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Cutoff values of NT-proBNP for the prediction of low functional capacity, decreased ejection fraction and cardiovascular events in patients with heart failure

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Abstract

Background: *It has been demonstrated in numerous studies that N-terminal pro-B-type natriuretic peptide (NT-proBNP) is strongly associated with left ventricular ejection fraction (LVEF), functional capacity (FC), and cardiovascular (CV) mortality in heart failure (HF) patients. The aim of the present study was to determine the predictive cutoff values of NT-proBNP for predicting these parameters.*

Methods: *One hundred HF patients (88 male, 12 female, mean age 53.6 ± 8.9 years) with left ventricular (LV) systolic dysfunction and impaired exercise capacity were enrolled into the study. Echocardiographic examination was performed. The NT-proBNP concentration was measured after resting for 20 min in the supine position. The modified Bruce protocol was utilized for exercise testing. The patients were followed for between 690 and 840 days (mean 750 ± 30 days) for the occurrence of CV events.*

Results: *There was a strong negative correlation between NT-proBNP concentration and LVEF ($p < 0.004$). It was found that NT-proBNP is a strong predictor of LVEF < 30% ($p < 0.001$). When 940 pg/mL was accepted as a cutoff value for NT-proBNP for the prediction of an LVEF < 30%, the sensitivity and the specificity were 89.8% and 71.4%, respectively. NT-proBNP and left atrial diastolic dimension were the most significant parameters for predicting FC ($p < 0.001$, each one). An NT-proBNP cutoff value of 940 pg/mL responded to 78.8% sensitivity and 81% specificity for the prediction of FC < 5 METs. The observed independent predictors for the CV events were NT-proBNP, LV mass index, and resting heart rate ($p < 0.001$, $p = 0.02$ and $p = 0.006$, respectively). Every 1000 pg/mL elevation in NT-proBNP level resulted in a 27% increase in the occurrence of CV events ($p < 0.006$). Moreover, 940 pg/mL NT-proBNP cutoff value revealed a sensitivity and specificity of 86.7% and 64.7% respectively for the prediction of incident CV events.*

Conclusions: *Use of NT-proBNP cutoff values is easy and reliable method for the prediction of low FC and decreased LVEF, and may aid identification of patients at the highest risk for future CV events. We suggest to use NT-proBNP cutoff value of 940 pg/mL for predicting these parameters.* (Cardiol J 2009; 16: 43–51)

Key words: NT-proBNP, heart failure, functional capacity, cardiovascular events

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Introduction

Numerous studies have shown that N-terminal pro-B-type natriuretic peptide (NT-proBNP) is strongly associated with left ventricular ejection fraction (LVEF), functional capacity (FC), and cardiovascular (CV) mortality in patients with heart failure (HF) [1–6]. In daily practice, the most commonly employed parameters for the treatment decision and determining prognosis of HF patients are FC and LVEF [7]. Although data have accumulated to demonstrate a strong association between HF and NT-proBNP, reported values regarding NT-proBNP have been quite variable, which limits its clinical use [1–6, 8, 9]. The aim of the present study was to identify predictive cutoff values of NT-proBNP for low FC, decreased LVEF, and CV events in patients with HF. To transform NT-proBNP into an effective and practical tool, the present study was held to identify cutoff values for predicting low FC, decreased LVEF, and future CV events in patients with HF.

Although NT-proBNP is an effective tool in the management of HF and data have accumulated to demonstrate a strong association between HF and NT-proBNP, its clinical use is relatively limited due to practical reasons.

