Int Cardiovasc Res J.2019;**13**(4):127-132.icrj.87529

International Cardiovascular Research Journal

www.ircrj.com

Correlates and Prognostic Value of NT-proBNP in Post-Acute Coronary Syndrome Patients with Preserved Left Ventricular Ejection Fraction

Marta Fontes-Oliveira [1, *], Filipe Martins [2], Luis Gomes [2], Maria Trepa [1], Raquel Baggen-Santos [1], Ricardo Costa [1], Patricia Rodrigues [1], Andre Luz [1], Sofia Cabral [1], Mario Santos [1, 3, 4], Severo Torres [1]

[1] Cardiology Department, University Hospital Center of Porto, Porto, Portugal
[2] Abel Salazar Biomedical Sciences Institute, University of Porto, Porto, Portugal
[3] Physiology and Cardiothoracic Surgery Department, Faculty of Medicine of University of Porto, Porto, Portugal
[4] Pulmonary Vascular Disease Unit, University Hospital Center of Porto, Porto, Portugal

ARTICLE INFO

Article Type:
Research Article

Article History:
Received: 3 Jul 2019
Revised: 17 Sep 2019
Accepted: 23 Sep 2019

Keywords:
Prognosis
NT-proBNP
Myocardial Infarction

ABSTRACT

Background: Patients with Acute Coronary Syndrome (ACS) with preserved Left Ventricular Ejection Fraction (LVEF) have an incidence of adverse outcomes despite the previously presumed benign prognosis.
Objective: We hypothesized that NT-pro-BNP could help refine the risk stratification of these patients.
Methods: In this observational retrospective study, laboratory and clinical data were collected from 232 consecutive patients with ACS and preserved LVEF (> 50%) and no previous history of Heart Failure (HF) at hospital discharge. Associations between NT-proBNP and the composite outcome of HF hospitalization, HF diagnosis de novo, and all-cause mortality were assessed by univariate and multivariable Cox models. Statistical analyses were performed using Stata software, version 12.1 and a two-sided P-value < 0.05 was considered to be statistically significant.
Results: The NT-proBNP median was 408 [IQR 177-853] pg/mL. Patients with increased NT-proBNP were older and were more likely to be female (P = 0.013), be non-smoker (P = 0.039), have worse renal function (P < 0.001), and have lower hemoglobin concentration (P < 0.001). They had more ST-Elevation Myocardial Infarction (STEMI) and evolved with higher Killip classes (P < 0.001). Increased NT-proBNP levels were also associated with higher peak values of Creatinine Kinase (CK) and troponin (r = 0.36, P < 0.001 and r = 0.37, P < 0.001), higher left ventricular mass (P = 0.021), larger left atria (P = 0.013), and higher prevalence of regional LV hypocontractility (P = 0.012 to P = 0.090). During the 4.2 [2.1-5.4] years of follow-up, the composite outcome occurred in 19 patients. After adjusting for age, sex, and Killip class, NT-proBNP was not associated with the composite outcome (HR = 1.18; 95% CI: 0.78 - 1.78).
Conclusion: Post-ACS patients with preserved LVEF and increased levels of NT-proBNP were older, had more comorbidities, and presented with a more severe myocardial infarction. However, NT-proBNP levels measured during ACS hospitalization did not predict the clinical adverse outcomes.

1. Background

Advances in pharmacological and mechanical reperfusion of Acute Coronary Syndrome (ACS) over the past decades led to a significant improvement in survival and an increasing proportion of post-ACS patients with preserved Left Ventricular Ejection Fraction (LVEF) (1). These patients have better prognosis than those with reduced LVEF (2); however, their clinical course is not as benign as previously presumed (2, 3). Sudden Cardiac Deaths (SCD) of this subgroup represent the greatest absolute number of SCD in the post-ACS setting (4). Atrial Fibrillation (AF), an important prognostic marker in patients with cardiovascular disease, complicates the clinical course of up to 58% of patients with preserved LVEF during two years following ACS (5). Little data is available on the incidence of Heart Failure (HF) amongst this specific subset of post-ACS patients (6).

*Corresponding author: Marta Fontes-Oliveira, Rua Heróis de França 301-1ºesq, 4450-159 Matosinhos, Portugal. Cellphone: +351-915517042, Email: marta.fontes.oliveira@gmail.com.

NT-pro-B-type Natriuretic Peptide (NT-proBNP) is a widely used validated prognostic biomarker in cardiovascular disease. It is associated with incident HF in the general population (7) and predicts worse prognosis in patients with HF with preserved and reduced LVEF (8). Recently, some studies suggested that the measurement of NT-proBNP during ACS hospitalization could improve risk stratification (9-11). Nonetheless, scarce data is available about its prognostic utility in post-ACS patients with preserved LVEF.

