

Hemodynamic Congestion at Hospital Discharge Predicts Rehospitalization During Short Term Follow Up in Acute Heart Failure Patients

Yoga Waranugraha, M. Saifur Rohman, Setyasih Anjarwani

Abstract

Background: Hemodynamic congestion is an increase in left ventricular diastolic pressure (LVEDP) without clinical symptoms and signs of congestion. Current acute heart failure (AHF) treatment goals only focused on improving clinical congestion. The purpose of this study was to investigate whether hemodynamic congestion measured by NT-proBNP level and ePCWP at hospital discharge could predict short term clinical outcomes in AHF patients.

Methods: This prospective cohort study was conducted at dr. Saiful Anwar General Hospital Malang from January to July 2018. All patients got AHF treatment according to the 2016 ESC guidelines for heart failure. All patients were discharged without symptoms and signs of clinical congestion. Hemodynamic congestion at hospital discharge was defined as failure of treatment during hospitalization to achieve NT-proBNP reduction of > 30% and/or ePCWP at hospital discharge > 16 mmHg. NT-proBNP level and ePCWP were measured at 0-12 hours after hospital admission and at hospital discharge. ePCWP was measured using echocardiography. The clinical outcomes assessed were AHF rehospitalization and cardiovascular mortality within 30 days after hospital discharge. Subgroup analysis was performed to determine treatment regimen that are effective in improving hemodynamic congestion.

Results: A total of 33 AHF patients were included in this study. 48% patients were discharged with hemodynamic congestion and 52% patients discharged without hemodynamic congestion. Patients with hemodynamic congestion at hospital discharge showed a higher rehospitalization within 30 days (8 [50%] vs 1 [5.9%]; $P = 0.007$). Mortality within 30 days in both groups did not show a significant difference (2 [12.5%] vs 0 [0%]; $P = 0.277$). Treatment regimen of optimal dose of ACEI/ARB, β -blocker, and diuretic was correlated with improvement of hemodynamic congestion ($P = 0.026$; $r = 0.454$), NT-proBNP reduction of > 66% ($P = 0.02$; $r = 0.574$), and achievement of ePCWP < 16 mmHg ($P = 0.013$; $r = 0.493$) at hospital discharge in HFrEF patients.

Conclusion: Hemodynamic congestion assessed using NT-proBNP level and ePCWP at hospital discharge increased 30 day rehospitalization in AHF patients. In HFrEF, improvements of hemodynamic congestion can be achieved by giving the treatment regimen of optimal dose of ACEI/ARB, β -blocker, and diuretic.

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Keyword: Acute heart failure, hemodynamic congestion, NT-proBNP, ePCWP

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Introduction

Heart failure is a global pandemic problem,¹ affecting more than 37.7 million people worldwide. According to the RISKESDAS 2013, the prevalence of heart failure in Indonesia was 0.3%.³ Patients with heart failure experience various kinds of clinical symptoms that

can reduce the quality of life.² Heart failure imposes a huge economic burden, estimated at 108 billion US dollar per year. AHF refers to rapid onset or worsening of symptoms and/or signs of heart failure. It is a life-threatening medical condition requiring urgent evaluation and treatment, typically leading to urgent hospital admission.⁵ Despite therapeutic advances, the prognosis of acute heart failure is poor, with in-hospital mortality ranging from 4% to 7%, 60- to 90-day mortality ranging from 7% to 11%, and 60- to 90-day rehospitalization from 25% to 30%.⁶

Hemodynamic congestion is defined as high ventricular diastolic pressures without overt clinical signs. Clinical congestion may resolve with treatment but hemodynamic congestion may persist, leading to a high risk of rehospitalization.^{7,8} Data from studies with implantable hemodynamic monitors have confirmed that chronically elevated filling pressures or hemodynamic congestion are associated with increased risk of future events.⁹ Hemodynamic congestion could be assessed by increasing levels of NT-proBNP and PCWP.^{10,11} Several studies have shown that the relative NT-proBNP reduction of < 30% at hospital discharge is a significant predictor of mortality and rehospitalization in AHF patients.^{12,13} In AHF patients, achieving PCWP < 16 mmHg at hospital discharge provides a better 1-year survival rate.^{14,15} PCWP can be estimated non-invasively using echocardiography.^{16,17} The purpose of this study was to investigate whether hemodynamic congestion measured by NT-proBNP level and ePCWP at hospital discharge could predict short term clinical outcomes in AHF patients.

