*-value |
|---|---|---|
| Age | −0.363 | <0.01 |
| LAVI | −0.217 | <0.01 |
| EF | 0.166 | 0.021 |
| e′ | 0.147 | 0.041 |
| E/E′ | −0.231 | <0.01 |
| S Wave | 0.215 | <0.01 |
| PSAP | −0.187 | 0.016 |
| MAPSE | 0.328 | <0.01 |
| METS | 0.260 | <0.01 |
| Max Stress (W) | 0.350 | <0.01 |
| HR Reserve | 0.162 | 0.024 |

**Abbreviations**: LAVI,- Left Atrial Volume Index; EF, Ejection Fraction; PSAP, Pulmonary Systolic Artery Pressure; MAPSE, Mitral Annular Plane Systolic Excursion; METS, Metabolic Equivalent of Task; Max Stress (W), Maximum Stress (Watts); HR Reserve, Heart Rate Reserve.

**Table 4** Expanded Logistic Regression Model for Predicting Heart Failure

| Variable | β | *p* | BCa 95% CI for β | |
|---|---|---|---|---|
| | | | Lower | Higher |
| AF/AFL | 2.24 | 0.004 | 0.25 | 21.88 |
| Diastolic dysfunction | 2.62 | 0.001 | 1.44 | 6.3 |
| MAPSE (mean-centered) | −1.13 | 0.002 | −1.96 | −0.65 |
| HRRI (mean-centered) | −0.21 | 0.008 | −0.38 | −0.08 |
| Maximum HR% (mean-centered) | −0.1 | 0.002 | −0.16 | −0.06 |
| HRReserve (mean-centered) | −0.02 | 0.482 | −0.09 | 0.03 |
| HRR1 (mean-centered) | −0.01 | 0.783 | −0.05 | 0.04 |
| Constant | −1.36 | 0.006 | −2.56 | −0.67 |

**Abbreviations**: AF/AFL, Atrial Fibrillation/Flutter; MAPSE, Mitral Annular Plane Systolic Excursion; HRRI, Heart Rate Recovery Index; HR, Heart Rate; HRReserve, Heart Rate Reserve; HRR1, Heart Rate Recovery at 1-minute postexercise; BCa, Bias-corrected and accelerated.

be seen in (Tables A8-A11). Furthermore, HRRI values were also significantly lower in patients receiving angiotensin receptor–neprilysin inhibitors (ARNI, $p < 0.01$) and sodium–glucose cotransporter-2 inhibitors (SGLT2i, $p < 0.01$).

## Logistic Regression and ROC Curves

The final binary logistic regression model for predicting the presence of heart failure included the following variables: the presence of atrial fibrillation or flutter, diastolic dysfunction, MAPSE (mean-centered), HRRI (mean-centered), and percentage achieved of target maximum HR (mean-centered). These variables were selected based on their significant associations with heart failure in bivariate analysis and retained through stepwise model refinement. The overall classification accuracy of the model was 82.5%, with a sensitivity of 89.0% for identifying heart failure cases and a specificity of 70.1% for correctly identifying non-HF individuals. Model calibration was acceptable, as indicated by a non-significant Hosmer–Lemeshow test ($p = 0.242$). Table A12 presents the regression coefficients, associated p-values, and bias-corrected and accelerated (BCa) 95% confidence intervals based on 1,000 bootstrap samples.

Among the predictors, the presence of atrial fibrillation or flutter and diastolic dysfunction was associated with increased odds of heart failure. In contrast, higher MAPSE, higher HRRI, and a greater percentage of target maximum heart rate achieved were associated with lower odds of heart failure. Diastolic dysfunction had the largest positive coefficient (β = 2.65), while HRRI showed the strongest negative association (β = –1.21).