Methods

Study group

One hundred HF patients (88 male, 12 female, mean age 53.6 ± 8.9 years) with left ventricular (LV) systolic dysfunction were included in this prospective study. We established, as inclusion criteria for our study, significantly depressed LV systolic dysfunction (LVEF < 45%) assessed with echocardiographic examination and impaired exercise capacity before or at the commencement of study. Patients with renal failure (creatinine > 2 mg/dL), chronic obstructive pulmonary disease, atrial and ventricular arrhythmias, left bundle branch block, clinical limitations to exercise including symptomatic peripheral vascular disease, a history of recent acute coronary syndrome, or valvular heart disease were excluded. After medical history and physical examination, the subjects were incorporated into four groups according to New York Heart Association (NYHA) classification. Patients were in a stable condition for ≥ 4 weeks before enrolment, and all were taking either angiotensin converting enzyme inhibitors or angiotensin receptor blockers. Sixty-five (65%), 68 (68%), 36 (36%) and 46 (46%) patients were receiving diuretics, beta-blockers, digitalis, or spironolactone therapy, respectively. Twenty-two (22%) patients had a history of coronary artery bypass grafting (CABG) before enrolment into the study. The local ethics committee approved the study and informed consent was obtained from all subjects. The patients were followed for between 690 ans 840 days (mean 750 ± 30 days) for the occurrence of CV events (cardiac death or hospitalization for decompensated heart failure, acute coronary syndromes, and arrhythmia).

Echocardiographic examinations

All echocardiographic examinations were obtained at rest. Standard echocardiography, pulsed wave, and tissue Doppler imaging were carried out using an Acuson Sequoia machine (Acuson Corporation, Mountain View, California) with a 2.5 or 3.5 MHz phased array transducer. A single experienced cardiologist (MK) performed echocardiography and the mean of three consecutive cycles was used to drive the analysis. M-mode evaluation was made according to the recommendations of the American Society of Echocardiography [10]. The smallest and largest images of the LV during systole and diastole were obtained with apical 4-chamber view. The LVEF was calculated using modified Simpson's technique [11]. The LV mass was calculated by using the Devereux formula [12] and indexed to body surface area. Pulsed-wave Doppler was assessed by measurement of transmitral flow parameters including early E and late A diastolic filling velocities, the E/A ratio, E deceleration, and isovolumic relaxation times (DT and IVRT), in the apical 4-chamber view. The same measurements were repeated during phase II of Valsalva's manoeuvre. Diastolic function was classified as follows [13]:

- normal: E/A > 1, DT < 220 ms, IVRT < 100 ms, E/A > 1 (with Valsalva's manoeuvre);
- impaired relaxation (mild diastolic dysfunction): E/A < 1, DT > 220 ms, IVRT > 100 ms;
- pseudonormalization (moderate diastolic dysfunction): E/A > 1, DT < 220 ms, IVRT < 100 ms, E/A < 1 (with Valsalva manoeuvre);
- restrictive pattern (severe diastolic dysfunction): E/A > 2, DT < 150 ms, IVRT < 60 ms.

The velocities of systolic wave S_m and early E_m and late A_m diastolic waves were obtained along with their ratio (E_m/A_m) at the end of expiration via tissue Doppler examination.

Exercise test

Exercise testing was conducted on a Marquette 2000 treadmill (Marquette Electronics, Milwaukee, USA) by using a modified Bruce protocol.

Table 1. Clinical and laboratory variables of the patients.

Variable	New York Heart Association classification				p
	Class I (n = 25)	Class II (n = 25)	Class III (n = 25)	Class IV (n = 25)	
Age (years)	52.5 ± 9.4	54.9 ± 8.5	52.9 ± 8.2	54.2 ± 9.3	0.775
Female/male	2/23	2/23	4/21	4/21	0.273
Body mass index [kg/m^2]	26.9 ± 3.7	27.6 ± 4.3§	24.3 ± 3.8	24.5 ± 3.8	0.005
Ischemic/non-ischemic heart failure	23/2	23/2	21/4	21/4	0.332
Systolic blood pressure [mm Hg]	127.6 ± 14.8$^{\dagger, \ddagger}$	129.0 ± 26.3$^{\S, \Delta}$	106.4 ± 17.1	98.7 ± 11.4	< 0.001
Diastolic blood pressure [mm Hg]	82.6 ± 8.3$^{\dagger, \ddagger}$	79.0 ± 12.9$^{\S, \Delta}$	68.8 ± 9.7	65.4 ± 8.9	< 0.001
Heart rate [bpm]	81.6 ± 6.9‡	83.4 ± 11.8	89.4 ± 15.4	94.1 ± 16.8	< 0.001
Blood urea nitrogen [mg/dL]	16.5 ± 4.7‡	19.8 ± 6.9$^{\Delta}$	26.3 ± 14.1¶	40.7 ± 18.7	< 0.001
Creatinine [mg/dL]	1.0 ± 0.17‡	1.1 ± 0.27$^{\Delta}$	1.2 ± 0.31¶	1.5 ± 0.38	< 0.001
Sodium [mmol/L]	138.1 ± 3.1$^{\dagger, \ddagger}$	137.9 ± 4.1$^{\S, \Delta}$	133.8 ± 4.0	130.1 ± 6.3	< 0.001
Potassium [mmol/L]	4.6 ± 0.7	4.5 ± 0.3	4.5 ± 0.7	4.8 ± 0.9	0.173
NT-proBNP [pg/mL]	192 (137–271)‡	716 (501–1022)$^{\Delta}$	3317 (2616–4207)¶	13275 (9236–19079)	< 0.001

