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Original Article

Internal Medicine Section

# Neutrophil to Lymphocyte Ratio, NTproBNP and Six-minute Walk Test as Predictors of Readmission and Mortality in Patients with Heart Failure: A Prospective Observational Study

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## ABSTRACT

**Introduction:** Heart Failure (HF) is a leading cause of morbidity and mortality worldwide, with a high-risk of hospital readmission. Identifying reliable prognostic markers is crucial for optimising clinical management. N-terminal pro-B-type natriuretic peptide (NTproBNP), Neutrophil-To-Lymphocyte Ratio (NLR), and the Six-Minute Walk Test (6MWT) have emerged as key predictors of HF outcomes.

**Aim:** The present study evaluates the predictive value of NTproBNP, NLR, and the 6MWT in assessing mortality and readmission risks in HF patients.

**Materials and Methods:** In the present prospective observational study, 170 HF patients were enrolled over 18 months. NTproBNP and NLR were measured at admission; 6MWT was conducted at discharge. Patients were followed for 90 days to assess mortality and readmission. Receiver Operating Characteristic (ROC) analysis determined cut-off values and predictive accuracy.

**Results:** Mortality occurred in 14 patients (8.2%) and readmission in 19 patients (11.2%). NTproBNP levels were significantly higher in mortality (28,114.29±6799.08 pg/mL) and readmission groups (21,242.63±9553.81 pg/mL) with AUCs of 0.98 and 0.92, respectively ($p<0.0001$). NLR was elevated in mortality (6.70±2.53; AUC=0.64) and readmission groups (7.88±4.93; AUC=0.67). 6MWT distances were reduced in mortality (170.00±49.92 m; AUC=0.978) and readmission (214.74±73.66 m; AUC=0.915).

**Conclusion:** NTproBNP and 6MWT are effective prognostic markers in HF, enhancing risk stratification. NTproBNP was the most predictive, 6MWT assessed functional status, and NLR reflected inflammation's role.


**Keywords:** Cardiac biomarkers, Cardiac failure, Prognosis, Ventricular function

## INTRODUCTION

HF is a major health problem, it affects around 26 million individuals worldwide [1]. It is progressive in nature and defined as the heart's inability to maintain enough blood circulation to meet metabolic demands, leading to systemic congestion and multi-organ dysfunction [2]. Despite advances in pharmacological and device-based therapies, HF remains a leading cause of hospitalisation, morbidity, and mortality. One of the primary challenges in HF management is identifying patients at increased risk of adverse outcomes, including readmission and mortality [3,4].

Several prognostic markers have been explored to improve risk stratification in HF, including NTproBNP, NLR, and the 6MWT [5]. NTproBNP is a well-established biomarker secreted by ventricular myocytes in response to increased myocardial wall stress [6]. Elevated NTproBNP levels correlate with HF severity and have been extensively validated as a predictor of hospital readmission and mortality [7,8]. The NLR is a haematological marker reflecting systemic inflammation and immune response. In HF, inflammation plays a critical role in disease progression, contributing to myocardial remodeling and worsening clinical status. A higher NLR is associated with increased hospitalisation rates and mortality risk in HF patients [9,10]. The 6MWT is a functional assessment tool used to evaluate exercise tolerance and physical capacity in HF patients. It measures the total distance a patient can walk in six minutes, providing insight into cardiopulmonary efficiency and overall functional status [11]. Reduced 6MWT distances are linked to worse clinical outcomes, including increased hospitalisation and mortality [12,13].

Despite numerous studies on HF prognostic markers, such as NTproBNP [1,7,8,14], NLR [9,10], and the 6MWT [11-13], very few have compared NTproBNP, NLR, and 6MWT in a single study [15]. Most studies assess these markers in isolation, with little focus on their integrated role in clinical practice, especially in Indian populations [15-17]. This study bridges that gap by comparing the utility of NTproBNP, NLR, and 6MWT to improve early risk prediction of readmission and mortality, offering a novel, holistic approach to enhance HF management and patient outcomes. Thus, the aim of this study was to evaluate the predictive value of NTproBNP, NLR, and the 6MWT in assessing mortality and readmission risks in HF patients.

## MATERIALS AND METHODS

The present prospective, observational study was conducted at SRM Medical College Hospital and Research Centre, Chengalpattu, Tamil Nadu, India, from September 15, 2023, to November 15, 2024. Institutional Ethics Committee approval was obtained prior to initiation (IEC No. SRMIEC-ST0723-569), and the study adhered to the ethical principles outlined in the Declaration of Helsinki. All participants gave written informed consent before enrollment.