We attempted to expand the final binary logistic regression model by adding heart rate reserve (HRReserve) and heart rate recovery at 1 minute (HRR1) to the predictors from the optimal model. The expanded model showed similar performance to the original (accuracy 83.0% vs 82.5%, sensitivity 89.0%, specificity 71.6% vs 70.1%) and neither HRReserve (p = 0.804) nor HRR1 (p = 0.496) were significant predictors. While model calibration remained acceptable (Hosmer–Lemeshow p = 0.257), their inclusion did not alter the effects of the original variables and, indicating no improvement in predictive capacity. Table 4 illustrates the regression coefficients, p-values, and BCa 95% confidence intervals for the expanded model.

Receiver operating characteristic (ROC) analysis was conducted to assess the performance of HRRI in identifying heart failure (Figure 2). The area under the curve (AUC) was 0.753, with a 95% confidence interval of 0.682 to 0.824 and a standard error of 0.036, indicating good discriminative ability. The result was statistically significant ($p < 0.001$), suggesting that HRRI provides a reliable distinction between patients with and without heart failure.

Moreover, further analysis was performed to assess the ability of HRRI to distinguish between patients with HFpEF and HFmrEF/HFrEF (Figure 3). The area under the curve was 0.647 (95% CI: 0.522–0.771; SE = 0.063), with statistical significance (p = 0.018). Although the discriminative performance was modest compared to the overall heart failure classification (AUC = 0.753), the result suggests that HRRI has potential value in differentiating between subtypes based on ejection fraction.

## Two-Step Cluster Analysis

A two-step cluster analysis using HRRI and ejection fraction was performed to explore their role in characterizing heart failure phenotypes, with the optimal number of clusters determined by Akaike's Information Criterion (AIC). Bivariate analyses were then used to assess associations between these clusters and key clinical and functional parameters linked to heart failure presence and prognosis.

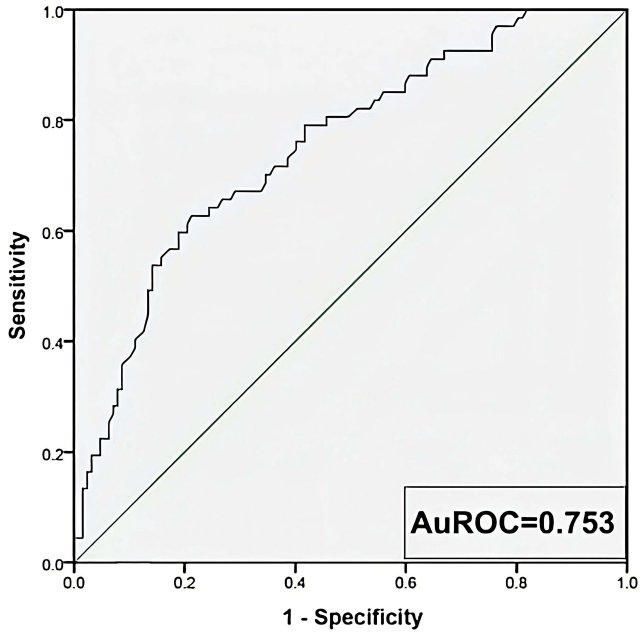


**Figure 2** ROC CURVEforHRRI Predicting Heart Failure.

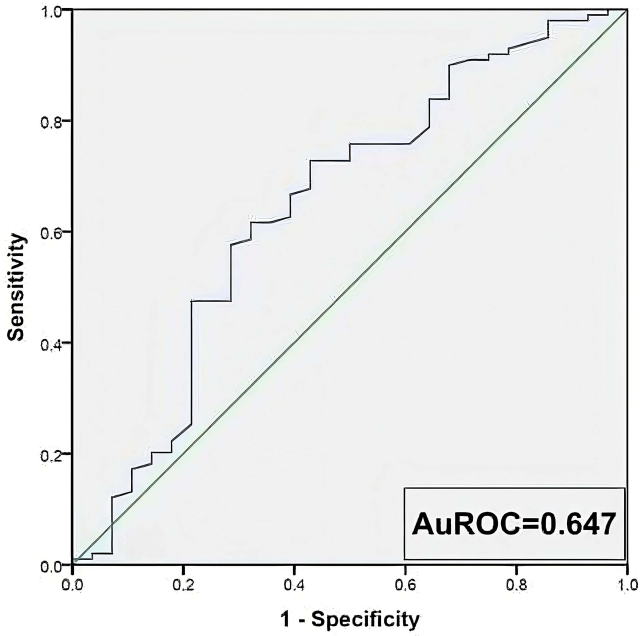


**Figure 3** ROC CURVE for HRRI Predicting HF Type: HFrEF/HFmrEF vs HFpEF HRRI.

Cluster 4: Represents patients with the most severe cardiac impairment. These individuals exhibit markedly reduced ejection fraction, the lowest HRRI, and significantly altered echocardiographic parameters.