Methods

Study Design and Populations

We conducted a prospective cohort study in dr. Saiful Anwar General Hospital Malang from January to June 2018. This research is a part of joint research by multi department entitled “*Additive Value of Monitoring Non Invasive Cardiac Hemodynamic and Total Body Water Content in Critical Care Patients Outcomes in Acute Medicine Department from ER Admission to Discharge*”. This study involved AHF patients aged 40 years or more. Exclusion criteria included pregnancy, acute coronary syndrome, patients on invasive mechanical ventilation,

cardiac arrest, cardiac tamponade, congenital heart disease, stenosis lesion of the heart valve, patients with mechanical or bioprosthetic valves, left atrial myxoma, thrombus in the left atrium, thrombus in pulmonary vein, patient with cardiac implantable electronic devices (Pacemaker, ICD, or CRT), patient discharged from hospital without ACEI/ARB and/or β -blocker, patients discharged from hospital with clinical congestion, pulmonary embolism, pulmonary hypertension other than due to dysfunction left ventricle, COPD, pneumothorax, CKD, hyperthyroidism, stroke/TIA, malignancy, and terminal disease.

We performed measurement of NT-proBNP and ePCWP in AHF who came to the emergency room (ER) of dr. Saiful Anwar General Hospital in 0-12 hours after hospital admission. All patients received AHF therapy based on the 2016 ESC guidelines for heart failure.⁵ All patients are discharged from the hospital without symptoms and signs of clinical congestion. The second measurement of NT-proBNP and ePCWP was performed at hospital discharge. Patients were classified into 2 groups based on the presence of hemodynamic congestion at hospital discharge. Hemodynamic congestion at hospital discharge was defined as failure of treatment during hospitalization to achieve NT-proBNP reduction of > 30% and/or ePCWP at hospital discharge \geq 16 mmHg. The primary endpoints were AHF rehospitalization and cardiovascular mortality within 30 days after hospital discharge. Subgroup analysis was performed to determine the effective therapeutic regimen to achieve secondary endpoints which included hemodynamic congestion, NT-proBNP level, and ePCWP.

BT-pro BNP and ePCWP Measurements

NT-proBNP level was obtained from venous blood and processed using the sandwich-type electrochemiluminescence sensor method. ePCWP was measured using echocardiography. ePCWP was calculated using the formula $ePCWP = 1.24 \times (E/e') + 1.9$, $e' = (\text{lateral } e' + \text{septal } e') / 2$.¹⁸ For patients with single transmitral flow due to sinus tachycardia, ePCWP was calculated using the formula $ePCWP = 1.47 \times (E/e') + 1.5$.¹⁹ Whereas for patients with atrial fibrillation, ePCWP was calculated using the formula $ePCWP = 0.821 \times (E/e') + 6.489$.¹⁷ In this study we used General

