Original Article

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Predictor of Mortality and Rehospitalization of Acute Decompensated Heart Failure at Six Months Follow Up

Siswanto BB, Sunanto, Munawar M, Kusmana D, Hanafiah A, Waspadji S, Bachtiar A

Abstract

Objective. **To look for predictors of mortality and rehospitalization, we conducted a prospective study using fifty variables from history, physical examination, ECG, CXR, Echocardiography and blood test (N Terminal proBNP, hsCRP, and lactate level) that suspected as predictors in heart failure**

Design. **Blinded prospective cohort study**

Setting. **Emergency room of Harapan Kita National Heart Center, Jakarta-Indonesia as entry site, with ICCU, wards, and OPD for evaluation.**

Patients population for study. **All consecutive patients with acute decompensated heart failure class III-IV that were hospitalized. Exclusion criteria were other concomitant severe diseases.**

Measurements and result. **Of 97 patients enrolled, variables were measured using standard protocols. During follow up period of six months, 11 (11.3%) patients died of cardiac origin and 29 (29.9%) rehospitalized. Logistic regression analysis revealed BMI >30 kg/m^2 with edema had OR 6.6 (95% CI: 1.33-32.72, p=0,021), acute lung edema had OR 3,65 (CI 0,99-13,35, p=0,037), NYHA class IV had OR 5,42 (CI 95% : 1,11-26,59, p=0,037), left ventricle wall thickness >11 mm had OR 0,79 (CI 95 %: 0,63-1,00, p= 0,05), using beta-blocker had OR 0,09 (CI 95%: 0,01-0,74, p= 0,025), hemoglobin <12 g/dL had OR 4,53 (CI 95%: 1,24-16,56, p= 0,022), sodium <130 mmol/dL had OR 3,78(CI 95%: 1,02-14,03,p=0,047), NT proBNP >17,860 pg/mL on admission had OR 9,02 (CI 95%: 2.30-35.30, p=0,02) or NT proBNP > 8,499 pg/dL at discharge had OR 13,2 (CI 95%: 1,32-132,01, p=0,028) and served as predictors of mortality respectively. Using Cox Proportional Hazards and Kaplan Meier survival analysis and log rank test it were found that NT proBNP level >17.860 pg/ml on admission had a HR of 7.15 (95%CI 2.08-24.56, p=002) for mortality, while NT proBNP level >8.499 at discharged showed a HR of 9.55 (95%CI 1.06-85.77, p=0.044) for mortality. A decrease >35% of NT proBNP had a HR 0.13 (95%CI 0.02-1.19, p=0.071) for mortality, 0.38 (95%CI 0.14-1.00, p=0.049) for rehospitalization, and 0.42 (95%CI 0.12-0.76, p=0.010) for both. NT proBNP on admission >17.860 pg/dL together with EF <20 %, BMI >30 kg/m^2 with edema and NYHA class IV were the most accurate predictor with AUC =0,94 (p=0.0001).**

Conclusion. **Non decreased NT proBNP > 35 % during hospitalization was the predictor of mortality and rehospitalization. NT proBNP > 17,860 pg/mL at entry, NT proBNP > 8,499 pg/mL at discharged, NYHA class IV, BMI >30 kg/m^2 with edema, EF <20%, acute pulmonary edema, Hb <12 g/dL, Na <130 mmol/dL and not using beta-blocker were found as predictors for mortality of heart failure.**

Keywords: heart failure, mortality, rehospitalization, N Terminal proBNP

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I. Introduction

The incidence of heart failure is increasing from 1.5-4% to 6.7-9.9% in developing countries [1,2]. In our national heart center, heart failure is the most common diagnosis with a high mortality [3-5]. Framingham Heart Study reported that nearly half of the patients with heart failure will die or be readmitted within a year [6]. About

40% will die of sudden cardiac death, 40% of progressive pump failure, and 20% of heart failure complications such as pulmonary embolism, stroke, renal failure, and respiratory failure.

Although treatments of heart failure using angiotensin converting enzyme inhibitor, aldosterone antagonist and beta-blocker can prolonged life expectation, but some of them still had a high mortality and rehospitalization rate [7]. In predicting which groups of patients with high risk for mortality and rehospitalization rate, we still need more accurate predictors [8]. All of this rationalizes the demand of risk stratification available in daily practice.