**Inclusion and Exclusion criteria:** The study included adult patients diagnosed with HF based on clinical symptoms and signs, with documented hospitalisation or a history of HF. Patients aged below 18 years, those with active infections, or those on immunosuppressive therapy were excluded from the study to prevent confounding effects on inflammatory markers. Additionally, patients with Chronic Kidney

Disease (CKD) in End-Stage Renal Disease (ESRD) with an eGFR of less than 15 mL/min/1.73m², advanced malignancies, or end-stage liver disease were excluded to ensure that readmission and mortality outcomes were primarily linked to HF rather than other terminal illnesses.

**Sample size selection:** A convenience sample of 170 patients was taken, classified into two equal groups of 85 based on left ventricular Ejection Fraction (EF). Group-A consisted of patients with an EF ≤40%, and Group-B included patients with EF >40%. The EF threshold was based on ESC guidelines that define HF with reduced EF (HFrEF; EF <40%), which has more prognostic and therapeutic implications, mid-range EF (HFmrEF; EF 40–49%), and preserved EF (HFpEF; EF ≥50%) [1].

### Study Procedure

At the time of hospital admission, history taking and physical examination were done, blood samples were collected to measure NTproBNP and calculate NLR from routine complete blood count data. At discharge, patients underwent the 6MWT conducted in a standardised manner as per guidelines from the American Thoracic Society [18]. The test was performed in a 30-meter-long, hard-surfaced corridor. Patients were instructed to walk at a self-selected pace for six minutes, with the ability to stop or rest if needed. The total distance covered was recorded in meters.

**Follow-up and outcome measures:** Patients were monitored for 30-day, 60-day, and 90-day readmission and mortality through hospital records and telephone follow-ups. Readmission was defined as any hospitalisation due to worsening HF symptoms within the follow-up period. Readmission and mortality data were collected from hospital records or confirmed through direct communication with family members.

## STATISTICAL ANALYSIS

All statistical analyses were performed using IBM Statistical Package for Social Sciences (SPSS) version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean±standard deviation and compared using independent t-tests. Categorical data were expressed as frequencies and percentages and analysed using chi-square tests. ROC curves were generated to identify optimal cut-off values of NTproBNP, NLR, and 6MWT for predicting mortality and readmission. Area Under the Curve (AUC), sensitivity, specificity, and predictive values were calculated. A p-value<0.05 was considered statistically significant.

## RESULTS

The baseline demographic and clinical characteristics of the 170 HF patients are presented in [Table/Fig-1]. The cohort had a mean age of 62.59±13.60 years, with a slight female predominance (93, 54.7%). Among co-morbid conditions, 110 patients (64.71%) had Diabetes Mellitus (DM), 84 patients (49.41%) had Systemic Hypertension (S.HTN), and 29 patients (17.06%) had Coronary Artery Disease (CAD). Mortality was observed in 14 patients (8.2%), while readmission occurred in 19 patients (11.2%). Mean values for key prognostic markers included NLR (5.76±3.84), NTproBNP (8022.25±8154.63 pg/mL), 6MWT distance (352.41±87.06 meters), and EF (44.92±11.44%).

| Characteristics | Observed values n=170 |
|---|---|
| **Demographics** | |
| Age (Mean±SD) | 62.59±13.60 |
| **Sex** | |
| Female, n (%) | 93 (54.7%) |
| Male, n (%) | 77 (45.3%) |
| **Co-morbidities** | |
| CAD, n (%) | 29 (17.06%) |
| CKD, n (%) | 4 (2.35%) |
| DM, n (%) | 110 (64.71%) |
| S.HTN, n (%) | 84 (49.41%) |
| Other cardiac diseases, n (%) | 4 (2.35%) |
| Others, n (%) | 3 (1.76%) |
| **Mortality** | |
| No, n (%) | 156 (91.8%) |
| Yes, n (%) | 14 (8.2%) |
| **Readmission** | |
| No, n (%) | 151 (88.8%) |
| Yes, n (%) | 19 (11.2%) |
| **Mean diagnostic indicators** | |
| NLR (Mean±SD) | 5.76±3.84 |
| NTproBNP (Mean±SD) | 8022.25±8154.63 pg/ml |
| 6 MWT (Mean±SD) | 352.41±887.06 meters |
| EF (Mean±SD) | 44.92±11.44 % |