Cluster 3: Comprises patients with predominantly preserved EF but low HRRI, frequently accompanied by clinical heart failure (HFpEF). Echocardiographic parameters are moderately impaired.

Cluster 2: Clinically and echocardiographically similar to Cluster 3 in terms of EF and diastolic function, but with higher HRRI values, suggesting better autonomic response or early-stage dysfunction.

Cluster 1: Characterized by normal EF and the highest HRRI values.

Table 5 summarizes the distribution of variables, significant differences in heart failure subtypes, NYHA functional class, and diastolic dysfunction across clusters ($p < 0.01$). Cluster 4 had the highest prevalence of HFREF and HFMREF, while Cluster 3 predominantly had HFPEF, and Cluster 1 had the most individuals without HF.

A visual representation of the model is shown in Figure 4.

**Table 5** Two-Step Cluster Analysis Results

| Variable | Characteristic | Cluster 1 (n=26) | Cluster 2 (n=44) | Cluster 3 (n=98) | Cluster 4 (n=26) | *p*-value |
|---|---|---|---|---|---|---|
| HRRI | Mean | 3.9 | 2.01 | 1.89 | 1.55 | <0.01 |
| | StdDev | 0.98 | 0.48 | 0.49 | 0.6 | |
| | Median | 3.66 | 2.02 | 1.86 | 1.48 | |
| | IQR | 1.08 | 0.7 | 0.68 | 0.66 | |
| | MIN | 2.89 | 1.03 | 0.77 | 0.62 | |
| | MAX | 7.61 | 2.97 | 2.97 | 3.55 | |
| | 95% CI | 3.50–4.29 | 1.87–2.16 | 1.79–1.99 | 1.31–1.79 | |

(*Continued*)


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**Table 5** (Continued).

| Variable | Characteristic | Cluster 1 (n=26) | Cluster 2 (n=44) | Cluster 3 (n=98) | Cluster 4 (n=26) | *p*-value |
|---|---|---|---|---|---|---|
| EF | Mean | 55.42 | 60.7 | 53.45 | 40.62 | <0.01 |
| | StdDev | 3.68 | 2.28 | 2.49 | 4.73 | |
| | Median | 55 | 60 | 55 | 40 | |
| | IQR | 7 | <0.01 | 5 | 5.5 | |
| | MIN | 48 | 57 | 48 | 30 | |
| | MAX | 60 | 68 | 57 | 47 | |
| | 95% CI | 53.94–56.91 | 60.01–61.4 | 52.95–53.95 | 38.7–42.53 | |
| HF | HFREF | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 14 (53.8%) | <0.01 |
| | HFMREF | 1 (3.8%) | 0 (0.0%) | 1 (1.0%) | 12 (46.2%) | |
| | HFPEF | 7 (26.9%) | 28 (63.6%) | 64 (65.3%) | 0 (0.0%) | |
| | NO HF | 18 (69.2%) | 16 (36.4%) | 33 (33.7%) | 0 (0.0%) | |
| NYHA CLASS (NO HF excluded) | I | 3 (37.5%) | 12 (42.9%) | 10 (15.4%) | 0 (0.0%) | <0.01 |
| | II | 5 (62.5%) | 15 (53.6%) | 54 (83.1%) | 23 (88.5%) | |
| | III | 0 (0.0%) | 1 (3.6%) | 1 (1.5%) | 3 (11.5%) | |
| Diastolic dysfunction | None | 6 (23.1%) | 11 (25.0%) | 24 (24.5%) | 0 (0.0%) | <0.01 |
| | 1 | 20 (76.9%) | 28 (63.6%) | 62 (63.3%) | 17 (65.4%) | |
| | 2 | 0 (0.0%) | 5 (11.4%) | 12 (12.2%) | 8 (30.8%) | |