Data are expressed as mean ± SD, number or median values (interquartile intervals); †p < 0.05 between patients in NYHA classes I and III; ‡p < 0.05 between patients in NYHA classes I and IV; §p < 0.05 between patients in NYHA classes II and III; Δp < 0.05 between patients in NYHA classes II and IV; ¶p < 0.05 between patients in NYHA classes III and IV

Patients with NYHA class IV were excluded from the test. Electrocardiogram and blood pressure were monitored throughout. Exercise time, exercise stage, and maximum workload (METs) were recorded.

Assessment of NT-proBNP

Blood samples were collected to the EDTA-containing tubes following 20-minutes of supine resting. Plasma was extracted after centrifugation at 3000 rpm for 10 minutes at 0°C. NT-proBNP was measured within 20 minutes of venipuncture on an Elecsys 1010 autoanalyser (Roche Diagnostics, Indianapolis, Indiana) with the use of a commercial kit (Roche Diagnostics) by electrochemiluminescent immunoassay method.

Statistical analysis

All analyses were performed using SPSS version 14.0 (SPSS, Inc., Chicago, Illinois). Results for normally distributed continuous variables are expressed as mean values ± standard deviation (SD), and continuous variables with non-normal distribution (NT-proBNP) are presented as median values (interquartile intervals). NYHA groups were compared by ANOVA or Kruskal-Wallis tests, and for multiple comparisons Scheffe or Tamhane analyses were used as *post hoc* tests. When the dependent variable was binary, *t* test or Mann-Whitney tests were applied. Discrete variables were compared by χ^2. Correlations between continuous variables were assessed using Pearson's or Spearman's rank correlation analysis. Three multivariate logistic regression analyses were performed to determine significant predictors for the FC < 5 METs, CV events, and LVEF < 30%. Significant variables in univariate analysis at level $p < 0.1$ were entered in logistic regression analysis. Additionally, two linear regression analyses were applied for LVEF and METs. A receiver-operating characteristic curve analysis was performed to identify the optimal cutoff point of NT-proBNP concentration for predicting LVEF, FC, and CV events. The area under the curve value was calculated to determine the accuracy of the test. A value of $p < 0.05$ was considered statistically significant.

Results

Age and sex distribution were similar among the NYHA groups (Table 1). In the study population, 88 patients had ischemic and 12 patients had non-ischemic HF (2 peripartum and 10 idiopathic cardiomyopathy). There was a decrease in systolic and diastolic blood pressure and an elevation in heart rate with increasing severity of NYHA class ($p < 0.001$, for each). There was a substantial increase in NT-proBNP concentration with worsening of NYHA class ($p < 0.001$), a finding that is consistent regardless of parameters investigated like age, sex, blood pressure and heart rate (Table 2). Severity of NYHA class was also associated with

Table 2. Echocardiographic and exercise variables of the patients.

