

The Value of NT-ProBNP in Predicting Cardiovascular Events in Patients Hospitalized for Decompensated Heart Failure

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Abstract

Background: Serum levels of natriuretic peptides at hospital admission and discharge, as well as their percentage reduction (delta NT-proBNP), have been associated with cardiovascular outcomes in decompensated heart failure.

Objective: To evaluate the prognostic accuracy of NT-proBNP parameters and determine the usefulness of in-hospital percentage reduction targets.

Methods: This was a retrospective cohort study including patients ≥ 18 years old admitted to a heart failure protocol between January 2022 and December 2023 at a tertiary hospital. The primary outcome was a composite of all-cause mortality and readmission for heart failure within 6 months.

Results: Two hundred and three patients were included (mean age 78.5 ± 14.4 years; 51.7% women). The outcome occurred in 67 (33.0%) within 6 months. The NT-proBNP at discharge showed the best accuracy (AUC 0.647; 95% CI 0.559–0.735; $p=0.002$). In multivariate analysis, only the NT-proBNP at discharge remained an independent predictor ($p<0.05$), outperforming continuous variation (delta). Regarding therapeutic goals, a reduction of $\geq 50\%$ was associated with a lower risk of events (HR 0.59; 95% CI 0.36–0.99; $p=0.048$), while a reduction of $\geq 30\%$ showed no association ($p=0.184$).

Conclusion: NT-proBNP at discharge was the best independent predictor of outcomes at 6 months. Additionally, achieving an in-hospital reduction of $\geq 50\%$ was associated with better prognosis, suggesting its usefulness as a therapeutic target.

Keywords: Heart Failure; Brain Natriuretic Peptide; Cardiovascular Diseases; Prognosis.

Introduction

Heart failure (HF) is a highly prevalent condition globally, affecting more than 55 million individuals.¹ Its incidence increases progressively with age, ranging from approximately 1% in the 55–64 age group to about 18% in individuals over 85 years of age.² Despite therapeutic advances, HF remains a leading cause of hospital admissions and significant morbidity and mortality.^{3,4} High hospital readmission rates have driven research into cardiac biomarkers capable of guiding in-hospital therapy, aiming to optimize disease compensation, reduce length of stay, and prevent readmissions.⁵

In this context, B-type natriuretic peptide (BNP) and the N-terminal fragment of its precursor proBNP (NT-proBNP)

stand out as cardiac biomarkers. Primarily produced by the left ventricle in response to hemodynamic stress, such as dilation and increased ventricular filling pressures,⁶ they are widely used in the management of HF.⁷ Previous studies in patients with chronic HF have demonstrated an association between reduced levels of natriuretic peptides and decreased rehospitalization rates.⁸ The levels of these biomarkers, measured at hospital admission and discharge, are consistently associated with prognosis and serve as strong predictors of mortality and readmission.^{9–11} Despite this, the literature still presents divergences regarding the ideal parameter: there remains uncertainty about which value (absolute or delta) should be prioritized for risk stratification and what percentage reduction target for hospital discharge should be sought to optimize the outcome. This uncertainty is aggravated by the fact that the role of using serial dosing to guide therapeutic titration is, in itself, not yet established.¹²

Given this knowledge gap, the present study aimed to evaluate and compare the accuracy of three parameters — NT-proBNP levels at hospital admission, at hospital discharge, or the percentage reduction between these two points — as predictors of major cardiovascular events in patients hospitalized for decompensated HF, with a 6-month follow-

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Manuscript received February 05, 2026, revised manuscript March 28, 2026,
accepted April 17, 2026
Editor responsible for the review: Humberto Villacorta

DOI: <https://doi.org/10.36660/abchf.20260008i>

Central Illustration: The Value of NT-ProBNP in Predicting Cardiovascular Events in Patients Hospitalized for Decompensated Heart Failure



ABC Heart Failure & Cardiomyopathy

NT-proBNP: The best predictor of outcomes at 6 months post-decompensated heart failure