Researches have been done in predicting mortality and rehospitalization using variables of functional capacity, cardiac output and ventricle's functions, metabolic products, hemodynamic, and neurohormonal [9-15]. However, only ventricle's functions that have been used widely in predicting mortality and morbidity [9,10]. Ventricle's functions are determined by echocardiography, which is not always available, expensive, requires modern equipment and particular skill. Non-cardiac neurohormones are also expensive and impractical [16]. Recent researches revealed that brain natriuretic peptide (BNP), a cardiac neurohormone, might play an important role in diagnosing, monitoring therapy, and determining prognosis of heart failure. This peptide can be detected easily and accurately in daily practice as N Terminal proBNP [17-19].

In summary, sufficient variables do not currently exist to predict mortality and rehospitalization in heart failure. This was the objective of this study, in which we studied 50 variables involved in heart failure to determine whether they could act as an accurate predictors of mortality and rehospitalization in heart failure.

II. Materials and Methods

II. A. Study population

From May to November 2005, 97 consecutive patients who hospitalized through the emergency room with heart failure were enrolled. To be eligible for the study, the patient have to be diagnosed by two independent physicians for heart failure based on Framingham's criteria with third or fourth of NYHA functional class. Patients with severe infection, chronic renal disease, liver disease, pulmonary disease with severe radiological finding, mechanical complication of myocardial infarction (ventricle septal defect, cardiac tamponade, acute mitral regurgitation), cardiogenic shock, dissecting aorta, congenital heart disease, idiopathic pulmonary hypertension, pulmonary embolism, and those who refused to participate in the study were excluded.

Once the patient was identified as having functional class III or IV heart failure, written informed consent was obtained, and a blood sample was collected for measurement of laboratory variables. Chest roentgenogram, electrocardiography, and echocardiography were also performed. A research assistant collected the data, including medical history, physical examination, and interpretation of chest roentgenogram, electro and echocardiography, and the result of the laboratory measurements. These results were blinded to the researcher. The patients were then treated based on national guideline of heart failure. All symptoms, vital signs, and medications were recorded until the patients were discharged, at home and at out patient department. On discharge, another blood test was performed. The patients were then followed-up for six months. If a patient died, a verbal autopsy was performed to the family to determine whether it was caused by heart disease or not.

II. B. Measurement of levels of NT proBNP, hs-CRP, and lactic acid

During the initial evaluation, a small sample of blood was collected into a tube containing potassium-EDTA. NT proBNP was measured by electro-chemiluminescent immunoassay with calibrated Roche diagnostic reagent (cat.lot.no.:03121640122) and Elecys 1010 machine. CRP was measured by immuno-turbidimeter while lactic acid by amperometric method. The precision, sensitivity, and stability characteristic of the systems have been previously described [20-21].

II. C. Statistical analysis

We examined the associations among clinical, electrocardiography (ECG), echocardiography, and chest roentgenogram findings, laboratory results, and treatments of heart failure with mortality and rehospitalization in six-month. These variables were analyzed by logistic regression. Kaplan Meier curve and Cox proportional hazard model were performed to predict rehospitalization and mortality risk using cut-off point determined by receiver operator characteristic (ROC). Log rank test was performed to examine significance of each group.

Multivariate analysis was performed using four models: all significant parameters in univariable analysis (model I), clinical findings and echocardiography (model II), clinical findings and NT proBNP level (model III),

and clinical findings together with echocardiography and NT proBNP level (model IV). Precision of each model was determined by area under the curve (AUC) of Receiver Operating Characteristic and Hosmer-Lemeshow test. Discrimination power of each model was examined by Area Under the Curve of Receiver operating charachteristic.

All analysis were performed using SPSS (version 13). A p value of less than 0.05 was considered to indicate statistical significance.

III. Results

Of 97 patients enrolled in the study, most had a high body mass index and systolic blood pressure. Patients' baseline characteristics are shown in **Table 1**.

During a follow-up period of 6 months, 11 (11.3%) patients died and 29 (29.9%) survived with rehospitalization. Body mass index, acute lung edema, beta-blocker medication, NYHA class IV, NT Pro BNP on admission and at discharged differ significantly between those who died and those that survived (37.4±8.7 vs. 30.5±8.4, p=0.014; 5 vs. 16, p=0.042; 10 vs. 41, p=0.007; 9 vs. 39, p=0.023; 18 080.55±12 175.90 vs. 9 211.70±9 506.77, p=0.006 respectively). Logistic regression analyses of these variables in prediciting mortality or rehospitalization are shown in **table 2**.