2. Objectives

The present study aims to examine the clinical correlates of plasma NT-proBNP levels and its prognostic significance in post-ACS patients with preserved LVEF at hospital discharge.

3. Patients and Methods

This observational retrospective study was conducted on 232 consecutive patients who completed a cardiac rehabilitation program after ACS in Hospital Santo António, Centro Hospitalar Universitário do Porto, Porto, Portugal between January 2010 and December 2012. The patients with LVEF ≥ 50% at the time of discharge who had plasma levels of NT-proBNP measured during index hospitalization were analyzed. The patients with previous diagnosis of HF were excluded from the study. Clinical, laboratory, and echocardiographic data were collected by chart review. This study conformed to the principles outlined in the Declaration of Helsinki and was approved by the institution's Ethics Committee (N/REF.ª 2016.236/199-DEFI/188-CES).

Supine transthoracic echocardiography was performed for all patients prior to discharge. LVEF was calculated using either the biplane Simpson method or eyeballing. The patients with a reported LVEF of lower than 50% were excluded from the study. Dimensions and volumes of cardiac chambers and left ventricular mass were measured according to the current international recommendations (12). Moreover, laboratory data were collected via blood analysis measurement during hospitalization. NT-proBNP was measured using the Roche® NT-proBNP assay. Anemia was defined as hemoglobin less than 12 g/dL for females and less than 13 g/dL for males. Besides, Chronic Kidney Disease (CKD) was defined as an estimated Glomerular Filtration Rate (eGFR) < 60 mL/min/1.73 m2 using EPI-CKD equation (13). Furthermore, incident outcome events were defined as the first occurrence of HF hospitalization, ACS, or all-cause mortality. All events were collected by chart review.

3.1. Statistical Analysis

Continuous variables have been expressed as mean ± Standard Deviation (SD) for normally distributed data and median [25th and 75th percentiles] for non-normally distributed data. Categorical variables have also been expressed as number and proportion [n (%)]. Comparisons of the study groups were performed using two-sided unpaired or paired t-tests for normally distributed data and Wilcoxon rank sums test for non-normally distributed data. Fisher's exact test was also applied to compare the proportions. Indeed, one-way ANOVA with Bonferroni correction was used to perform multiple group comparisons. Correlations between hemodynamic and metabolic variables were determined using Pearson's and Spearman's correlation for normally and non-normally distributed data, respectively. Moreover, univariate and multivariate Cox proportional hazards regression models were employed to assess the unadjusted and adjusted associations between NT-proBNP and the composite outcome. The proportional hazards assumption was assessed by visual inspection of Schoenfeld residuals. All statistical analyses were performed using Stata software, version 12.1 (Stata Corp LP, College Station, TX, USA) and a two-sided P-value < 0.05 was considered to be statistically significant.

4. Results

4.1. Studied Population

Clinical and demographic characteristics of the studied population have been summarized in Table 1. Accordingly, most patients were male (78%) with the mean age of 59 ± 11 years. Dyslipidemia (74%), hypertension (60%), present or past smoking (62%), and diabetes (29%) were the most common cardiovascular risk factors. In addition, 15% of the patients had previously been diagnosed with Coronary Artery Disease (CAD). Moreover, clinical presentation with an ST-Segment Elevation Myocardial Infarction (STEMI) was found in 48% of the patients. Three-vessel CAD was also seen in one-third of the patients. Left anterior descendent was the culprit vessel in 41% of the patients and Percutaneous Coronary Intervention (PCI) was performed in 88% of them. The median and interquartile range of the peak values of troponin and Creatinine Kinase (CK) were 1.25 [0.24 - 2.86] ng/mL and 490 [164 - 1494] U/L, respectively. The echocardiographic characteristics of the patients have been displayed in Table 2.

During the index hospitalization, almost 8% of the patients showed the signs and symptoms of HF (7% in Killip class II and 1% in class III). The median and interquartile range of NT-proBNP was 408 [IQR = 177 - 853] pg/mL for the studied population and 554 [IQR = 175 - 1534] pg/mL for the patients with Killip class II or above.

At the time of discharge, more than 96% of the patients were medicated with dual antiplatelet therapy and statins. The medications used at discharge have been displayed in Table 1.

4.2. Clinical and Echocardiographic Correlates of NT-pro-BNP

Patients with higher NT-proBNP levels were older and were more likely to be female, be a non-smoker, and have a STEMI. Patients in the upper quartiles of NT-proBNP also had a lower prevalence of Killip class I. They also had a higher incidence of impaired renal function and a higher prevalence of anemia (Table 1). CK and troponin T (TnT) levels were moderately correlated to NT-proBNP level ($r = 0.36$, $P < 0.001$ and $r = 0.37$, $P < 0.001$) (Figure 1).