At discharge



AUC: 0,647 (p=0,002)

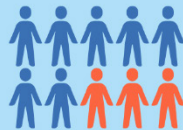
RR: 1,019 (P<0,001)

Delta (variance)



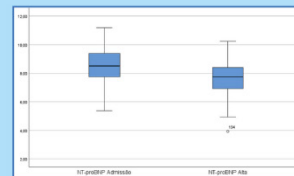
Reduction $\geq$ 30%
HR: 0,69 (p=0,184)

redução $\geq$ 50%
HR: 0,59 (p=0,048)



203 patients

(Average age $78,5 \pm 14,4$ anos;
51,7% Women; 107 with reduced
ejection fraction;)



Distribution of
NT-proBNP levels
at admission and
discharge

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Schematic summary of the prognostic value of NT-proBNP in decompensated heart failure. The panel highlights the serum level at hospital discharge as the most accurate independent marker for predicting death or readmission within 6 months. The illustration also details that achieving an in-hospital reduction of 50% or more is associated with a significantly lower risk of events, a benefit not observed for a 30% reduction.

up. As a secondary objective, it sought to determine whether achieving different thresholds of percentage reduction between admission and discharge is associated with a reduction in events at 6 months, thus evaluating the potential of these parameters as a therapeutic target.

Methods

This is a retrospective, single-center cohort study conducted at a private, tertiary hospital in the city of Salvador, Brazil, between January 1, 2022, and December 31, 2023.

Patients aged 18 years or older, hospitalized for decompensated HF, were included. Eligibility was based on the institution's HF protocol, which incorporates the Boston Criteria.¹³ In this context, a score lower than 4 points indicates ineligibility, a score between 8 and 12 confers direct insertion, and a score between 5 and 7 requires NT-proBNP measurement for confirmation of the condition. Individuals with NT-proBNP < 125 pg/mL, the cutoff point established by the institutional protocol, were excluded.

The exclusion criteria were: patients admitted under other institutional protocols (such as acute coronary syndrome and tachyarrhythmias); those without a record of NT-proBNP within 72 hours of admission or before hospital

discharge; and patients who requested discharge at their own request or were transferred to other units. Laboratory NT-proBNP values were measured using the ELFA technique (fluorescence immunoassay). The variation between NT-proBNP levels at admission and discharge was calculated. Patient follow-up was conducted by telephone contact, or, in case of readmission, data were collected directly by the healthcare professional.

Additionally, the patients' clinical profile was evaluated according to the New York Heart Association (NYHA) functional classification, and their hemodynamic profile in acute HF was assessed.¹⁴ Echocardiographic variables, including left ventricular ejection fraction, and supplementary demographic data were collected from electronic medical records.

The primary outcome was all-cause mortality and hospital readmission for HF, assessed at 6 months.

Statistical analysis

Categorical variables were presented as frequencies and percentages, and comparisons were performed using the Chi-square test. The normality of the distribution of continuous variables was verified using the Shapiro-Wilk test. Those with a normal distribution were described by means and standard deviations and compared using the

Student's t-test. Variables with non-parametric distributions were presented as medians and interquartile ranges and compared using the Mann-Whitney test. Diagnostic accuracy was assessed by the Area Under the Curve (AUC) of the Receiver Operating Characteristics (ROC) curve.

NT-proBNP values were logarithmically transformed into Cox models. The association between biologically plausible variables and the outcome was assessed by univariate Cox regression, selecting those with a p-value <0.05 for the multivariate model. The multivariate Cox model was adjusted for age, sex, hemodynamic profile, and left ventricular ejection fraction. Categorical NT-proBNP reduction target variables ($\geq 30\%$ and $\geq 50\%$) were evaluated in separate models to determine the association with the primary outcome. A p-value <0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistical Package, version 21.0 (IBM Corporation, Armonk, NY).

Ethical considerations

In accordance with resolution 466/2012 of the National Health Council, this study was approved by the local research ethics committee, with informed consent waived due to the retrospective design, and all procedures were performed in accordance with the Declaration of Helsinki.