Variable	New York Heart Association classification				p
	Class I (n = 25)	Class II (n = 25)	Class III (n = 25)	Class IV (n = 25)	
Septal wall thickness [mm]	9.8 ± 1.8	9.7 ± 1.8	9.3 ± 1.4	9.7 ± 1.8	0.825
LV posterior wall thickness [mm]	9.4 ± 1.3	9.3 ± 1.2	9.4 ± 1.1	9.6 ± 1.1	0.845
LV end-diastolic dimension [mm]	63.1 ± 6.3†, ‡	64.1 ± 6.2§, Δ	71.8 ± 7.8	71.6 ± 9.2	< 0.001
LV end-systolic dimension [mm]	50.1 ± 7.9†, ‡	52.1 ± 7.2§, Δ	63.1 ± 8.1	61.4 ± 10.8	< 0.001
LV ejection fraction (%)	35.3 ± 5.2†, ‡	33.4 ± 6.2§, Δ	25.8 ± 6.3	29.4 ± 7.5	< 0.001
LV mass index [g/m^2]	134 ± 31†, ‡	136 ± 33§, Δ	174 ± 32	181 ± 43	< 0.001
LA end-diastolic dimension [mm]	43.8 ± 6.11†, ‡	47.7 ± 8.0§	53.7 ± 5.9	51.6 ± 5.5	< 0.001
LA end-systolic dimension [mm]	30.5 ± 5.9†	33.5 ± 7.2	38.6 ± 8.1	38.3 ± 7.1	0.014
LV E/A ratio	0.97 ± 0.79†, ‡	1.98 ± 1.87	2.41 ± 1.57	2.79 ± 1.05	< 0.001
LV deceleration time [ms]	184 ± 59†, ‡	159 ± 64	120 ± 54	115 ± 48	< 0.001
LV isovolumic relaxation time [ms]	123 ± 26†	106 ± 39	104 ± 42	96 ± 24	0.032
LV S_m velocity [cm/s]	11 ± 3.1†, ‡	11 ± 2.8§, Δ	8.2 ± 1.6	7.6 ± 1.5	< 0.001
LV E_m/A_m ratio	0.9 ± 0.5†, ‡	1.4 ± 0.9	1.7 ± 0.9	1.7 ± 1.0	0.007
Normal/mild/moderate/severe diastolic dysfunction (n)	5/16/3/1	3/13/1/8	2/7/3/13	1/5/5/14	< 0.001
Exercise stage	3.4 ± 0.9*, †	2.0 ± 0.7§	0.6 ± 0.3	—	< 0.001
Exercise time [min]	15 ± 2.3*, †	11 ± 1.5§	4.6 ± 1.7	—	< 0.001
Maximum workload [METs]	11 ± 2.1*, †	6.6 ± 1.7§	3.0 ± 0.7	—	< 0.001

Data are expressed as mean ± SD or numbers; LA — left atrium, LV — left ventricle; *p < 0.05 between patients in NYHA classes I and II; †p < 0.05 between patients in NYHA classes I and III; ‡p < 0.05 between patients in NYHA classes I and IV; §p < 0.05 between patients in NYHA classes II and III; Δp < 0.05 between patients in NYHA classes II and IV; ¶p < 0.05 between patients in NYHA classes III and IV

deterioration in echocardiographic parameters of systolic and diastolic function (Table 2).

Correlates of NT-proBNP and left ventricular functions

There was a considerable negative correlation between NT-proBNP and LVEF (Fig. 1). Multivariate linear regression analysis showed that NT-proBNP is the most significant predictor for LVEF (beta = = –0.336, p < 0.004). The only independent predictor of the LVEF < 30% was the NT-proBNP (p < 0.001). Logistic regression analysis revealed that every 500-pg/mL increase in the concentration of NT-proBNP was associated with a 14.2% increase in the risk of having LVEF < 30% (odds ratio 0.852, 95% confidence interval 0.798–0.990). In the receiver-operating characteristic (ROC) curve analysis a 940 pg/mL NT-proBNP cutoff value yielded sensitivity and specificity of 89.8% and 71.4%, respectively, for the prediction of LVEF < 30% (Fig. 2A).

Left ventricular E/A and E_m/A_m ratios were significantly increased with the worsening of NYHA class. Diastolic dysfunction and restrictive pattern were detected in 89 (89%) and 36 (36%) patients, respectively. Severity of diastolic dysfunction was also markedly related with the increase in NYHA