Regarding echocardiographic data (Table 2), patients with higher NT-proBNP levels had higher left ventricle mass and larger left atria. Increased prevalence of regional LV hypocontractility was also associated with higher NT-proBNP levels. Higher pulmonary arterial systolic

Table 1. Clinical Characteristics of the Studied Patients

Characteristics	Total (n = 232)	NT-pro-BNP Q1 (n = 58)	NT-pro-BNP Q2 (n = 58)	NT-pro-BNP Q3 (n = 58)	NT-pro-BNP Q4 (n = 58)	P-value
Age, y	58.83 ± 10.94	55.90 ± 9.39	56.62 ± 9.87	59.64 ± 11.89	63.16 ± 11.15	< 0.001
Male, n (%)	181 (78.0%)	50 (86.2%)	46 (79.3%)	47 (81.0%)	38 (65.5%)	0.013
BMI, kg/m²	26.61 ± 3.94	26.96 ± 4.02	26.58 ± 3.85	26.61 ± 4.11	26.27 ± 3.85	0.38
Hypertension, n (%)	139 (60.2%)	31 (53.4%)	37 (63.8%)	31 (54.4%)	40 (69.0%)	0.20
Smoking status						
Never smoked, n (%)	85 (36.6%)	15 (25.9%)	25 (43.1%)	21 (36.2%)	24 (41.4%)	0.039
Past smoker, n (%)	59 (25.4%)	21 (36.2%)	15 (25.9%)	12 (20.7%)	11 (19.0%)	
Current smoker, n (%)	88 (37.9%)	22 (37.9%)	18 (31.0%)	25 (43.1%)	23 (39.7%)	
Diabetes, n (%)	67 (29.1%)	17 (29.3%)	17 (29.8%)	15 (26.3%)	18 (31.0%)	0.95
Dyslipidemia, n (%)	171 (74.0%)	42 (72.4%)	44 (77.2%)	35 (60.3%)	50 (86.2%)	0.34
History of atrial fibrillation, n (%)	3 (1.3%)	0 (0.0%)	0 (0.0%)	2 (3.4%)	1 (1.7%)	0.20
Stroke, n (%)	6 (2.6%)	2 (3.4%)	1 (1.7%)	1 (1.7%)	2 (3.4%)	1.00
CAD, n (%)	33 (14.2%)	9 (15.5%)	7 (12.1%)	6 (10.3%)	11 (19.0%)	0.68
COPD, n (%)	5 (2.2%)	8 (3.9%)	8 (3.9%)	8 (3.9%)	8 (3.9%)	0.85
OSA, n (%)	3 (1.3%)	2 (3.4%)	1 (1.7%)	0 (0.0%)	0 (0.0%)	0.07
ACS hospitalization features						
STEMI, n (%)	111 (47.8%)	16 (27.6%)	27 (46.6%)	31 (53.4%)	37 (63.8%)	< 0.001
Killip class						
II, n (%)	14 (6.9%)	1 (2.1%)	1 (1.9%)	5 (10.0%)	7 (13.7%)	< 0.001
III, n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (5.9%)	
IV, n (%)	2 (1.0%)	1 (2.1%)	0 (0.0%)	0 (0.0%)	1 (2.0%)	
Number of coronaries with significant disease						
One-vessel, n (%)	80 (34.8%)	22 (38.6%)	17 (29.8%)	25 (43.1%)	16 (27.6%)	0.50
Two-vessel, n (%)	73 (31.7%)	16 (28.1%)	19 (33.3%)	17 (29.3%)	21 (36.2%)	
Three-vessel, n (%)	76 (33.0%)	18 (31.6%)	21 (36.8%)	16 (27.6%)	21 (36.2%)	
Culprit coronary						
LAD, n (%)	93 (41.3%)	25 (44.6%)	25 (44.6%)	20 (35.1%)	23 (41.1%)	0.49
RCA, n (%)	81 (36.0%)	21 (37.5%)	15 (26.8%)	23 (40.4%)	22 (39.3%)	
LCx, n (%)	50 (22.2%)	10 (17.9%)	16 (28.6%)	13 (22.8%)	11 (19.6%)	
PCI, n (%)	204 (87.9%)	46 (79.3%)	50 (86.2%)	55 (94.8%)	53 (91.4%)	0.10
Atrial fibrillation, n (%)	7 (3.0%)	1 (1.7%)	2 (3.4%)	1 (1.7%)	3 (5.3%)	0.38
Blood analysis at discharge						
GFR, mL/min/1.73 m²	85.81 ± 18.18	92.86 ± 13.18	88.60 ± 17.26	84.83 ± 15.71	76.94 ± 21.93	< 0.001
GFR < 60 mL/min/1.73 m², n (%)	23 (9.9%)	1 (1.7%)	4 (6.9%)	6 (10.3%)	12 (20.7%)	< 0.001
Hb, g/dL	13.50 ± 1.46	13.90 ± 1.19	13.78 ± 1.46	13.62 ± 1.26	12.71 ± 1.61	< 0.001
Anemia, n (%)	58 (25%)	8 (13.8%)	12 (20.7%)	15 (25.9%)	23 (39.7%)	0.001
Peak CK, U/L	1028.52 ± 1256.46	193 [104 - 419]	340 [136 - 1290]	870 [334 - 1835]	1059 [305 - 2206]	< 0.001
Peak TnT, ng/mL	2.82 ± 4.73	0.5 [0.0 - 1.7]	0.7 [0.3 - 2.5]	2.0 [0.5 - 5.2]	4.5 [2.9 - 9.7]	< 0.001
NT-ProBNP, ng/mL	827.13 [129 - 632]	88 [47 - 126]	297 [237 - 348]	562 [489 - 700]	1543 [1071 - 2129]	< 0.001
Medication at discharge						
Aspirin, n (%)	228 (99.1%)	55 (96.5%)	58 (100.0%)	58 (100.0%)	57 (100.0%)	0.06
Clopidogrel/ticagrelor, n (%)	226 (98.3%)	53 (93.0%)	58 (100.0%)	58 (100.0%)	57 (100.0%)	0.006
Statin, n (%)	222 (96.5%)	54 (94.7%)	56 (96.6%)	58 (100.0%)	54 (94.7%)	0.75
B-blocker, n (%)	213 (92.6%)	52 (91.2%)	58 (100.0%)	51 (87.9%)	52 (91.2%)	0.43
ACEI/ARB, n (%)	164 (71.9%)	41 (73.2%)	42 (73.7%)	40 (69.0%)	41 (71.9%)	0.75
Diuretic, n (%)	16 (6.9%)	0 (0.0%)	1 (1.7%)	3 (5.2%)	12 (21.1%)	< 0.001