Table 1. Baseline characteristics of AHF patients at hospital admission

	Hemodynamic congestion (+)	Hemodynamic congestion (-)	P-value
	n = 16	n = 17	
Age, years, mean + SD	57,50±12,03	66,47±12,25	0,034
Men (%)	10(62,5%)	8(47,1%)	0,373
NYHA IV functional class (%)	16(100%)	17(100%)	-
Dyspnea (%)	16(100%)	17(100%)	-
Orthopnea (%)	15(93,8%)	11(64,7%)	0,085
PND (%)	10(62,5%)	11(64,7%)	0,895
GCS, mean + SD	15,00±0,00	15,00±0,00	1
SBP, mmHg, mean + SD	144,63±37,17	144,12±33,86	0,986
DBP, mmHg, mean + SD	85,88±17,58	85,00±15,33	0,828
MAP, mmHg, mean + SD	107,00±25,92	105,18±20,69	0,9
HR, bpm, mean + SD	104,50±20,59	106,00±15,14	0,626
RR, tpm, mean + SD	31,25±4,31	30,00±3,67	0,355
S3 (%)	4(25%)	3(17,6%)	0,688
Rhales (%)	16(100%)	17(100%)	-
JVP cmH2O, mean + SD	9,19±1,79	9,18±0,88	0,573
Asites (%)	6(37,5%)	1(5,9%)	0,039
Hepatomegaly (%)	6(37,5%)	6(35,3%)	0,895
Leg edema (%)	10(62,5%)	2(11,8%)	0,002
Atrial Fibrillation (%)	4(25%)	3(17,6%)	0,688
Supraventricular arrhythmia (%)	1(6,3%)	0(0%)	0,485
Ventricular arrhythmia (%)	4(25%)	3(17,6%)	0,688
CTR, %, mean + SD	72,94±5,95	69,71±4,82	0,116
Interstitial congestion (%)	15(93,8%)	17(100%)	0,485
Alveolar congestion (%)	3(18,8%)	2(11,8%)	0,656
Pleural effusion (%)	2(12,5%)	3(17,6%)	1
Hemoglobin, g/dl, mean + SD	13,46±2,62	13,71±15,4	0,719
NT-proBNP, pg/ml, mean + SD	17547,75±12178,83	13286,06±12788,50	0,366
Ureum, mg/dl, mean + SD	48,04±20,31	50,73±28,51	1
Creatinine, mg/dl, mean + SD	1,39±0,54	1,33±0,64	0,614
eGFR, ml/min/1.73 m2, mean + SD	60,99±33,67	61,5±28,29	0,54
AST, mg/dl, mean + SD	42,50±49,63	28,18±16,16	0,159
ALT, mg/dl, mean + SD	33,38±45,34	35,12±36,18	0,287
Oxygen supplementation, %, mean + SD	77,06±27,54	69,41±28,29	0,299
PH, mean + SD	7,33±0,08	7,39±0,10	0,097
PaCO2, mmHg, mean + SD	35,43±11,76	32,67±12,81	0,387
PaO2, mmHg, mean + SD	112,36±44,34	114,65±28,35	0,494
HCO3-, mmol/l, mean + SD	18,85±4,81	19,59±4,18	0,54
Base excess, mmol/l, mean + SD	-8,56±3,55	-6,08±4,43	0,077
SaO2, %, mean + SD	95,85±3,82	97,69±1,54	0,97
RWMA (%)	13(81,3%)	15(88,2%)	0,656
EF Biplane, %, mean + SD	34,31±11,88	35,88±8,89	0,54
E/e', mean + SD	18,42±3,05	19,41±2,99	0,46
ePCWP, mmHg mean + SD	24,13±4,09	25,35±3,90	0,302
LVEDD, cm, mean + SD	5,98±1,15	5,61±0,88	0,517
LVESD, cm, mean + SD	4,89±1,26	4,69±0,97	0,639

LAVI, ml/m ² mean + SD	50,56±15,54	49,94±14,63	0,957
Mitral regurgitation (%)	14(87,5%)	14(82,4%)	1

PND = Paroxysmal nocturnal dyspnea; GCS = Glasgow coma scale; SBP = Systolic blood pressure; DBP = Diastolic blood pressure; MAP = Mean arterial pressure; HR: heart rate; RR: respiratory rate; S3 = third heart sound; JVP = jugular venous pressure; CTR = cardiothoracic ratio; eGFR = Estimated glomerular filtration rate; AST = Aspartate aminotransferase; ALT = Alanine aminotransferase; PaCO₂ = partial pressure of carbon dioxide in the arterial blood; PaO₂ = partial pressure of oxygen in the arterial blood; HCO₃⁻ = bicarbonate; RWMA = regional wall motion abnormality; EF = Ejection fraction; E/e' = ratio between early mitral inflow velocity and mitral annular early diastolic velocity; LVEDD = left ventricular end systolic diameter; LAVI: left atrial volume index.

electronic Vivid e and Vivid 5 echocardiography machines. Echocardiographic examination was performed by two senior cardiology and vascular medicine residents. The interobserver variability was tested using the Cohen's Kappa test. No significant difference in echocardiography interpretations between both operators.

Statistical Analysis

Numerical variables are presented as mean ± SD. Categorical variables are presented as frequencies and percentages. The comparison between 2 numerical variables was tested using the Mann Whitney test. The comparison between 2 categorical variables was tested using the Chi square test or Fisher's test. AHF rehospitalization and cardiovascular mortality within 30 days after hospital discharge were presented in the Kaplan-Meier curve. The cut off point of some variables was tested using the ROC curve. The relationship between 2 nominal variables is tested using the contingency coefficient test. P value ≤ 0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics 21.

Results

Baseline Characteristics

A total of 33 AHF patients with NYHA IV functional class were included in this study. 48% of patients were discharged from the hospital with hemodynamic congestion and 52% of patients were discharged from the hospital without hemodynamic congestion. In general, the basic characteristics of the two groups were not different. Patients discharged from the hospital with hemodynamic congestion were younger than patients

discharged from the hospital without hemodynamic congestion (57.50 ± 12.03 vs 66.47 ± 12.25; P = 0.034). Ascites and limb edema at hospital admission were more prevalent in patients discharged from the hospital with hemodynamic congestion than in patients discharged from the hospital without hemodynamic congestion (6 (37.5%) vs 1 (5.9%); P = 0.039 and 10 (62.5%) vs 2 (11.8%); P = 0.002 respectively) (Table 1). The length of stay between the two groups was not different (Table 2). All patients were discharged from the hospital without clinical congestion. The treatment regimen at hospital discharge between the two groups were not different.