**[Table/Fig-1]:** Demographics and baseline characteristics of the study population. SD: Standard deviation; CAD: Coronary artery disease; CKD: Chronic kidney disease; DM: Diabetes mellitus; S.HTN: Systemic hypertension; NLR: Neutrophil-to-lymphocyte ratio; NTproBNP: N-terminal pro-B-type natriuretic peptide; 6 MWT: Six-minute walk test distance in meters; EF: Ejection fraction

**Comparison of biomarkers and functional parameters in mortality and readmission:** Key prognostic markers showed clear differences between outcome groups as summarised in [Table/Fig-2]. Patients who experienced mortality had higher NLR (6.70±2.53 vs. 5.67±3.93) (p=0.098) and NTproBNP levels (28,114.29±6799.08 pg/mL vs. 6219.12±5375.18 pg/mL) (p<0.0001), along with significantly reduced 6MWT distances (170.00±49.92 meters vs. 368.78±69.14 meters) (p<0.0001) and EF (37.64±10.24% vs. 45.57±11.35%) (p=0.003) compared to survivors. Similarly, patients who were readmitted had elevated NLR (7.88±4.93 vs. 5.49±3.61) (p=0.038) and NTproBNP levels (21,242.63±9553.81 pg/mL vs. 6358.76±6248.51 pg/mL) (p<0.0001), along with lower 6MWT distances (214.74±73.66 meters vs. 369.74±72.01 meters) (p<0.0001) and EF (38.53±11.21% vs. 45.72±11.25%) (p=0.008).

**Comparison of predictive markers for mortality in Heart Failure (HF):** Among patients with NLR >5.72, 10 experienced mortality, while 4 deaths occurred in those with NLR ≤5.72 (p=0.071) [Table/Fig-3,4a]. For NTproBNP, 13 deaths occurred in patients with levels >16,250 pg/mL, while one death was observed below this threshold (p<0.0001; [Table/Fig-4b]). Similarly, 13 deaths were noted in those walking less than 255 meters on the 6MWT, compared to one death in those walking more than 255 meters (p<0.0001; [Table/Fig-4c]). EF <41% was associated with 10 deaths, versus four in patients with EF >41% (p=0.016; [Table/Fig-4d]). The prognostic performance of NLR, NTproBNP, 6MWT, and EF for predicting mortality is summarised in [Table/Fig-3]. NTproBNP and 6MWT showed excellent predictive accuracy with AUC values of 0.98 and 0.978, respectively (p<0.0001 for both). NLR and EF also demonstrated moderate discriminative ability, with p-values of 0.071 and 0.016, respectively [Table/Fig-4a-d].

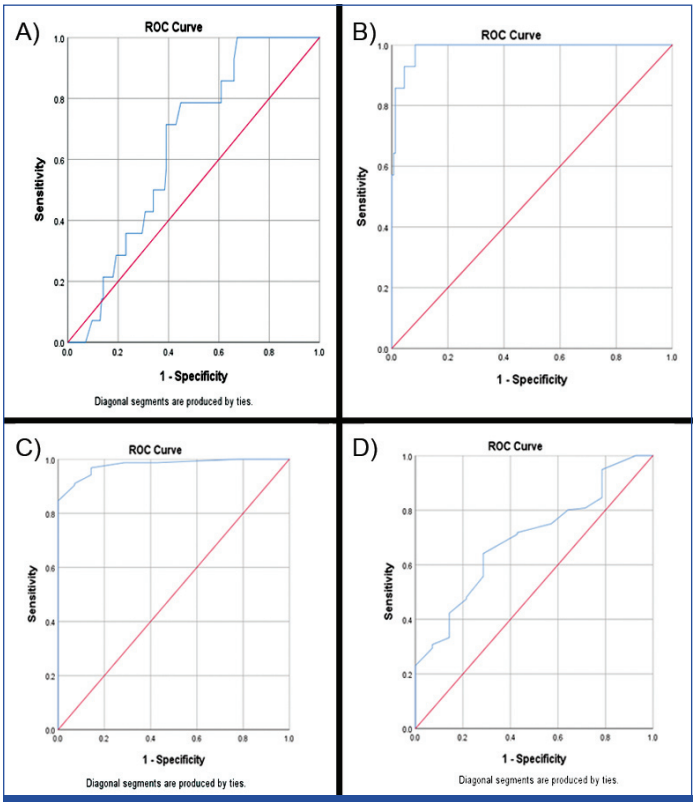
**Comparison of predictive markers for readmission in Heart Failure (HF):** At an NLR cut-off of 4.55, 15 patients with an NLR of more than 4.55 were readmitted, compared to 4 with lower values (p=0.015; [Table/Fig-5a]). NTproBNP >11,550 pg/mL was associated with 16 readmissions, while three were readmitted below this threshold (p<0.0001; [Table/Fig-5b]). A 6MWT distance of less than 270 meters was associated with 15 readmissions, whereas four readmissions occurred among those walking more than 270 meters (p<0.0001; [Table/Fig-5c]). EF <41% was associated with 13 readmissions, while six were observed in those with EF >41% (p=0.012; [Table/Fig-5d]). As shown in [Table/Fig-3], NTproBNP and 6MWT again emerged as strong predictors of readmission, with AUCs of 0.92 and 0.915, respectively (p<0.0001 for both). NLR and