Abbreviations: BMI, body mass index; HF, heart failure; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; OSA, obstructive sleep apnea; ACS, acute coronary syndrome; STEMI, ST-segment elevation myocardial infarction; LAD, left anterior descending artery; RCA, right coronary artery; LCX, left circumflex artery; PCI, percutaneous coronary intervention; GFR, glomerular filtration rate; Hb, hemoglobin; CK, creatinine kinase; TnT, troponin T; Pro-BNP, Pro-B-type natriuretic peptide; ACEI/ARB, angiotensin-converting-enzyme inhibitor/angiotensin II receptor blocker; MRA, mineralocorticoid receptor antagonist.

pressure was also associated with higher NT-proBNP levels. According to the results of the multivariate linear regression analysis, age, STEMI, Killip class, and troponin level were the only independent predictors of NT-proBNP plasma level (Table 3).

4.3. Prognostic Value of NT-proBNP

Over a follow-up of 4.2 [2.1 - 5.4] years, composite outcome occurred in 19 (8%) patients (nine deaths, five HF hospitalizations, and five ACSs). The overall incidence rate was 2.2 events per 100 000 person-years. The event rate for patients across NT-proBNP quartiles were 1.7 [0.6; 4.5], 2.1 [0.9; 5.1], 2.5 [1.1; 6.1], and 2.3 [0.9; 5.4] (Figure 2). NT-proBNP level was not associated with the composite outcome in univariate [HR = 1.10; 95% CI: 0.78 - 1.75] and multivariate [HR = 1.18; 95% CI: 0.78 - 1.78] Cox

Table 2. Echocardiographic Features of the Studied Patients

Characteristics	NT-pro-BNP Q1 (n = 58)	NT-pro-BNP Q2 (n = 58)	NT-pro-BNP Q3 (n = 58)	NT-pro-BNP Q4 (n = 58)	P-value
IVS, mm	12 ± 2	12 ± 2	12 ± 2	12 ± 2	0.26
PWT, mm	11 ± 1	11 ± 2	11 ± 2	11 ± 2	0.32
LV mass indexed, g/m²	101 ± 16	99 ± 20	99 ± 24	111 ± 28	0.021
LVEDD, mm	46 ± 4	47 ± 5	45 ± 6	47 ± 5	0.88
LVESD, mm	29 ± 5	30 ± 6	30 ± 5	31 ± 6	0.32
LA diameter, mm	39 ± 4	38 ± 4	38 ± 4	40 ± 6	0.07
LA area, cm²	20 ± 3	20 ± 4	20 ± 4	21 ± 5	0.013
Segmental motion abnormalities					
Anterior, n (%)	12 (20.7%)	16 (28.1%)	17 (30.4%)	20 (35.1%)	0.09
Posterior, n (%)	18 (31.0%)	25 (43.9%)	38 (52.6%)	30 (52.6%)	0.012
Inferior, n (%)	26 (44.8%)	31 (54.4%)	38 (67.9%)	36 (63.2%)	0.019
Moderate/severe MR, n (%)	1 (1.7%)	2 (3.5%)	2 (3.5%)	3 (5.3%)	0.33
PSAP	25 ± 5	25 ± 4	26 ± 5	28 ± 7	0.012
RV systolic dysfunction, n (%)	1 (1.7%)	1 (1.8%)	2 (3.7%)	2 (3.6%)	0.44