Clinical outcomes

Patients were followed for 30 days after hospital discharge. 30 day cardiovascular mortality in both groups was not significantly different (2 [12.5%] vs 0 [0%]; P=0,277). Patient with hemodynamic congestion at hospital discharge showed a higher 30 day rehospitalization than patient without hemodynamic congestion at hospital discharge (8 [50%] vs 1 [5.9%]; P = 0.007). Survival analysis using Kaplan-Meier curve showed significant differences in 30 day rehospitalization after hospital discharge (Log rank, P = 0.004) but not mortality (Log rank, P = 0.138) (Picture 1). After hospital discharge, daily drug dose regimen between the two groups were not different generally. Patients with hemodynamic congestion received a lower daily dose of furosemide than patients without hemodynamic congestion (25.33 + 9.15 mg vs. 33.33 + 9.75 mg; P = 0.031) after hospital discharge (Table 4).

Subgroup Analysis

NT-proBNP is a well-known prognostic biomarker for AHF rehospitalization, but its value greatly varies among individuals. The ROC curve showed that the NT-

Table 2. Treatment during hospitalization

	Hemodynamic congestion (+) n = 16	Hemodynamic congestion (-) n = 17	P-value
O2 supplementation (%)	16(100%)	17(100%)	-
NIV (%)	2(12,5%)	1(5,9%)	0,601
Inotropic (%)	2(12,5%)	2(11,8%)	1
Diuretic (%)	16(100%)	17(100%)	-
Nitrate (%)	6(37,5%)	8(47,1%)	0,579
ACEI/ARB (%)	16(100%)	17(100%)	-
CCB (%)	3(18,8%)	4(23,5%)	1
MRA (%)	9(56,3%)	14(82,4%)	0,104
OAC/NOAC (%)	4(25%)	3(17,6%)	0,688
Antiplatelet (%)	12(75%)	15(88,2%)	0,398
Statin (%)	14(87,5%)	16(94,1%)	0,601
β-blocker (%)	16(100%)	17(100%)	-
Digoxin (%)	2(12%)	4(23,5%)	0,656
OAD (%)	1(6,3%)	3(17,6%)	0,601
Insulin (%)	2(12,5%)	1(5,9%)	0,601
Length of stay, day, mean + SD	5,63±2,92	5,29±2,54	0,798

NIV = Non invasive ventilation; ACEI = Angiotensin converting enzyme inhibitor; ARB = Angiotensin receptor blocker; CCB = Calcium channel blocker; MRA = Mineralocorticoid receptor antagonist; OAC = Oral anticoagulant; NOAC = Novel oral anticoagulant; OAD = Oral anti diabetes.

proBNP reduction during in-hospital treatment (cut off 66%; sensitivity 75%; specificity 76%; AUC 0.755; P = 0.032) was better than single NT-proBNP value at hospital discharge (cut off 2813 pg/mL; sensitivity 75%; specificity 68%; AUC 0.755; P = 0.032) in predicting AHF rehospitalization (Picture 2).

We tried to find out the correlation between heart failure drug therapy regimen during in-hospital treatment with the achievement of secondary endpoints which included hemodynamic congestion, NT-proBNP reduction of > 66%, and ePCWP <16 mmHg at the hospital discharge. In the HFmrEF patients, administration of treatment regimen of optimal dose of ACEI/ARB, β-blocker, and diuretic was not associated with secondary endpoints (Table 5). Administration of treatment regimen of optimal dose of ACEI/ARB, β-blocker, and diuretic was associated with improvement of hemodynamic congestion (P = 0.026; r = 0.454), NT-proBNP reduction of > 66% (P = 0.02; r = 0.574), and achievement of ePCWP < 16 mmHg (P = 0.013; r = 0.493) at hospital discharge in the HFREF patients (Table 6).

Discussion

In this study, we tried to combine biomarker and hemodynamic parameters measured noninvasively in assessing hemodynamic congestion. We used cut off point according to the results of several previous studies.^{12,13,14,15} Previous studies used pulmonary artery catheter to measure PCWP.^{14,15} No previous study used ePCWP measured by echocardiography as a hemodynamic parameter in AHF.