Results

A total of 203 patients were included, with a mean age of $78.5 (\pm 14.4)$ years, predominantly female, with 105 (51.7%). Of the total, 107 (52.7%) had reduced ejection fraction, and 196 (96.6%) exhibited a type B hemodynamic profile at hospital admission. The main causes of decompensation were infection in 80 (39.4%) and inappropriate medication use in 24 (11.8%), with 56 (27.6%) having been hospitalized for HF in the previous 12 months. Baseline characteristics are detailed in Table 1. The median NT-proBNP levels were 4940 pg/mL (IQR: 2260–12000 pg/mL) at admission and 2360 pg/mL (IQR: 1010–4490 pg/mL) at discharge (Figure 1). The primary outcome occurred in 67 (33.0%) patients, with 17 (8.4%) deaths and 50 (24.6%) readmissions within 6 months.

In predicting the combined outcome at 6 months, the NT-proBNP at discharge had an area under the curve of 0.647 (CI: 0.559–0.735; $p=0.002$), compared to 0.556 (CI: 0.464–0.649; $p=0.235$) at admission and 0.603 (CI: 0.513–0.693; $p=0.300$) for the delta NT-proBNP (Figure 2). The point of best accuracy for NT-proBNP at discharge was 1,550 pg/mL, showing a sensitivity of 68.7% and a specificity of 49.4%. With a median follow-up time of 178 days (IQR: 73–357 days), Kaplan-Meier survival analysis (Figure 3) demonstrated that patients with levels at discharge above this threshold had a significantly higher rate of the composite outcome ($p=0.019$).

Discharge NT-proBNP showed an association with the combined outcome (HR 1.019; CI: 1.011–1.028; $p<0.001$), as did delta NT-proBNP (HR 1.006; CI: 1.001–1.011; $p=0.023$). Admission values, however, showed no association (HR 0.997; CI: 0.991–1.003; $p=0.282$). In a multivariate model adjusted for age, sex, hemodynamic

profile, and left ventricular ejection fraction, only discharge NT-proBNP maintained an independent association with the composite outcome at 6 months ($p<0.05$).

In the multivariate analysis to assess the reduction in NT-proBNP levels between hospital admission and discharge, a reduction greater than 50% was associated with a lower composite outcome at 6 months (HR 0.59; CI: 0.36–0.99; $p=0.048$). On the other hand, a reduction greater than 30% was not associated with a reduction in events (HR 0.69; CI: 0.40–1.18; $p=0.184$) (Figure 4).

Discussion

This study demonstrated that, in patients hospitalized for decompensated HF, NT-proBNP at discharge was the only independent predictor of mortality and hospital readmission at 6 months, presenting an AUC of 0.647 for predicting these events (Central Figure). This finding is a relevant contribution to the literature, reinforcing the prognostic value of biomarkers after clinical stabilization and offering a practical perspective for post-discharge risk stratification in a real-world setting.¹⁵

Our results, which indicate that high NT-proBNP is the best predictor of six-month outcomes, are consistent with previous evidence in the literature.^{10,16–18} Studies such as that of Logeart et al., in 2004, have already revealed pre-discharge BNP as a strong independent marker of death or readmission after decompensated HF.¹⁰ Similarly, data from the OPTIMIZE-HF registry in 2011, with a robust cohort of 7039 patients, corroborated that BNP levels at hospital discharge are better predictors of mortality and/or readmission within 1 year, especially in elderly patients with HF.¹⁶ This pathophysiological reasoning is understandable, given that natriuretic peptides primarily reflect left ventricular wall stress. Thus, measurement before hospital discharge tends to more accurately reflect the decrease in ventricular filling pressure and the degree of hemodynamic stability achieved after acute treatment, as well as the severity of underlying diastolic dysfunction, positioning it as an important predictor of early to medium-term outcome.