**Abbreviations**: N, number; HRRI, Heart Rate Recovery Index; EF, Ejection Fraction; StdDev, Standard Deviation; IQR, Interquartile Range; MIN, Minimum; MAX, Maximum; CI, Confidence Interval; HF, Heart Failure; HFREF, Heart Failure with Reduced Ejection Fraction; HFMREF, Heart Failure with Mid-Range Ejection Fraction; HFPEF, Heart Failure with Preserved Ejection Fraction; NYHA CLASS, New York Heart Association Classification.

## Discussion

In this study, we introduce the HRRI as a novel, dynamic tool for characterizing and stratifying heart failure (HF) during exercise testing.

Unlike traditional heart rate recovery (HRR), which measures an absolute heart rate decline after exercise, HRRI offers a more comprehensive evaluation by capturing the temporal aspects of heart rate acceleration and deceleration during exertion and recovery. This provides a dynamic reflection of the underlying autonomic nervous system balance, which is frequently disrupted in HF.[35] Autonomic dysfunction, marked by heightened sympathetic and reduced parasympathetic activity, plays a critical role in HF progression. This imbalance is reflected in impaired heart rate recovery[36] and may be better captured by HRRI.

We conducted a prospective study that involved 194 patients who underwent exercise testing for various clinical reasons. Our study population had a high prevalence of hypertension (HTN), dyslipidaemia, obesity, type 2 diabetes mellitus (T2DM), and chronic coronary syndrome (CCS). Atrial fibrillation/flutter (AF/AFL) and chronic kidney disease (CKD) were also frequent. These comorbidities are established risk factors for heart failure development and progression.[37]

Echocardiographic analysis revealed significant differences between heart failure and non-heart failure patients. Those with heart failure had larger left atrial volume indices (LAVI), higher E/e' ratios, reduced MAPSE, and Tissue