| Parameters | Mortality | | | Readmission | | |
|---|---|---|---|---|---|---|
| | Yes | No | p-value | Yes | No | p-value |
| NLR | 6.70±2.53 | 5.67±3.93 | 0.098 | 7.88±4.93 | 5.49±3.61 | 0.038 |
| NTproBNP | 28114.29±6799.08 | 6219.12±5375.18 | <0.0001 | 21242.63±9553.81 | 6358.76±6248.51 | <0.0001 |
| 6 MWT | 170.00±49.92 | 368.78±69.14 | <0.0001 | 214.74±73.66 | 369.74±72.01 | <0.0001 |
| EF | 37.64±10.24 | 45.57±11.35 | 0.003 | 38.53±11.21 | 45.72±11.25 | 0.008 |

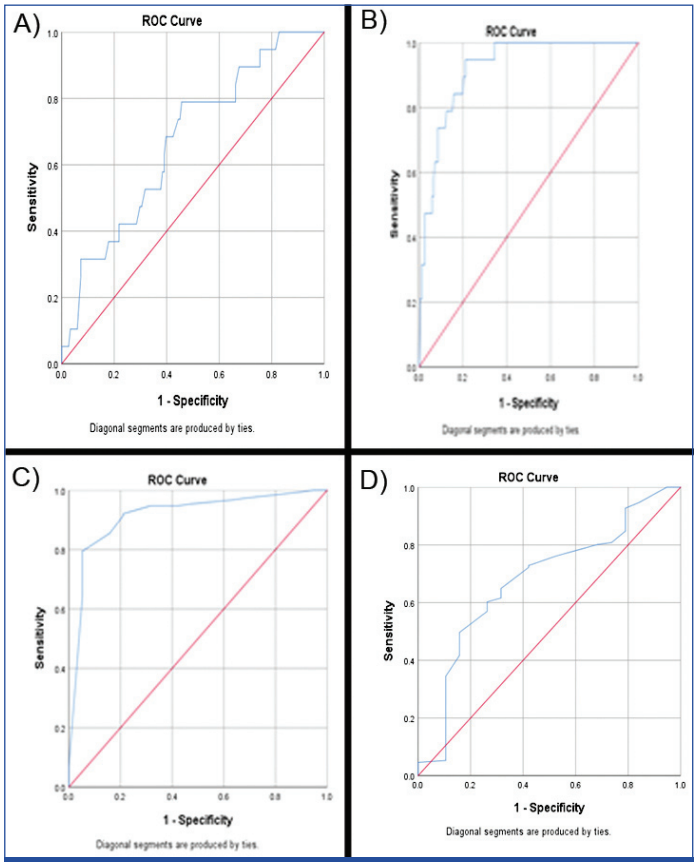
**[Table/Fig-2]:** Biomarker and functional parameter comparison in mortality and readmission groups.
SD: Standard deviation; NLR: Neutrophil-to-lymphocyte ratio; NTproBNP: N-terminal pro-B-type natriuretic peptide; 6 MWT: Six-minute walk test distance in meters; EF: Ejection fraction. Test of significance used: independent t-test.

| Parameters | Cut-off | AUC | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | p-value |
|---|---|---|---|---|---|---|---|
| NLR (Mortality) | 5.72 | 0.64 | 71.43 | 60.9 | 14.08 | 95.96 | 0.071 |
| NTproBNP (Mortality) | 16,250 pg/mL | 0.98 | 92.86 | 93.59 | 56.52 | 99.32 | <0.0001 |
| 6MWT (Mortality) | 255 m | 0.978 | 92.86 | 91.03 | 48.15 | 99.3 | <0.0001 |
| EF (Mortality) | 41% | 0.695 | 71.43 | 64.1 | 15.15 | 96.15 | 0.016 |
| NLR (Readmission) | 4.55 | 0.671 | 78.95 | 51.66 | 17.05 | 95.12 | 0.015 |
| NTproBNP (Readmission) | 11,550 pg/mL | 0.92 | 84.21 | 83.44 | 39.02 | 97.67 | <0.0001 |
| 6MWT (Readmission) | 270 m | 0.915 | 78.95 | 91.39 | 53.57 | 97.18 | <0.0001 |
| EF (Readmission) | 41% | 0.678 | 68.42 | 64.9 | 19.7 | 94.23 | 0.012 |