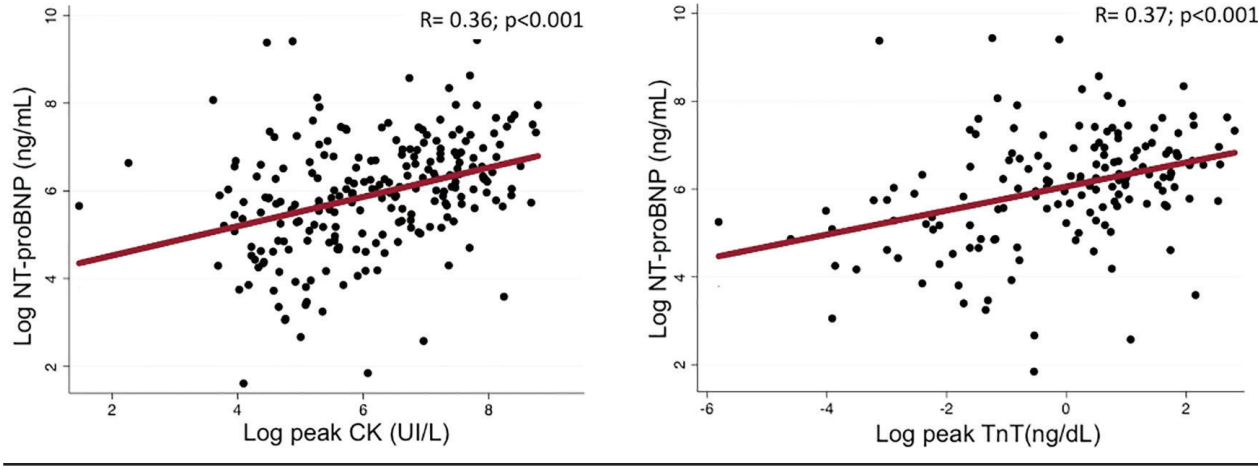
Abbreviations: IVS, interventricular septum; PWT, posterior wall thickness; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; LA, left auricle; MR, mitral regurgitation; LV, left ventricle; LVH, left ventricular hypertrophy.

Table 3. Multivariate Linear Analysis of NT-pro-BNP Correlates

	B-coefficient (95% CI)	P-value
Age	0.036 (0.01 - 0.06)	0.004
Male sex	0.13 (-0.68 - 0.42)	0.641
Smoking status	0.41 (-1.15 - 0.97)	0.147
Diabetes	2.43 (1.14 - 5.17)	0.021
STEMI	0.55 (0.08 - 1.02)	0.022
Killip class	2.20 (1.24 - 3.91)	0.007
Hemoglobin	- 0.10 (-0.25 - 0.05)	0.181
GFR	- 0.01 (-0.02 - 0.01)	0.263
Peak TnT	0.13 (0.05 - 0.21)	0.002
LA diameter	0.05 (-0.01 - 0.10)	0.080

Abbreviations: STEMI, ST-elevation myocardial infarction; GFR, glomerular filtration rate; TnT, troponin T; LA, left atrial.
* log-NTproBNP

Figure 1. The Correlation between NT-proBNP and Peak Values of CK and Troponin T



NT-proBNP, NT-pro-B-type natriuretic peptide; CK, creatinine kinase; TnT, troponin T.

proportional hazards regression models after adjusting for age, sex, and Killip class (Table 4). Peak TnT level during hospitalization did not predict the composite outcome, too [HR = 0.99; 95% CI: 0.75 - 1.31].

5. Discussion

This study on post-ACS patients with preserved LVEF had the following major findings. First, NT-proBNP levels were correlated to the patients' baseline characteristics, such as age, sex, and renal function, as well as to the severity of the indexed ACS hospitalization (Killip class, myocardial infarction size, and regional LV contractility). Second, NT-proBNP levels measured during ACS hospitalization did not predict the clinical adverse outcomes.