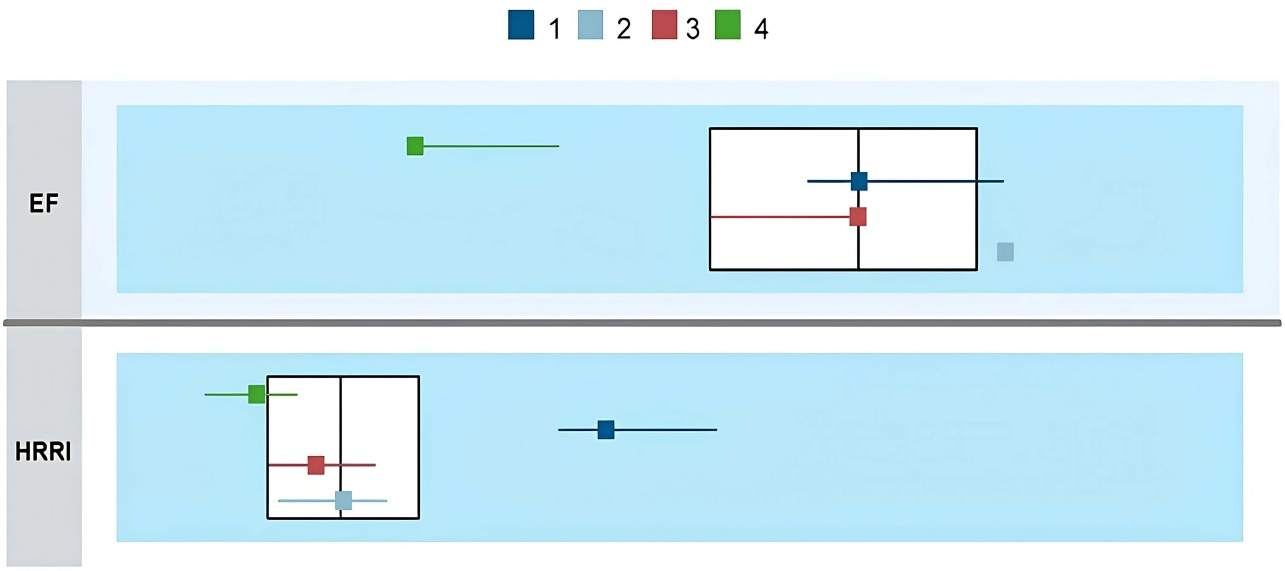


**Figure 4** Cluster-based classification using HRRI and EF. Cluster 1 (high HRRI, normal EF); Cluster 2 (moderate HRRI, preserved EF; Cluster 3 (low HRRI, preserved EF); Cluster 4 (lowest HRRI, reduced EF).
**Abbreviations**: EF, ejection fraction; HRRI, heart rate recovery index.

Doppler-derived systolic velocities (S'). These findings reflect both diastolic dysfunction and early impairment in longitudinal systolic function, similar to a previously published study.[38]

Table 2 reveals significant differences in exercise parameters between heart failure and non-heart failure patients. HRRI and HRR1 were markedly lower in HF patients, indicating impaired autonomic regulation during recovery. The acceleration time was shorter, and patients achieved a lower percentage of age-predicted maximum heart rate, demonstrating chronotropic incompetence among HF patients, as shown in previously published studies.[39,40]

Microvascular rarefaction within the sinoatrial (SA) node has been identified as a key contributor to SA node dysfunction, especially in HFpEF patients. This microvascular impairment leads to cellular hypoxia and altered pacemaker activity, ultimately causing chronotropic incompetence—a common feature in HFpEF characterized by an inadequate heart rate response to exercise.[41]

Exercise capacity was reduced in HF patients, with lower METs, peak maximum blood pressure, and heart rate reserve. These findings collectively reflect comprehensive impairments in both exercise performance and recovery in heart failure patients.[42] HRRI yielded statistical significance concerning both exercise capacity, defined as the maximal level of physical exertion an individual can sustain, and functional capacity, referring to the ability to perform daily activities involving submaximal effort. These parameters reflect complex pathophysiological mechanisms, including reduced cardiac and pulmonary reserve as well as a dysfunction of respiratory and peripheral muscle perfusion.[5]

Regarding beta-blocker therapy or other antiarrhythmic drugs, our study did not identify significant differences in HRRI among patients. In contrast, Ivabradine, by selectively inhibiting the If ("funny") current in the sinoatrial node, reduces heart rate without directly altering autonomic tone or myocardial contractility, but its impact on intrinsic heart rate kinetics may slow both heart rate acceleration and deceleration slopes, thereby reducing HRRI. Moreover, current guidelines recommend Ivabradine in symptomatic patients with HFrEF, in sinus rhythm, with a baseline heart rate of $\geq 70$ beats per minute, who already receive evidence-based dosage of beta-blockers, or those who do not tolerate/have contraindications for beta-blockers.[1] Additionally, ivabradine can also be administered in HFpEF patients with coronary artery disease for its anti-anginal properties.[43] These findings imply that while HRRI remains a reliable diagnostic marker in beta-blocker-treated populations, its interpretation should be more cautious in patients receiving Ivabradine, where slower sinoatrial recovery dynamics may confound its diagnostic significance independently of true autonomic dysfunction.[23]

An important finding consists of HRRI as the only exercise parameter that showed significant differences across heart failure phenotypes (Table A5). Specifically, HRRI progressively declined from HFpEF to HFmrEF and further to HFrEF, suggesting that autonomic dysfunction measured by HRRI may parallel the severity of systolic dysfunction.

Table 3 demonstrates significant associations between HRRI and key clinical and echocardiographic parameters. HRRI exhibited notable negative correlations with age, LAVi E/E' ratio, and sPAP. Conversely, positive correlations were observed with ejection fraction, septal E' velocity, septal S' velocity, MAPSE, exercise capacity, maximal workload, and heart rate reserve.