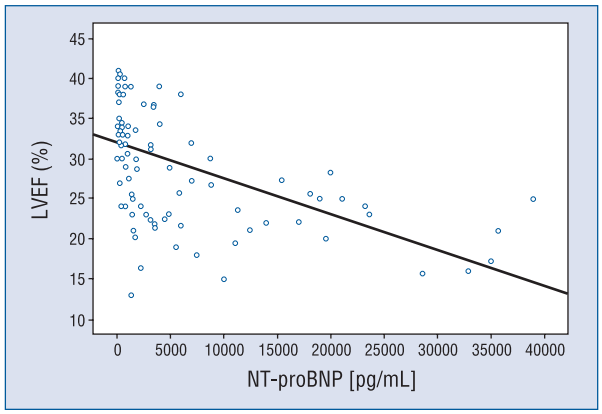
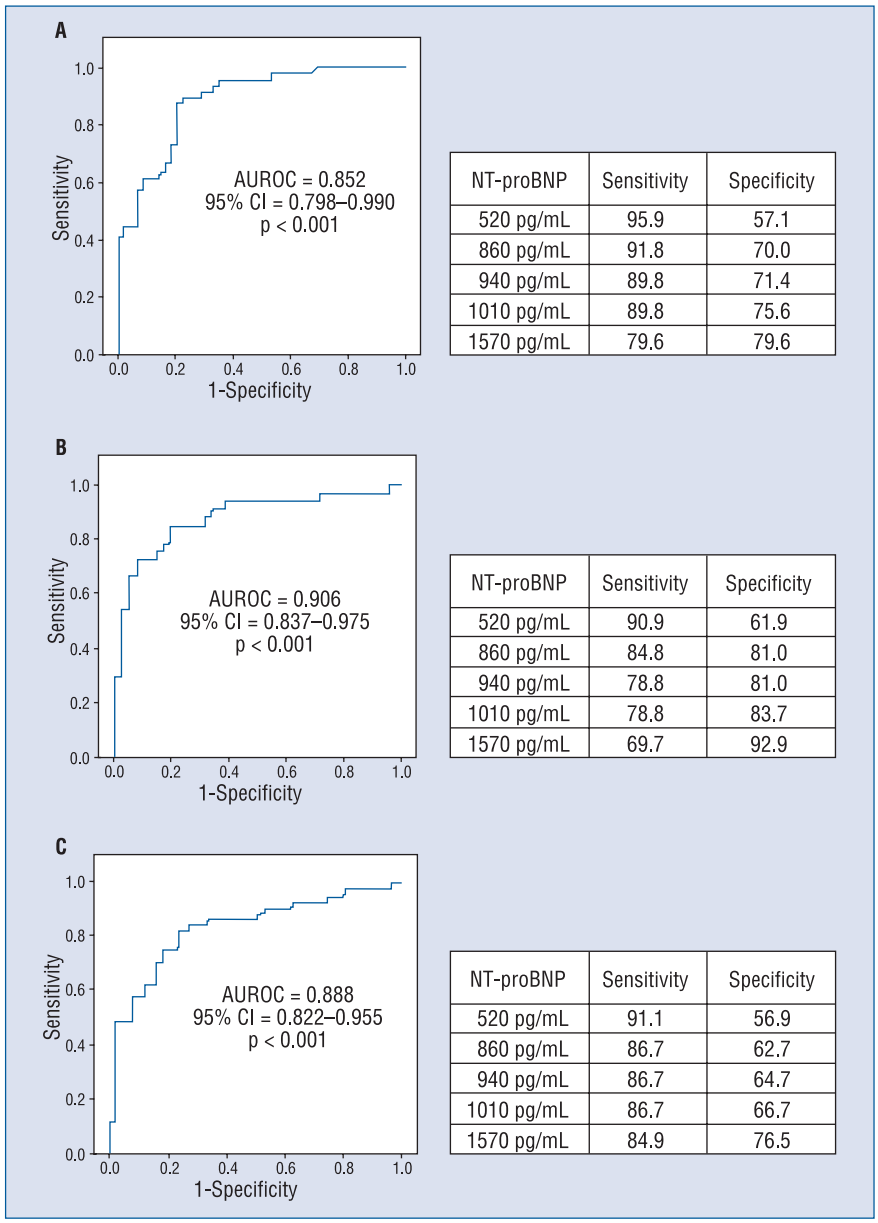


Figure 1. The relationship between left ventricular ejection fraction (LVEF) and N-terminal pro-B-type natriuretic peptide (NT-proBNP).