NT proBNP level >17.860 pg/ml on admission had a hazard ratio of 7.15 (95%CI 2.08-24.56, p=002) for mortality while NT proBNP level >8.499 pg/mL had a hazard ratio of 9.55 (95%CI 1.06-85.77, p=0.044.). A decreased of NT proBNP level >35% during hospitalization had a hazard ratio of 0.13 (95%CI 0.02-1.19, p=0.071) for mortality, 0.38 (95%CI 0.14-1.00, p=0.049) for rehospitalization, and 0.42 (95%CI 0.12-0.76, p=0.010) for both rehospitalization and mortality.

Hosmer and Lemeshow test for model I revealed a p value of 0.983, 0.288 for model II, 0.351 for model III, and 0.439 for model IV. The discrimination power of each model is shown in **Figure 1**. Model I had an AUC of 0,98 (95%CI 0.99-1.01, p=0.000).

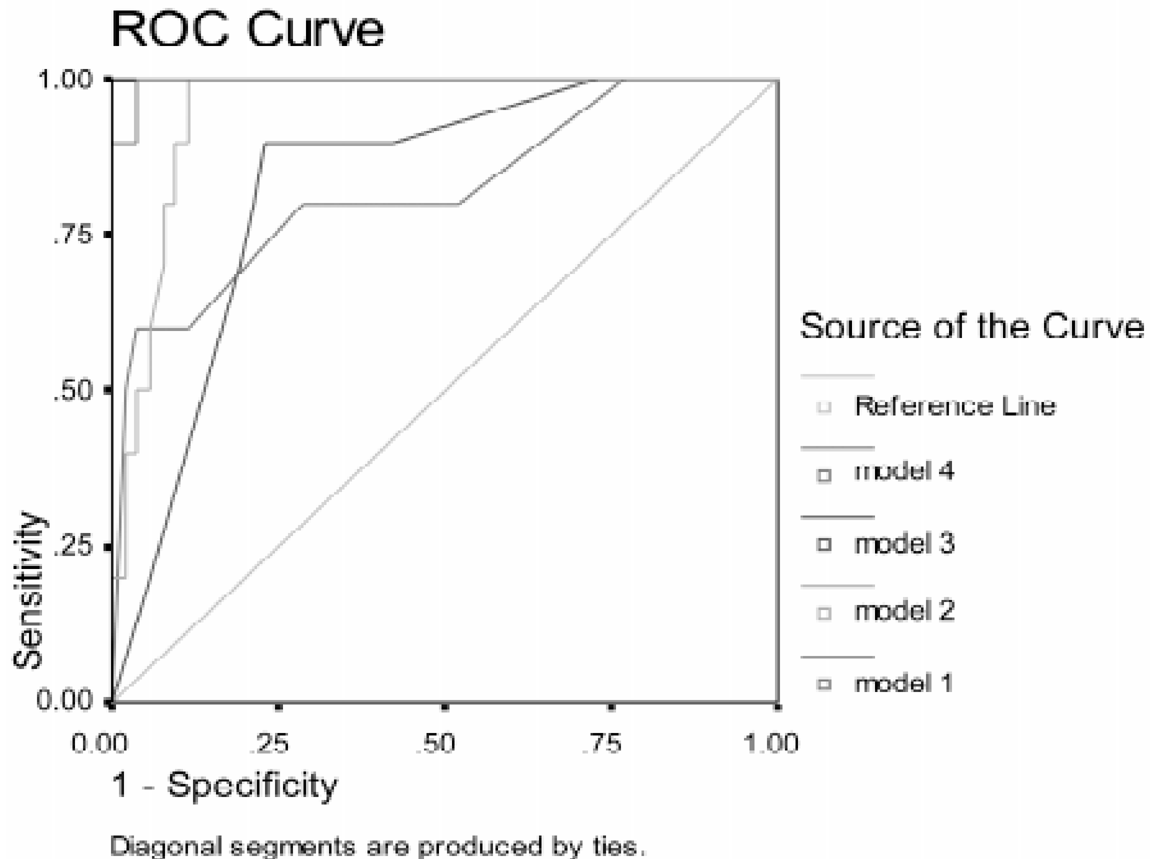

Figure 1. The discrimination power of each model

TABLE 1. BASELINE CHARACTERISTICS OF THE PATIENTS (N=97)