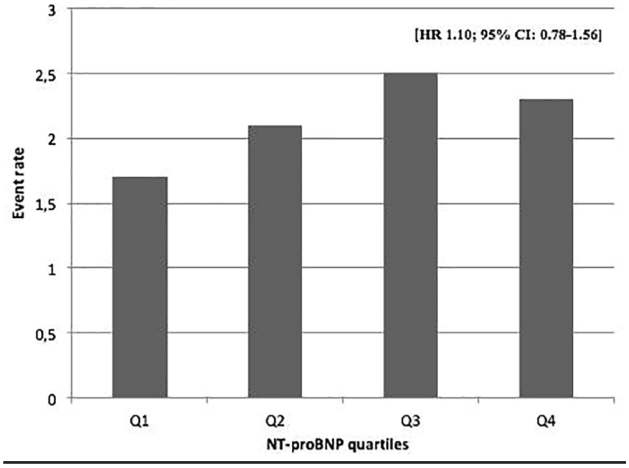
NT-proBNP is a peptide primarily released from atrial and ventricular transmural distention (14, 15). High NT-

Table 4. Cox Proportional Hazards Regression Model

	Univariate Hazard Ratio (95% CI)	Multivariate Hazard Ratio (95% CI) **
NT-pro-BNP Q1* (n = 58)	-	-
NT-pro-BNP Q2* (n = 58)	1.24 (0.33 - 4.62)	1.19 (0.32 - 4.44)
NT-pro-BNP Q3* (n = 58)	1.50 (0.40 - 5.60)	1.47 (0.39 - 5.52)
NT-pro-BNP Q4* (n = 58)	1.34 (0.36 - 5.03)	1.27 (0.32 - 4.93)

Abbreviations: NT-proBNP, NT-pro-B-type natriuretic peptide.
* log-NTproBNP; ** Adjusting for age, sex, and Killip class

Figure 2. Event Rate per 100 000 Person-Years for Patients across NT-proBNP Quartiles. For Each Quartile, N = 58.



NT-proBNP, NT-pro-B-type natriuretic peptide

proBNP levels reflect elevated ventricular filling pressures, an important indicator of cardiac dysfunction. Its plasma concentrations tend to be higher in elderly individuals (16) and patients with chronic kidney disease (17) and lower in obese patients (18). In the present study, higher NT-proBNP levels were detected in the patients who were older and anemic and had lower eGFR, which might signal the reduced cardiac reserve to handle with myocardial suffering associated with this clinical profile. The results revealed no significant difference between the patients with high and low NT-proBNP levels concerning Body Mass Index (BMI). However, most of the patients' BMIs were < 35 kg/m2. Similar to the previous studies (19, 20), female patients had higher NT-pro-BNP levels.

Acute myocardial ischemia can elevate NT-proBNP values (21-23). Furthermore, decreased blood flow and the consequent ischemia impair diastolic and systolic function with a consequent elevation in ventricular filling pressures (22). This mechanistic link was supported by the observed significant correlation between the surrogates of the myocardial ischemic burden (peak values of TnT and CK) and NT-proBNP levels. In addition, the higher prevalence of STEMI and regional LV contractility impairment in patients with higher NT-proBNP levels supported this peptide as a marker of the severity of myocardial injury. The presumed higher left ventricular filling pressures was also corroborated by the phenotypic cardiac characterization provided by echocardiography. Patients with higher levels of NT-proBNP presented with higher LV mass, larger left atria, and higher Pulmonary Artery Systolic Pressure (PASP), all indicative of chronic higher LV filling pressures.

One of the main attributes of NT-proBNP explored in clinical practice is the prognostic value it shows in several clinical scenarios. In HF with reduced LVEF, NT-proBNP was demonstrated to be an independent and powerful prognostic marker (24, 25). In HF with preserved LVEF also, NT-proBNP was shown to be a robust prognostic marker in both observational and interventional trials (26). In the ACS setting, Richards M. et al. demonstrated a 14% mortality risk and 8% HF hospitalization rate in patients with preserved LVEF and elevated NT-proBNP levels during the first three years after acute myocardial infarction (11). In stable CAD, NT-proBNP was the most important variable in a multi-marker panel to predict cardiovascular death (27). In contrast to our working hypothesis, NT-proBNP did not show any prognostic value in the studied population. This might be explained by the fact that firstly, this biomarker might have little or no predictive value in this specific subset of post-AMI patients. This was not corroborated by the previous studies, which indicated the prognostic value of this biomarker across CAD spectrum from ACS to stable CAD (27-30). Secondly, patients with higher NT-proBNP levels might have been treated more aggressively and, consequently, developed fewer composite outcomes than expected. This hypothesis was not supported by the pharmacological treatment at hospital discharge that was similar across patients with different levels of NT-proBNP, except for diuretics, which did not modify the prognosis. Non-pharmacological treatment, such as cardiac rehabilitation, is not a potential confounder as all patients completed the program. Thirdly, the low event rate seen in this cohort and the low sample size limited the statistical power to detect the predictive value provided by the NT-proBNP level.