Regarding the other NT-proBNP parameters, we observed a divergence in relation to some data from the literature. Although previous studies, such as that of Fonarow and the ADHERE registry, have associated elevated BNP levels at admission with a higher risk of hospital mortality.¹⁹ In our cohort, the NT-proBNP level at admission did not maintain an association with the combined outcome at 6 months. The usefulness of the percentage (delta) reduction in natriuretic peptides is also a point of debate in the literature. While some observational studies suggest that patients with a significant reduction in natriuretic peptide levels have better outcomes,⁹ Randomized clinical trials have not demonstrated any benefit in therapy strategies guided by these variations, even leading to studies being discontinued due to futility.²⁰ However, in our analysis, although delta NT-proBNP showed an association with the outcome in the univariate assessment, this relationship did not hold in the adjusted multivariate model. This finding, however,

Table 1 – Demographic data

	Total (n=203)
Age (mean ± standard deviation), years	78.5 (± 14.4)
Sex, n (%)	
Feminine	105 (51.7%)
Comorbidities, n (%)	
Systemic Arterial Hypertension	173 (85.2%)
Atrial Fibrillation	95 (46.8%)
Coronary Artery Disease	87 (42.9%)
Diabetes Mellitus	74 (36.5%)
Chronic Kidney Disease	67 (33.0%)
Smoking	26 (12.8%)
Reason for Decompensation, n (%)	
Infection	80 (39.4%)
Inappropriate Use of Medication	24 (11.8%)
Acute Coronary Syndrome	16 (7.9%)
Dietary transgression	9 (4.4%)
Arrhythmia	21 (10.3%)
Length of hospital stay, in days	8 (5 – 14.5)
Previous Hospitalization (last 12 months), n (%)	56 (27.6%)

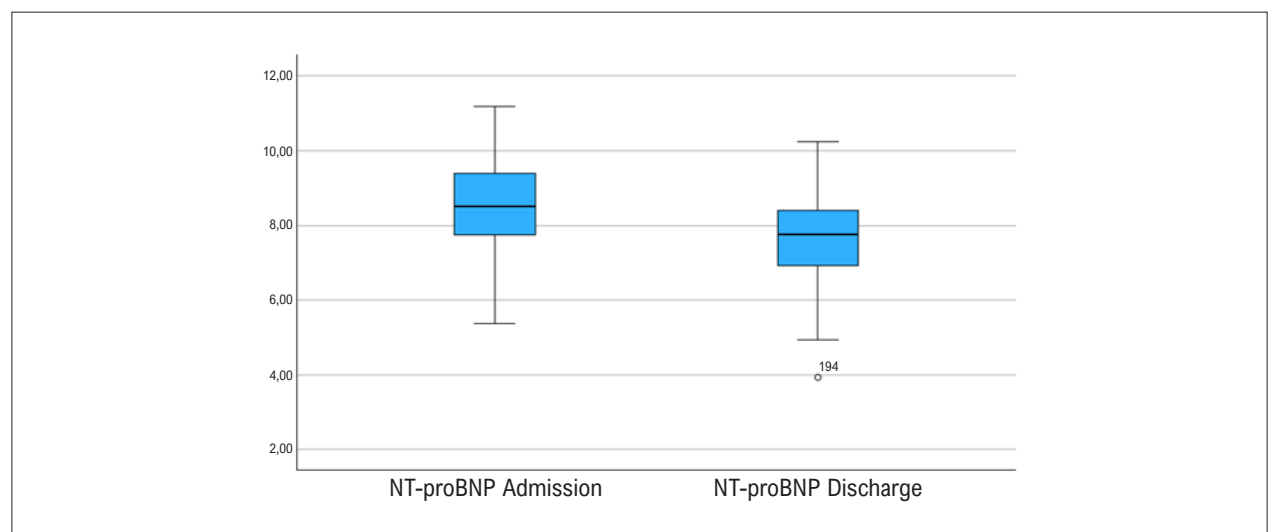


Figure 1 – Distribution of serum NT-proBNP levels at hospital admission and discharge. Absolute values were subjected to logarithmic transformation to attenuate the skewness of the distribution. The horizontal line inside the boxes represents the sample median, the upper and lower limits of the box indicate the interquartile range, and the rods show the minimum and maximum values of the sample.

should not negate the clinical utility of dynamic variation. Linear analysis likely masks the benefit of achieving more aggressive therapeutic targets, suggesting that the magnitude of the response, and not just any variation, is a crucial clinical determinant for risk stratification.