	Mean ± Deviation standard *(total percentage)*	median (25th–75th percentile)
Clinical		
Male	73 (75.3%)	
Age (years)	55.2 ± 10.3	56 (49 - 62)
Height (cm)	162.4 ± 7.3	163 (157 - 168)
Weight (kg)	63.5 ± 10.3	63 (56 - 69.5)
Body mass index (kg/m^2, including edema)	31.4 ± 8.7	28.4 (24.2 - 38.4)
Smoking/ex-smoker	59 (60.85%)	
Diabetes mellitus	27 (27.8%)	
Hypertension or history of hypertension	75 (77.3%)	
Family history	22 (22.7%)	
Dyslipidemia	42 (43.3%)	
Systolic blood pressure (mmHg)	135.6 ± 32.6	127 (112 - 149)
Diastolic blood pressure (mmHg)	85.0 ± 17.9	80 (73 - 92)
Heart rate (times/minute)	100.5 ± 19.0	100 (87 - 110)
Gallop	25 (25.8%)	
Lower limb edema	63 (64.9%)	
Cardio-thoracic ratio >60 %	65 (67.0%)	
Acute lung edema	21 (21.6%)	
NYHA Class III	49 (50.5%)	
Electrocardiography		
Atrial fibrillation	23 (23.7%)	
Intra ventricular conduction disturbances	30 (30.9%)	
Old myocardial infarction	57 (58.8%)	
Left ventricle hypertrophy	56 (57.7%)	
Echocardiography		
Left atrial diameter (mm)	42.0 ± 7.1	42.0 (38.8 - 46.0)
End diastolic left ventricle diameter (mm)	64.0 ± 12.9	63.5 (56.0 - 73.0)
End systolic left ventricle diameter (mm)	54.2 ± 15.3	53.0 (46.0 - 64.8)
Ejection fraction (%)	30.5 ± 13.8	26.0 (20.0 - 36.0)
Left ventricle wall thickness (mm)	13.2 ± 3.4	13.0 (11.0 - 15.0)
E/A ratio >2 (diastolic dysfunction)	49 (50.5%)	
Valve regurgitation	20 (20.6%)	
Valve stenosis	5 (5.2%)	
Valve disorder	25 (25.8%)	
Treatment		
Intervention	27 (27.8%)	
Intra venous diuretic	56 (57.7%)	
ACE inhibitor	72 (74.2%)	
Beta-blocker	46 (47.4%)	
Angiotensin Receptor Blocker	31 (32.0%)	
Digoxin	48 (49.5%)	
Aldosterone antagonist	73 (75.3%)	
Nitrat	67 (69.1%)	
Dobutamine	16 (16.5%)	
Hidralazine	11 (11.3%)	
Laboratory		
Haemoglobin (g/dL)	13.47 ± 2.04	13.90 (11.95 - 14.90)
Na (mmol/L)	132.05 ± 18.65	136.0 (130.0 - 139.0)
Uric acid (mg/mL)	8.80 ± 2.64	8.30 (7.00 - 10.68)
NT proBNP on admission (pg/mL)	10.283.76 ± 10.210.61	6.113 (2.127 - 16.108)
NT proBNP on discharge (pg/mL)	6.681.44 ± 7.641.37	3.865.5 (1.285.5 - 9.416.75)
Lactic acid on admission (mmol/L)	2.96 ± 2.44	2.30 (1.80 - 2.90)
Lactic acid on discharge (mmol/L)	2.28 ± 1.45	2.00 (1.55 - 2.60)
hsCRP on admission (mg/mL)	30.78 ± 57.43	9.27 (5.89 - 36.70)
hsCRP on discharge (mg/mL)	17.35 ± 27.59	6.22 (2.96 - 18.42)

Table 2. Logistic regression analysis in predicting mortality and rehospitalization

Variables	OR	95 % CI	P value
Clinical			
Body mass index >30 kg/m^2	6.6	1.33 – 32.72	0.021
Acute lung edema	3.65	0.99 – 13.45	0.052
NYHA functional class IV	5.42	1.11 – 26.59	0.037
Echocardiography			
Left ventricle wall thickness >11 mm	0.79	0.63 – 1.00	0.05
Therapy			
Not using beta-blocker	0.09	0.01 – 0.74	0.05
Laboratory			
Hemoglobin <12 g/dL	4.53	1.24 –16.56	0.022
Na <130 mmol/L	3.78	1.02 – 14.03	0.047
NT proBNP on admission >17.860 (ROC method)	9.02	2.30 – 35.30	0.002
NT proBNP on discharge >8.499 (ROC method)	13.2	1.32 – 132.01	0.028

Discussion

We found that NYHA functional class IV was a predictor of mortality and rehospitalization. The mortality rate was 5.42 times higher than those with functional class III. This could be explained that severe dyspnea was associated with severe pulmonary edema caused by pump failure. However, since this study only examined patients with class III and IV heart failure, we could not determine whether NYHA class correlate linearly with mortality and rehospitalization.