class (Table 2), and serum NT-proBNP levels increased significantly with the severity of diastolic dysfunction (p = 0.024). Linear regression analysis showed that left atrial (LA) end-diastolic dimension and NT-proBNP are the most significant predictors for LV E/A (beta = 0.377, p < 0.001 and beta = 265, p = 0.007, respectively). In the ROC curve analysis a 940 pg/mL NT-proBNP cutoff value yielded



NT-proBNP	Sensitivity	Specificity
520 pg/mL	95.9	57.1
860 pg/mL	91.8	70.0
940 pg/mL	89.8	71.4
1010 pg/mL	89.8	75.6
1570 pg/mL	79.6	79.6

NT-proBNP	Sensitivity	Specificity
520 pg/mL	90.9	61.9
860 pg/mL	84.8	81.0
940 pg/mL	78.8	81.0
1010 pg/mL	78.8	83.7
1570 pg/mL	69.7	92.9

NT-proBNP	Sensitivity	Specificity
520 pg/mL	91.1	56.9
860 pg/mL	86.7	62.7
940 pg/mL	86.7	64.7
1010 pg/mL	86.7	66.7
1570 pg/mL	84.9	76.5

Figure 2. Receiver-operating characteristic curve analysis of (**A**) NT-proBNP in obtaining ejection fraction < 30%, (**B**) NT-proBNP in determining functional capacity < 5 METs, and (**C**) NT-proBNP in predicting cardiovascular events.

a sensitivity and specificity of 88.9% and 60.2%, respectively, for the prediction of restrictive pattern.

Correlates of NT-proBNP and functional capacity

A significant negative correlation was found regarding serum NT-proBNP and exercise time, exercise stage, and maximum METs value ($p < 0.001$, for each). Linear regression analysis showed that NT-proBNP level and LA diastolic dimension were the most important predictors of maximum METs value (beta = –0.478, $p < 0.001$, beta = –0.359, $p = 0001$, respectively) in NYHA I–III patients. Furthermore, the independent predictors of low FC (< 5 METs) were NT-proBNP level and LA diastolic dimension ($p = 0.002$ and $p = 0.049$, respectively). Logistic regression analysis showed that every 500-pg/mL elevation in NT-proBNP concentration resulted in a 15.2% increase in the risk of having FC < 5 METs (odds ratio 1.152, 95% confidence interval 1.051––1.262). ROC curve analysis showed that when 940 pg/mL was accepted as a cutoff for NT-proBNP in the prediction of FC < 5 METs, the sensitivity and the specificity were 78.8% and 81.0%, respectively. The area under the curve (AUROC) was

Table 3. Significant variables of the patients with and without cardiovascular events.

Variables	Cardiovascular events (+) n = 46	Cardiovascular events (–) n = 54	p
Systolic blood pressure [mm Hg]	107 ± 22	123 ± 20	0.001
Diastolic blood pressure [mm Hg]	69 ± 11	79 ± 12	< 0.001
Heart rate [bpm]	94 ± 15	81 ± 9	< 0.001
NT-proBNP [pg/mL]	5417 (3655–8029)	496 (337–731)	< 0.001
BUN [mg/dL]	33.9 ± 18.7	20.10 ± 8.6	< 0.001
Creatinine [mg/dL]	1.33 ± 0.38	1.07 ± 0.27	0.001
Sodium [mmol/L]	133 ± 5.5	137 ± 4.9	< 0.001
LV end-diastolic dimension [mm]	71.3 ± 8.8	64.2 ± 6.7	< 0.001
LV end-systolic dimension [mm]	61.0 ± 10.4	52.4 ± 8.5	< 0.001
LV end-diastolic volume [mL]	264 ± 68	213 ± 53	0.001
LV end-systolic volume [mL]	187 ± 67	140 ± 52	0.005
LV ejection fraction (%)	25.4 ± 6.6	33.1 ± 6.4	< 0.001
LA end-diastolic dimension [mm]	52.5 ± 7.1	45.9 ± 6.1	< 0.001
LA end-systolic dimension [mm]	43.2 ± 4.4	31.2 ± 5.7	0.01
LV mass index (g/m^2)	177.3 ± 40.2	136.7 ± 31.7	< 0.001
LV E/A ratio	2.75 ± 1.30	1.43 ± 1.44	< 0.001
LV S_m velocity [cm/s]	7.4 ± 1.4	10.2 ± 2.9	< 0.001
LV E_m/A_m ratio	1.79 ± 1.05	1.28 ± 0.80	0.021
Maximum workload [METs]	4.26 ± 2.62	8.12 ± 3.13	< 0.001

Data are expressed as mean ± SD or median values (interquartile intervals); LA — left atrium, LV — left ventricle

Table 4. Multivariate logistic regression analysis for the prediction of cardiovascular events.