In this context, our analysis of therapeutic goals revealed an important distinction: while a 30% reduction was not associated with improved prognosis, achieving a reduction of $\geq 50\%$ conferred protection. The lack of benefit with the 30% cutoff aligns with the results of the

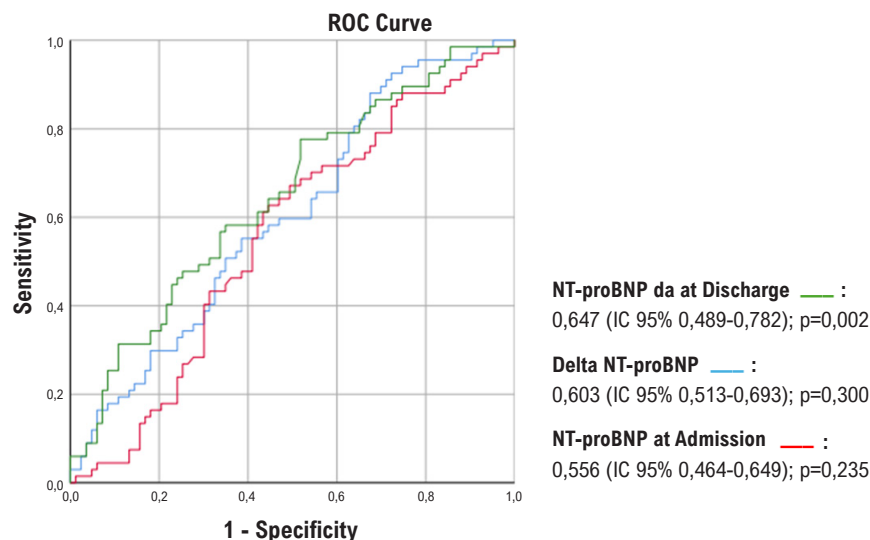


Figure 2 – Receiver Operating Characteristics Curve to assess the diagnostic accuracy of biomarker parameters. The graph compares the ability of NT-proBNP levels at admission, discharge, and their continuous variation to predict risk. The composite outcome includes all-cause mortality and hospital readmission for heart failure during the 6-month follow-up period.