These correlations suggest that HRRI integrates both systolic and diastolic cardiac function, with lower values associated with echocardiographic markers of elevated filling pressures, atrial remodelling, and reduced longitudinal contractility. The significant correlation with exercise parameters further suggests HRRI reflects autonomic regulation and overall cardiovascular functional capacity. These findings are aligned with previous data about HRR, which was corroborated to decreased exercise capacity in a study involving post-myocardial infarction patients,[44] or patients who were evaluated before and after trans aortic valve implantation (TAVI), in whom HRR was an important predictor of exercise capacity after the intervention.[45] These results are consistent with previous reports linking impaired HRR with diastolic dysfunction and elevated filling pressures.[46,47]

The ROC curve analysis demonstrates the discriminative power of HRRI in heart failure assessment. Figure 2 illustrates the distinguishing ability of HRRI for detecting heart failure. Figure 3 further explores HRRI's capacity to differentiate heart failure phenotypes. The identification of distinct cut-off values for overall heart failure identification versus phenotypic classification highlights HRRI's potential utility across the heart failure spectrum, with different thresholds reflecting the progressive nature of autonomic dysfunction in advanced systolic impairment. The modest AUC for phenotypic discrimination suggests that while HRRI provides valuable physiological information, it should be integrated with other clinical and imaging parameters for optimal classification of heart failure subtypes.

A related study by Cozlac et al evaluated HRRI in a different context, namely as a predictor for CRT response. Their analysis revealed a stronger discriminatory performance, with an AUC of 0.844 and an optimal HRRI cut-off value of 1.51. The lower cut-off identified in Cozlac's study reflects the more advanced autonomic dysfunction typically found in CRT candidates compared to the broader population assessed for heart failure diagnosis. These differences underscore how HRRI's diagnostic thresholds can vary depending on disease severity and clinical application.[19]

The multivariate regression analysis demonstrates that HRRI remains an important predictor of heart failure, even after adjusting for established clinical and echocardiographic parameters. Similarly, previous studies have shown that heart rate recovery independently predicts mortality risk in patients with chronic heart failure, even after accounting for exercise capacity, heart failure severity scores, and other clinical measures.[48] Moreover, data from another article reveal that HRR can independently predict clinical outcomes in patients with acute decompensated HF as well.[49]

Although heart rate reserve and HRR1 were examined in the expanded model (Table 4), they did not significantly contribute to the prediction. This suggests that HRRI may capture distinct aspects of autonomic and cardiovascular recovery not reflected by traditional exercise test measures.

Beyond evaluating HRRI as a discriminatory marker of HF status, cluster analysis provided additional insight into the heterogeneity of heart failure phenotypes. The two-step cluster analysis, based on HRRI and EF, identified four distinct groups characterized by differing degrees of autonomic and systolic dysfunction.

Cluster 1 included individuals with preserved EF and high HRRI values, representing patients with intact cardiac-autonomic regulation and minimal disease burden. This highlights the value of early HRR assessment in routine clinical practice, given its proven predictive power for morbidity, mortality, and disease progression.[50]

Cluster 2, while maintaining preserved EF, exhibited intermediate HRRI reductions, suggestive of early-stage autonomic impairment. Moreover, data published on this subject exposed that impaired HRR is linked to a higher probability of HF development.[7]

Cluster 3 was composed predominantly of HFpEF patients with further declines in HRRI despite preserved EF, reflecting more advanced functional limitation.

Finally, Cluster 4 demonstrated both significantly reduced EF and markedly depressed HRRI, consistent with HFrEF/HFmrEF and advanced heart failure.

Along with the deterioration of the EF and a lower HRRI, the identified clusters also highlight a decline in echocardiographic parameters. Specifically, as HRRI becomes blunter and EF worsens, there is a corresponding increase in the incidence of diastolic dysfunction. The progressive decline in HRRI across these clusters parallels increasing disease severity, indicating that HRRI captures physiological deterioration earlier than EF alone. This suggests that HRRI may serve not only as a functional marker but also as a means of stratifying risk within HF populations, particularly in identifying vulnerable HFpEF patients often missed by traditional measures.