Variable	Odds ratio	95% confidence interval	p
NT-pro-BNP (1000 pg/mL)	1.270	1.072–1.505	0.006
Left ventricular mass index [g/m^2]	1.019	1.003–1.036	0.020
Heart rate [bpm]	1.081	1.023–1.143	0.006

0.906 (95% confidence interval 0.837–0.975) indicating a good discriminatory power (Fig. 2B).

NT-proBNP and cardiac outcome

During the follow up period, 25 cardiac related deaths and 21 hospitalizations (14 patients with decompensated HF, 5 patients with acute coronary syndromes, and 2 patients with arrhythmia) occurred. Two patients with NYHA class IV underwent cardiac resynchronization therapy for worsening HF. Significant characteristics of patients with and without CV events are listed in Table 3. Patients with high baseline NT-proBNP were more prone to cardiac events than those with low NT-proBNP. Multivariate logistic regression analysis demonstrated that independent predictors for CV events were NT-proBNP, LV mass index, and resting heart rate ($p < 0.001$, $p = 0.02$, and $p = 0.006$, respectively). Moreover, every 1000 pg/mL elevation in NT-proBNP level resulted in a 27% increase in the occurrence of CV events (odds ratio 1.270, 95% confidence interval 1.072–1.505) (Table 4).

In the ROC curve analysis a 940 pg/mL NT-proBNP cutoff value revealed sensitivity and specificity of 86.7% and 64.7%, respectively, for the prediction of incident CV events. The AUROC in predicting CV events was found to be 88.8%, 75.0% and 64.9% for NT-proBNP, LV mass index and resting heart rate, respectively. The AUROC was calculated at 0.888 (95% confidence interval 0.822–0.955) indicating a good discriminatory power (Fig. 2C).

Discussion

Our study has shown a strong correlation between NT-proBNP and LVEF, functional capacity, and CV events in patients with heart failure. Furthermore it can be used as an effective tool for predicting these parameters. A cutoff NT-proBNP value of 940 pg/mL is highly predictive for decreased ejection fraction (LVEF < 30%), low FC (< 5 METs), and future CV events.

Previously, numerous studies have demonstrated a strong association between NT-proBNP concentration and LV dimensions, volumes, and functions in HF patients [8, 9, 14–16]. The relationship was also significant in asymptomatic patients and healthy controls. In a study involving asymptomatic individuals with HF, the sensitivity and specificity of the 33 pmol/L NT-proBNP cutoff value was 84% and 85%, respectively, for predicting LVEF > > 58% [15]. Kotaska et al. [8] found that the AUROC in predicting ejection fraction < 40% was 60% and 69% for BNP and NT-proBNP, respectively. In our study, an NT-proBNP cutoff value of 940 pg/mL revealed a sensitivity and specificity of 89.8% and 71.4%, respectively, for the prediction of LVEF < < 30%. Restrictive filling pattern in systolic HF patients was associated with increased NT-proBNP level, impaired functional capacity and worse prognosis [17, 18]. Troughton et al. [16] demonstrated that, BNP levels reflect the severity of diastolic abnormality in patients with systolic HF. Our study is in accordance with previous studies and a significant positive correlation was found between NT-proBNP and LV E/A ratio. When 940 pg/mL was accepted as a cutoff value for NT-proBNP in the prediction of restrictive pattern, the sensitivity and specificity were 88.9% and 60.2%, respectively.