**[Table/Fig-3]:** Diagnostic performance of prognostic markers in predicting mortality and readmission in Heart Failure (HF).




**[Table/Fig-4]:** ROC curve analysis for mortality risk prediction.
ROC: Receiver operating characteristic; A-NLR: Neutrophil-to-lymphocyte ratio; B-NTproBNP: Nterminal pro-B-type natriuretic peptide; C-6MWT: Six-minute walk test; D-EF: Ejection fraction.




**[Table/Fig-5]:** ROC curve analysis for readmission prediction.
ROC: Receiver operating characteristic; A-NLR: Neutrophil-to-lymphocyte ratio; B-NTproBNP: N-terminal pro-B-type natriuretic peptide; C-6MWT: Six-minute walk test; D-EF: Ejection fraction.

EF had lower but significant predictive value, with p-values of 0.015 and 0.012, respectively [Table/Fig-5a-d].

**Association of demographics and readmission in mortality groups:** The mean age of patients who experienced mortality was 66.14±15.20 years, compared to 62.27±13.45 years in those who survived (p=0.309), showing no statistically significant difference.

Regarding sex distribution, 10 females (10.8%) and four males (5.2%) experienced mortality. The difference in mortality between males and females was not statistically significant (p=0.189). Readmission status was significantly associated with mortality. Among those who were not readmitted, five patients (3.3%) experienced mortality, while 146 (96.7%) survived. In contrast, among readmitted patients, 9 (47.4%) experienced mortality, whereas 10 (52.6%) survived. This association was highly significant (p<0.0001), indicating a strong relationship between readmission and mortality [Table/Fig-6].

## DISCUSSION

This study aimed to evaluate the predictive role of NTproBNP, NLR, and 6MWT in assessing mortality and readmission risk among HF patients. The primary outcome revealed that elevated NTproBNP levels were significantly associated with increased mortality and hospital readmission rates, elevated NLR levels were significantly associated with higher hospital readmission rates, and reduced 6MWT distances were associated with worse clinical outcomes. NTproBNP emerged as the strongest predictor, with an optimal cut-off value of 16,250 pg/mL, achieving a sensitivity of 92.86% and

| Parameters | | Mortality | | p-value |
|---|---|---|---|---|
| | | Yes | No | |
| Age | | 66.14±15.20 | 62.27±13.45 | 0.309 |
| Sex | Female | 10 (10.8%) | 83 (89.2%) | 0.189 |
| | Male | 4 (5.2%) | 73 (94.8%) | |
| Diabetes Mellitus (DM) | | 9 (8.18%) | 101 (91.82%) | 0.973 |
| Systemic Hypertension (S.HTN) | | 6 (7.14%) | 78 (92.86%) | 0.608 |
| Coronary Artery Disease (CAD) | | 1 (3.45%) | 28 (96.55%) | 0.473 |
| Chronic Kidney Disease (CKD) | | 1 (25%) | 3 (75%) | 0.228 |
| Readmission | No | 5 (3.3%) | 146 (96.7%) | <0.0001 |
| | Yes | 9 (47.4%) | 10 (52.6%) | |

**[Table/Fig-6]:** Comparison of age, gender and co-morbidities between mortality and non-mortality groups and correlation between readmission and mortality.

specificity of 93.59% for mortality prediction. Similarly, the 6MWT demonstrated an excellent discriminatory ability, with a cut-off of 255 meters yielding an AUC of 0.978 and a high NPV (99.30%) for predicting survival. NLR at a cut-off of 5.72 showed moderate predictive value (AUC=0.64) but was statistically insignificant (p=0.071). Readmission was significantly associated with mortality (p<0.0001), reinforcing its prognostic value in HF patients.