The current study had significant limitations that should be considered. First, the study had a retrospective design with a relatively small cohort size from a single center, which limited the statistical power and the generalizability of the findings. Second, the most fragile patients with more comorbidities were less likely to complete the cardiac rehabilitation program. Therefore, using this approach might have increased the risk of selection bias. Third, LVEF was calculated using either biplane Simpson or eyeballing method. Finally, NT-proBNP was not ordered by protocol, but at the assistant physician's discretion, which could limit the straightforward extrapolation of the findings to all post-ACS patients.

5.1. Conclusion

The study results indicated that the patients' baseline characteristics and the severity of ACS were the determinants of NT-proBNP levels in post-ACS patients with preserved LVEF referred to a cardiac rehabilitation

program. The results revealed no associations between NT-proBNP plasma concentration measured during ACS hospitalization and the clinical outcomes. Further studies are needed to determine how to improve risk stratification in this specific and very prevalent group of post-ACS patients.

Acknowledgements

There is no acknowledgements.

Authors' Contribution

Conception and Design of the study: M. S.; Data collection: M. F. O., F. M., L. G., M. T., R. B. S., R. C.; Statistical analysis: M. S., M. O.; Manuscript writing: M. O., F. M., L. G.; Interpretation of the data, manuscript revision: A. L., S. C., P. R.

Funding/Support

There is no funding/ support.

Financial Disclosure

The authors have no financial interests related to the material in the manuscript.