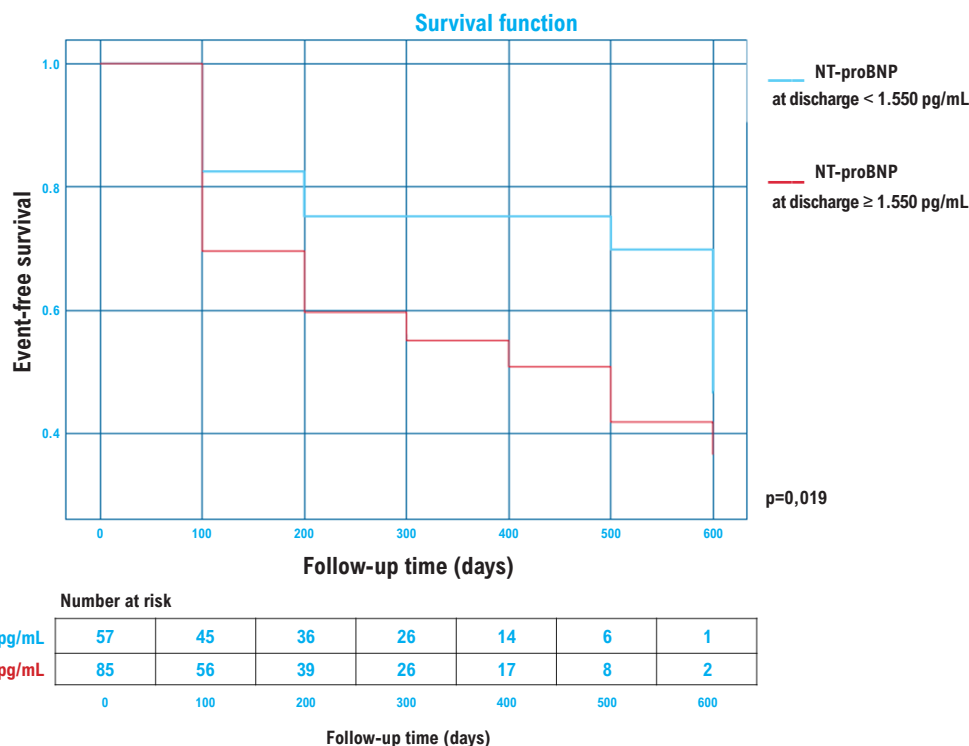


Figure 3 – Kaplan-Meier survival curve for the composite outcome at 6 months, stratified by NT-proBNP level at hospital discharge. The cohort was dichotomized based on the optimal predictive threshold of 1,550 pg/mL. The probability of event-free survival is presented for patients with NT-proBNP levels at discharge below 1,550 pg/mL (blue line) and for those with levels equal to or greater than 1,550 pg/mL (red line). The lower table quantifies the number of remaining individuals at risk at 100-day intervals.

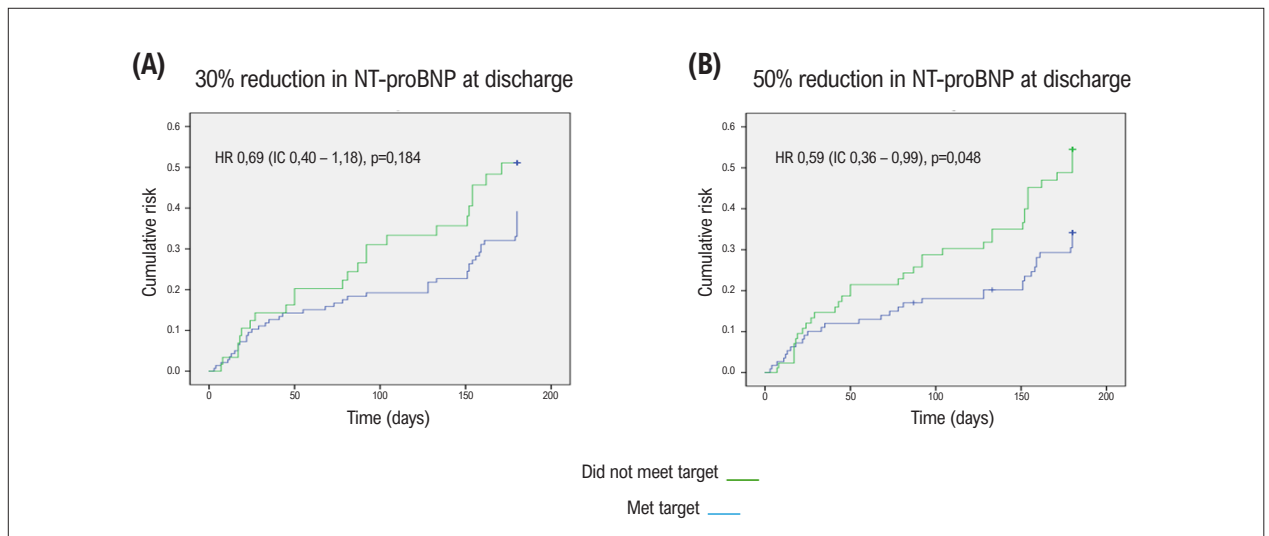


Figure 4 – Cumulative risk curves for the composite outcome at 6 months, evaluating the prognostic impact of achieving in-hospital therapeutic targets. Panel A compares the clinical evolution of patients who did or did not achieve the target of a 30% reduction in NT-proBNP levels between admission and discharge. Panel B illustrates the same survival analysis for the 50% reduction target. Risk was estimated using adjusted Cox regression models.