Furthermore, we found that HRRI values decline progressively across HF subtypes, with intermediate values in HFmrEF and the lowest values in HFrEF. This gradient aligns with known pathophysiological severity and supports HRRI as a stratification tool in clinical settings.

The diagnostic landscape for heart failure, particularly HFpEF, remains challenging due to the nonspecific nature of symptoms and overlap with comorbidities such as obesity, diabetes, and COPD. In many cases, dyspnea and fatigue may precede measurable declines in EF or overt signs on imaging. Tools like natriuretic peptides can support diagnosis, but are influenced by age, obesity, and renal function.[51]

HRRI serves as a comprehensive cardiovascular risk marker by integrating both chronotropic competence and autonomic recovery function. Within the broader concept of HRR, HRRI could guide medication optimization, inform exercise prescription in cardiac rehabilitation programs,[16] or sports cardiology,[52] and even provide valuable feedback for programming rate response parameters in patients with CIEDs.[20] Furthermore, it could provide valuable information in resource-limited settings where biomarker testing may not be readily available.

HRRI can be easily integrated into existing clinical workflows since it is calculated from standard exercise stress tests without additional equipment. The parameter's ability to identify patients with cardiovascular risk factors makes it valuable for risk stratification and guiding treatment intensity.

In this setting, HRRI has the potential as a low-cost, accessible, and reproducible screening tool that can be integrated into routine exercise testing protocols. Moreover, HRRI could complement diagnostic scores eg, H2FPEF or HFA-PEFF scores, by providing a dynamic marker of autonomic and cardiovascular integration, considering the limitations of conventional diagnostic tools in HFpEF. In the future, HRRI might be integrated into multiparametric diagnostic algorithms alongside the electrocardiogram, natriuretic peptides, and imaging findings, thereby proving the importance of innovative scores in heart failure management.[53–55]

## Limitations and Future Directions

Several limitations should be acknowledged. Although this was a dual-center study, the sample size, particularly for patients with HFmrEF and HFrEF, was modest, limiting the statistical power for subgroup analyses.

Following the outpatient protocols applied to stable patients undergoing exercise testing, NT-proBNP levels were not uniformly available and were therefore excluded from the statistical analysis. This reflects common clinical practice, as NT-proBNP assessment is more frequently utilized in acute or decompensated settings. In contrast, our study population primarily consisted of patients with chronic, stable heart failure evaluated through scheduled day-care admissions.

While NT-proBNP can provide valuable diagnostic information, its interpretation is influenced by age, body mass index, renal function, and atrial fibrillation, which may reduce its specificity. There is no single definition that combines imaging or natriuretic peptides to provide a clear rule-in or rule-out assessment for HFpEF.[56] HRRI, in contrast, may offer a more accessible and reproducible parameter in such settings, but further studies are necessary to confirm these beliefs.

Future research should focus on validating HRRI in larger, multicentre cohorts, assessing its incremental diagnostic value over current tools, and exploring whether HRRI predicts outcomes such as HF hospitalization or cardiovascular death. Incorporating cardiopulmonary exercise testing (CPET), wearable monitoring, or machine learning approaches may also refine HRRI's clinical utility.

## Conclusion

In conclusion, HRRI arises as a novel and promising marker for the assessment of heart failure. It could serve as a complementary approach to HF evaluation, especially when echocardiographic findings are inconclusive, with

significant utility in HFpEF. By capturing the dynamic shifts of sympathetic and parasympathetic activity, HRRI reflects the underlying autonomic dysfunction of HF. These findings support its integration into exercise testing protocols as a non-invasive, accessible parameter that adds functional context to structural and biological markers.

Further studies are needed to confirm its role in wider clinical situations and at different stages of heart failure.

## Ethical Statement

All the subjects included in the study gave their informed consent before inclusion. This study was conducted according to the guidelines of the Declaration of Helsinki, and the Institutional Ethics Committee of the Institute of Cardiovascular Diseases Timisoara, approved the protocol (Nr. 62/30.10.2023, rev 2024) and the Ethics Committee of the Clinical County Hospital of Sibiu (Nr. 5046/02.09.2024).

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## Disclosure

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