References

1. Schmidt M, Jacobsen JB, Lash TL, Bøtker HE, Sørensen HT. 25 year trends in first time hospitalisation for acute myocardial infarction, subsequent short and long term mortality, and the prognostic impact of sex and comorbidity: a Danish nationwide cohort study. *Bmj*. 2012;**344**:e356.
2. Ersboll M, Valeur N, Mogensen UM, Andersen MJ, Moller JE, Velazquez EJ*, et al.* Prediction of all-cause mortality and heart failure admissions from global left ventricular longitudinal strain in patients with acute myocardial infarction and preserved left ventricular ejection fraction. *J Am Coll Cardiol*. 2013;**61**(23):2365-73.
3. Perelshtein Brezinov O, Klempfner R, Zekry SB, Goldenberg I, Kuperstein R. Prognostic value of ejection fraction in patients admitted with acute coronary syndrome: A real world study. *Medicine (Baltimore)*. 2017;**96**(9):e6226.
4. Makikallio TH, Barthel P, Schneider R, Bauer A, Tapanainen JM, Tulppo MP*, et al.* Prediction of sudden cardiac death after acute myocardial infarction: role of Holter monitoring in the modern treatment era. *Eur Heart J*. 2005;**26**(8):762-9.
5. Romanov A, Martinek M, Purerfellner H, Chen S, De Melis M, Grazhdankin I*, et al.* Incidence of atrial fibrillation detected by continuous rhythm monitoring after acute myocardial infarction in patients with preserved left ventricular ejection fraction: results of the ARREST study. *Europace*. 2018;**20**(2):263-70.
6. Gerber Y, Weston SA, Berardi C, McNallan SM, Jiang R, Redfield MM*, et al.* Contemporary trends in heart failure with reduced and preserved ejection fraction after myocardial infarction: a community study. *Am J Epidemiol*. 2013;**178**(8):1272-80.
7. Taylor CJ, Roalfe AK, Iles R, Hobbs FD. The potential role of NT-proBNP in screening for and predicting prognosis in heart failure: a survival analysis. *BMJ Open*. 2014;**4**(4):e004675.
8. van Veldhuisen DJ, Linssen GC, Jaarsma T, van Gilst WH, Hoes AW, Tijssen JG*, et al.* B-type natriuretic peptide and prognosis in heart failure patients with preserved and reduced ejection fraction. *J Am Coll Cardiol*. 2013;**61**(14):1498-506.
9. Galvani M, Ottani F, Oltrona L, Ardissino D, Gensini GF, Maggioni AP*, et al.* N-terminal pro-brain natriuretic peptide on admission has prognostic value across the whole spectrum of acute coronary syndromes. *Circulation*. 2004;**110**(2):128-34.
10. Pesaro AE, Katz M, Caixeta A, Makdisse MR, Correia AG, Pereira C*, et al.* Prognostic value of serial brain natriuretic Peptide measurements in patients with acute myocardial infarction. *Cardiology*. 2015;**131**(2):116-21.t
11. Richards AM, Nicholls MG, Espiner EA, Lainchbury JG, Troughton RW, Elliott J*, et al.* B-type natriuretic peptides and ejection fraction for prognosis after myocardial infarction. *Circulation*. 2003;**107**(22):2786-92.
12. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L*, et al.* Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2015;**16**(3):233-70.
13. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI*, et al.* A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;**150**(9):604-12.
14. Hall C. Essential biochemistry and physiology of (NT-pro)BNP. *Eur J Heart Fail*. 2004;**6**(3):257-60.
15. Pemberton CJ, Johnson ML, Yandle TG, Espiner EA. Deconvolution analysis of cardiac natriuretic peptides during acute volume overload. *Hypertension*. 2000;**36**(3):355-9.
16. Januzzi JL, Jr., Camargo CA, Anwaruddin S, Baggish AL, Chen AA, Krauser DG*, et al.* The N-terminal Pro-BNP investigation of dyspnea in the emergency department (PRIDE) study. *Am J Cardiol*. 2005;**95**(8):948-54.
17. Tsutamoto T, Wada A, Sakai H, Ishikawa C, Tanaka T, Hayashi M*, et al.* Relationship between renal function and plasma brain natriuretic peptide in patients with heart failure. *J Am Coll Cardiol*. 2006;**47**(3):582-6.
18. Daniels LB, Clopton P, Bhalla V, Krishnaswamy P, Nowak RM, McCord J*, et al.* How obesity affects the cut-points for B-type natriuretic peptide in the diagnosis of acute heart failure. Results from the Breathing Not Properly Multinational Study. *Am Heart J*. 2006;**151**(5):999-1005.
19. Cameron SJ, Green GB, White CN, Laterza OF, Clarke W, Kim H*, et al.* Assessment of BNP and NT-proBNP in emergency department patients presenting with suspected acute coronary syndromes. *Clin Biochem*. 2006;**39**(1):11-8.
20. O'Donoghue M, Chen A, Baggish AL, Anwaruddin S, Krauser DG, Tung R*, et al.* The effects of ejection fraction on N-terminal ProBNP and BNP levels in patients with acute CHF: analysis from the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) study. *J Card Fail*. 2005;**11**(5 Suppl):S9-14.
21. Goetze JP, Gore A, Moller CH, Steinbruchel DA, Rehfeld JF, Nielsen LB. Acute myocardial hypoxia increases BNP gene expression. *FASEB J*. 2004;**18**(15):1928-30.
22. Sabatine MS, Morrow DA, de Lemos JA, Omland T, Desai MY, Tanasijevic M*, et al.* Acute changes in circulating natriuretic peptide levels in relation to myocardial ischemia. *J Am Coll Cardiol*. 2004;**44**(10):1988-95.
23. Staub D, Jonas N, Zellweger MJ, Nusbaumer C, Wild D, Pfisterer ME*, et al.* Use of N-terminal pro-B-type natriuretic peptide to detect myocardial ischemia. *Am J Med*. 2005;**118**(11):1287.
24. Kristensen SL, Jhund PS, Mogensen UM, Rorth R, Abraham WT, Desai A*, et al.* Prognostic Value of N-Terminal Pro-B-Type Natriuretic Peptide Levels in Heart Failure Patients With and Without Atrial Fibrillation. *Circ Heart Fail*. 2017;**10**(10).
25. Tsutamoto T, Wada A, Maeda K, Hisanaga T, Maeda Y, Fukai D*, et al.* Attenuation of compensation of endogenous cardiac natriuretic peptide system in chronic heart failure: prognostic role of plasma brain natriuretic peptide concentration in patients with chronic symptomatic left ventricular dysfunction. *Circulation*. 1997;**96**(2):509-16.
26. Kang SH, Park JJ, Choi DJ, Yoon CH, Oh IY, Kang SM*, et al.* Prognostic value of NT-proBNP in heart failure with preserved versus reduced EF. *Heart*. 2015;**101**(23):1881-8.
27. Lindholm D, Lindback J, Armstrong PW, Budaj A, Cannon CP, Granger CB*, et al.* Biomarker-Based Risk Model to Predict Cardiovascular Mortality in Patients With Stable Coronary Disease. *J Am Coll Cardiol*. 2017;**70**(7):813-26.
28. de Lemos JA, Morrow DA, Bentley JH, Omland T, Sabatine MS, McCabe CH*, et al.* The prognostic value of B-type natriuretic peptide in patients with acute coronary syndromes. *N Engl J Med*. 2001;**345**(14):1014-21.
29. Kragelund C, Gronning B, Kober L, Hildebrandt P, Steffensen R. N-terminal pro-B-type natriuretic peptide and long-term mortality in stable coronary heart disease. *N Engl J Med*. 2005;**352**(7):666-75.
30. Omland T, Persson A, Ng L, O'Brien R, Karlsson T, Herlitz J*, et al.* N-terminal pro-B-type natriuretic peptide and long-term mortality in acute coronary syndromes. *Circulation*. 2002;**106**(23):2913-8.