Several echocardiographic and laboratory parameters were related with functional capacity in this study. Among these, NT-proBNP level and LA end diastolic dimension were the only independent predictors of FC. In daily practice the NYHA classification and six-minute walk test are usually the preferred methods for the evaluation of FC [19, 20]. The NYHA is a subjective classification, depending on a description of patients' complaints and the evaluation of the practitioners [19, 21]. Currently, maximal oxygen (O_2) consumption (VO_{2max}) measurement is the most reliable method in determining FC. However, METs values obtained during the exercise test are also a valuable method [22, 23]. Passino et al. [2] suggested that NT-proBNP plasma values predict FC and ventilator efficiency in HF patients. In this study, NT-proBNP was an independent predictor of VO_{2max}, and an NT-proBNP cutoff value of 537 pg/mL was able to discriminate patients with VO_{2max} < 14 mL/kg/min. In another study, Kallistratos et al. [3] showed that NT-proBNP plasma levels exceeding 1190 pg/mL showed 83% sensitivity and 86% specificity for detecting VO_{2max} < 14 mL/kg/min, which was a good indicator of low FC [3]. However, Hogenhuis et al. [24] observed a weak correlation between six-minute walk test and serum NT-proBNP levels. Our finding also confirmed those studies. We found a negative correlation between NT-proBNP level and METs, exercise time and exercise stage, which was in agreement with reports of Passino and Kallistratos et al. [2, 3]. Additionally, we also demonstrated that NT-proBNP levels and LA diastolic dimensions were the independent predictors of FC < 5 METs. When 940 pg/mL was used as a cutoff value for NT-proBNP in the prediction of FC < 5 METs, the sensitivity and the specificity were 78.8% and 81.0%, respectively.

Our results suggested that NT-proBNP, LV mass index, and resting heart rate were independent predictors for future CV events. LVEF is an important parameter in predicting survival [7]. Numerous studies have shown that serum BNP levels may predict prognosis better than LVEF [25–27]. We also found that NT-proBNP level is a more important parameter than LVEF in predicting cardiovascular events. However, the SOLVD trial showed that LV mass index was a more important parameter than LVEF in detecting mortality and morbidity [28]. Our findings are in concordance with the SOLVD trial. NT-proBNP is also a very important parameter in predicting mortality and morbidity in both HF and post myocardial infarction patients [4, 29]. In a study, the AUROC in predicting mortality was found to be 73.8%, 64%, 65% and 65.4% for NT-proBNP, LVEF, VO_{2max} and HF survival score, respectively [4]. This finding suggests that NT-proBNP has the highest diagnostic value for mortality. In our study, among the parameters analyzed as predictors of CV events, the ROC curve analysis for NT-proBNP had the highest value. The AUROC were found to be 88.8%, 75.0% and 64.9% for NT-proBNP, LV mass index and resting heart rate, respectively.

There are different cutoff values for BNP measurement in predicting prognosis. This difference may be due to the different characteristics of the study population and the use of a different BNP kit and analyses system. Among these values, the COPERNICUS trial showed that the combined 1-year risks for all-cause mortality or hospitalization for HF were 14%, 25.6% or 46.7% in patients with NT-proBNP levels < 199 pmol/L, 199–504 pmol/L or > 504 pmol/L, respectively [9]. Bayes-Genis et al. [5] found that when 908 ng/L was accepted as a cutoff value for NT-proBNP in the prediction of sudden cardiac death, the sensitivity and the specificity were 81% and 55%, respectively. BNP and NT-proBNP may predict all causes of mortality in patients admitted to emergency departments [6]. In this study, optimal cutoff level for the prediction of survival was 2060 ng/L for NT-proBNP.

In a study [30] suggested that a single measurement of NT-proBNP in patients with advanced chronic HF can help identify patients with the highest risk of death. In this study, the median value for NT-proBNP was 1494 pg/mL. Gardner et al. [4] reported that a 1490 pg/mL cutoff value for NT-proBNP level predicts one-year mortality in NYHA class II–IV patients. In a recent study the cutoff value for NT-proBNP has been proposed at 1500 pg/mL as a discriminating marker of short-term survival [31]. Our cutoff value was 940 pg/mL for two years CV events, and confirms previous studies.

Limitations of the study

Our study had some limitations. The sample size of the study was small, the patients were on different medications with different dosages, we did not take the medication into account, which may have had some influence on the NT-proBNP levels and the prognosis.

Conclusions

Different cutoff values of NT-proBNP are an easy and reliable method for the prediction of low FC and decreased LVEF and can help in the identification of patients at highest risk of CV events. However, 940 pg/mL may be used to anticipate decreased ejection fraction, low FC, and CV events.

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