PRIMA II randomized clinical trial, which demonstrated that guiding therapy towards a reduction target of $>30\%$ failed to reduce mortality and readmissions at 6 months, suggesting that modest thresholds may be insufficient to define optimal stabilization.²¹ On the other hand, the benefit observed with the 50% reduction corroborates classic observational data and recent meta-analyses, such as those by Bayés-Genís et al. and Vergaro et al., who identified an average 50% drop in NT-proBNP levels in survivors, contrasting with a reduction of only 15% in patients who progressed to cardiovascular death.^{22,23} Thus, the 50% reduction target emerges as a practical bedside tool: it serves as a marker of ‘diuretic efficiency’, identifying the patient who has responded adequately to treatment and who, consequently, is on the right track to achieving safe absolute levels at hospital discharge.

The event rate observed in our cohort (33.0% composite outcome at 6 months) is consistent with the high morbidity and mortality and high readmission rates expected in populations of patients with decompensated HF. The median NT-proBNP values at admission (The levels of 4940 pg/mL at the peak (2360 pg/mL) observed in our study are also consistent with the levels typically found in patients with decompensated and clinically severe HF.^{9,24} Although the NT-proBNP score at discharge was the best predictor in our study, its Area Under the Curve (0.647) indicates a discriminatory capacity that, while statistically significant, can be considered modest. This finding suggests that NT-proBNP, by itself, is not an absolutely definitive indicator of prognosis. It is crucial that its interpretation be made in conjunction with other clinical factors and complementary data for a more accurate risk stratification.¹⁸

Several limitations inherent to the study design deserve highlighting. The retrospective nature and the fact that

it was conducted in a single specialized center require caution in extrapolating the findings. Additionally, the requirement for paired NT-proBNP measurements (admission and discharge) to calculate the percentage reduction introduces a selection bias, since it excludes patients who died during hospitalization or those who did not undergo the second measurement due to a clinical decision.

Conclusions

In conclusion, NT-proBNP at discharge proved to be the best predictor of all-cause mortality and hospital readmission for decompensated heart failure at 6 months, demonstrating that the absolute value of the biomarker after treatment is a crucial determinant of patient vulnerability. Additionally, the assessment of therapeutic goals confirmed that achieving a 50% reduction in NT-proBNP levels during hospitalization is associated with a lower event rate, while a 30% reduction showed no association. This finding suggests that, although NT-proBNP at discharge is the most robust independent predictor, a 50% reduction can be used as a practical and clinically relevant marker of in-hospital therapeutic efficacy, justifying the intensification of treatment in those patients who do not achieve this goal to reduce residual risk at discharge.

Author Contributions

Conception and design of the research: Siqueira RFC, Coutinho NV, Barros RMF, Melo RMV; Acquisition of data: Siqueira RFC, Barroso ND, Martins LPO, Gonçalves JPF, Almeida PV, Rocha DHS, Barros RMF; Analysis and interpretation of the data and Critical revision of the manuscript for intellectual content: Viana TT, Barroso

ND, Melo RMV; Statistical analysis: Viana TT, Melo RMV; Writing of the manuscript: Siqueira RFC, Coutinho NV.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the Hospital São Rafael under the protocol number

84674724.7.0000.0048. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013.

Use of Artificial Intelligence

During the preparation of this work, the author(s) used Gemini Pro for for writing optimization and language revision.. After using this tool/service, the author(s) reviewed and edited the content as needed and take full responsibility for the content of the published article.

Availability of Research Data

The data cannot be made publicly available because the underlying data consists of sensitive clinical information extracted from medical records. Unrestricted public sharing is prohibited due to legal issues of patient privacy and the ethical guidelines of the local Ethics and Research Committee.

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