NTproBNP, a widely accepted biomarker for HF severity, showed a significant association with both mortality and readmission in the study. A cut-off value of 16,250 pg/mL was significantly associated with mortality, with an AUC of 0.98, sensitivity of 92.86%, specificity of 93.59%, and a high Negative Predictive Value (NPV) of 99.32%. These findings align with previous studies, where NTproBNP has been consistently identified as an independent predictor of poor outcomes in HF patients [7,14]. In a study conducted by Ališauskas A et al., NTproBNP levels ≥332.0 pmol/L were strongly associated with cardiovascular death in elderly HF patients, confirming its prognostic significance [19]. Furthermore, Godhiwala P et al., found that NTproBNP levels above 8990 pg/mL were predictive of mortality in advanced HF, with an AUC of 0.81, highlighting its role in risk stratification [15]. Likewise studies reported NTproBNP's role in risk stratification for Acute Decompensated HF (ADHF) [8,14,20].

Inflammation plays a critical role in HF pathophysiology, making NLR an emerging biomarker for disease progression and outcomes. This study identified an NLR cut-off of 5.72 for predicting mortality (AUC: 0.64, sensitivity: 71.43%, specificity: 60.90%) and a cut-off of 4.55 for readmission (AUC: 0.671, sensitivity: 78.95%). These findings align with previous studies demonstrating that elevated inflammatory markers, including NLR, were associated with higher HF readmission and mortality rates [9,16,21].

In addition, Frankenstein L et al., (2011) developed a risk stratification model incorporating NLR, NTproBNP, and 6MWT and found that inflammatory markers significantly impacted HF prognosis [22]. The association between elevated NLR and increased mortality was further validated in a meta-analysis by Simpson CE et al., confirming that inflammation contributes to HF progression [23].

The 6MWT is an established tool for assessing functional capacity and prognosis in HF patients. This study identified a cut-off distance of 255 meters for mortality prediction (AUC: 0.978, sensitivity: 92.86%, specificity: 91.03%) and 270 meters for readmission (AUC: 0.915, sensitivity: 78.95%). These findings are in agreement with a study by Myhre PL et al., (2024), which demonstrated that a 50-meter increase in 6MWT distance was associated with a 17% reduction in mortality risk [24]. Similarly, Fan Y et al., (2018) conducted a meta-analysis and confirmed that each 50-meter decrease in 6MWT increased the risk of mortality by 18% and the risk of readmission by 43%, highlighting the test's prognostic value [25]. The heart and soul study by Beatty A et al., (2012) also demonstrated that 6MWT was comparable to treadmill exercise testing in predicting cardiovascular events, reinforcing its clinical utility [26].

The combined use of NTproBNP, NLR, and 6MWT provided a more comprehensive risk assessment in this study. While NTproBNP exhibited the highest predictive accuracy, 6MWT offered a functional perspective, and NLR reflected underlying inflammation. The study by Ingle L et al., confirmed that 6MWT and NTproBNP independently predicted long-term mortality, reinforcing the need for a multifaceted approach [27]. Additionally, Palmieri V et al., (2022) identified NTproBNP as a superior predictor for HF decompensation, while 6MWT and echocardiographic parameters added prognostic value. These findings support the integration of biomarkers and functional assessments for optimal risk stratification in HF patients [28].

The present study provides crucial insights into the predictive value of NTproBNP, NLR, and 6MWT in assessing mortality and readmission risks in HF patients. The strength of this study lies in its prospective design and the evaluation of multiple biomarkers and functional parameters to enhance risk stratification. This study highlights the clinical utility of combining NTproBNP, NLR, and 6MWT for improved HF risk stratification, warranting further large-scale studies to validate these findings across diverse patient populations.

### Limitation(s)

The single-center design limits the generalisability of the findings. Other limitations are short follow-up, exclusion criteria, and lack of multivariable modeling or external validation. Confounding factors and absence of Quality-of-life data also restrict the comprehensiveness of its findings. Future multicenter studies with larger cohorts and long follow-up periods may help to address these limitations.

## CONCLUSION(S)

The present study confirms that elevated NTproBNP levels, along with reduced 6MWT distance, were significantly associated with mortality and readmission risks. Surprisingly, low-cost and easily performed 6MWT was highly sensitive and specific in the prediction of HF mortality and readmission. This was an important finding of this study. EF is still a key parameter; however, it proved to have moderate predictive value in this analysis. The findings highlight the importance of biomechanical stress, inflammation, and exercise capacity in HF progression. Integrating biomarkers with functional assessments enhances risk stratification, allowing for early identification of high-risk patients and targeted interventions. Further multicenter studies are required to confirm these findings and optimise treatment strategies, ensuring better patient outcomes and survival.

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