From many cardiovascular disease's risk factors examined in the study, only body mass index was found to predict mortality and rehospitalization. Our results were consistent with those of Bozkuts *et al*. [22]. However, these results should be interpreted carefully since high body mass index often co-morbid with other risk factors such as hypertension, diabetes, and dyslipidemia. Moreover, we did not differentiate high body mass index as obesity or edema in our study.

Among clinical variables, acute lung edema was found to predict mortality or rehospitalization. Acute lung edema is often followed by respiratory arrest, retaining of waste product, and fall in blood pressure and heart rate, all of which may cause death [23].

Mean arterial pressure, being reported as a predictor [24], was not proved in our study. This might be due to the fact that most samples in our study had a high blood pressure. Moreover, patients with shock (defined as having very low blood pressure) were not included in the study.

We found that electrocardiography finding might not predict mortality and rehospitalization in heart failure. We suggested that ECG was important in predicting arrhythmic death but not pump failure. Our finding contradicts previous findings in which QRS width > 12 ms [25], atrial fibrillation [26], and left ventricular hypertrophy [10,27] were reported as predictors of mortality and rehospitalization.

Contradictory to Cohn *et al*. [28] we found that cardiomegaly determined by chest roentgenogram could not predict mortality or rehospitalization in heart failure. This may due to the limitation that a patient with heart failure was too short of breath that posteroanterior imaging was impossible. Anteroposterior imaging might have altered the accuracy in determining cardiomegaly.

We found that, inconsistent with that of Faris *et al.* [29] and Tei *et al.* [30], ejection fraction or myocardial performance index could predict mortality or rehospitalization. However, while combined with other variables such as body mass index and clinical finding, ejection fraction might predict mortality or rehospitalization.

We also found that ventricle's posterior wall thickness might predict mortality and rehospitalization in heart failure. This suggests that ventricle posterior wall thickness may act as a protective factor in heart failure.

Patients with beta-blocker were more likely to survive in our study. Beta-blocker has been used as a standard therapy for heart failure [31]. It prevents both mortality and rehospitalization with a level-A evident. Our finding re-emphasized the role of beta-blocker in treating heart failure.

We found that simple laboratory test such as hemoglobin and sodium level might act as a predictor for mortality and rehospitalization in heart failure. Our finding is similar to that of Shamagian *et al*. [32] and deLuca *et al*. [14]. In addition, we also found that mortality risk of high NT proBNP level was 9.02-9.23 compared to 4.87-5.29 for lactic acid level. Lactic accumulation will depress myocardium and result in death. Contrary to that of

Alonso-Martinez [33], hsCRP was not found to predict rehospitalization in our study; this may due to that most patients in our study consumed statin which could normalized hsCRP level.

Hartmann *et al*. [34] reported that NT proBNP level on admission was a predictor of mortality and rehospitalization risk. This finding is similar to ours though we did not find the peptide's level a predictor of rehospitalization. However, we found that not only NT proBNP level on admission but also the peptide level on discharge might predict mortality risk. The peptide level on discharge had been reported to be more important than that on admission and more cost effective than another measurement such as echocardiography in predicting mortality and rehospitalization [35]. Moreover, we found that a persistent high or a decrease of less than 35% level of NT proBNP during hospitalization might predict rehospitalization and mortality too. This finding is consistent with that of Bettencourt *et al.* [36]. A persistent high level of the peptide was reported as a marker of remodeling in heart failure [37].

Of four models suggested, we found model I the most powerful predictor of mortality and rehospitalization in heart failure. This could be understood since each variable included in this model itself was an independent predictor.

In our study, samples were drawn from patients who entered the national cardiac center and might not represent all heart failure patients in our country. Therefore, we suggest further multi-centered study with a larger sample.

Conclusion

In conclusion, not all factors involved in heart failure may predict mortality and rehospitalization. Our results indicate that only high body mass index, acute lung edema, beta-blocker medication, NYHA functional class IV, left ventricle wall thickness, hemoglobin and sodium level, NT proBNP level on admission and discharge, and also persistent level of NT proBNP during hospitalization may serve as predictors of mortality and rehospitalization in heart failure.

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