Hemodynamic congestion occurs within a few days or weeks before clinical congestion.²⁰ In our study, the 30 day rehospitalization was higher in patient with hemodynamic congestion at hospital discharge. Patient with hemodynamic congestion suffered from symptoms of clinical congestion in few days or weeks after hospital discharge. Those conditions forced them for urgent hospital admission. In this study, patients who were discharged from the hospital with hemodynamic congestion received lower dose of furosemide. We were unable to intervene the therapeutic regimen which given by the physician in charge because our study design

Table 3. Symptoms, signs, and medical treatment at hospital discharge

	Hemodynamic congestion (+) n = 16	Hemodynamic congestion (-) n = 17	P-value
Dyspnea (%)	0%	0%	-
Orthopnea (%)	0%	0%	-
PND (%)	0%	0%	-
GCS, mean + SD	15,00±0,00	15,00±0,00	1
SBP, mmHg, mean + SD	122,13±16,72	117,41±19,21	0,37
DBP, mmHg, mean + SD	76,75±11,93	71,29±6,20	0,09
MAP, mmHg, mean + SD	92,63±11,83	86,59±9,25	0,111
HR, bpm, mean + SD	78,81±6,38	74,76±6,60	0,112
RR, tpm, mean + SD	19,50±0,89	19,24±0,97	0,381
S3 (%)	0%	0%	-
Rhales (%)	0%	0%	-
JVP cmH2O, mean + SD	6,44±0,63	5,64±0,61	0,002
Ascites (%)	0%	0%	-
Hepatomegaly (%)	0%	0%	-
Leg edema (%)	0%	0%	-
Diuretic (%)	15 (93,8%)	15 (88,2%)	1
Nitrate (%)	8(50%)	6(35,3%)	0,393
ACEI/ARB (%)	16(100%)	17(100%)	-
CCB (%)	3(18,8%)	4(23,5%)	1
MRA (%)	9(56,3%)	14(82,4%)	0,141
OAC/NOAC (%)	4(25%)	3(17,6%)	0,688
Antiplatelet (%)	11(68,8%)	15(88,2%)	0,225
Statin (%)	14(87,5%)	16(94,1%)	0,601
β-blocker (%)	16(100%)	17(100%)	-
Digoxin (%)	2(12,5%)	4(23,5%)	0,656
OAD (%)	1(6,3%)	3(17,6%)	0,601
Insulin (%)	2(12,5%)	1(5,9%)	0,601

PND = Paroxysmal nocturnal dyspnea; GCS = Glasgow coma scale; SBP = Systolic blood pressure; DBP = Diastolic blood pressure; MAP = Mean arterial pressure; HR: heart rate; RR: respiratory rate; S3: third heart sound; JVP: jugular venous pressure; ACEI = Angiotensin converting enzyme inhibitor; ARB = Angiotensin receptor blocker; CCB = Calcium channel blocker; MRA = Mineralocorticoid receptor antagonist; OAC = Oral anticoagulant; NOAC = Novel oral anticoagulant; OAD = Oral anti diabetes

was an observational study. The decision of physician in charge to discharge the patient was made based on the absence of the clinical congestion according to the 2016 ESC guidelines for heart failure.⁵ We performed measurement of NT-proBNP level and ePCWP after the patients were decided to be discharged from the hospital by the physician in charge. Hemodynamic congestion and inadequate dose of furosemide could accelerate the

occurrence of clinical congestion and rehospitalization. Moreover, there were several confounding factors which were difficult to be managed that could exacerbate AHF and rehospitalization such as acute coronary syndromes, non-compliance with medications, arrhythmia, or infection. In this study, cardiovascular mortality in both groups was not significantly different because the duration of follow-up is shorter than several previous

Table 4. Daily dose of the heart failure drugs after hospital discharge

Drugs	Hemodynamic congestion (+)	Hemodynamic congestion (-)	P-value
	n = 16	n = 17	
Furosemide mg, mean + SD	25,33+9,15	33,33+9,75	0,031
Nitrat mg , mean + SD	15,00+0,00	18,33+6,61	0,197
Ramipril mg, mean + SD	10,00+0,00	10,00+0,00	1
Lisinopril mg, mean + SD	20,00+0,00	20,00+0,00	1
Valsartan mg, mean + SD	192,00+121,33	240,00+80,00	0,536
Candesartan mg, mean + SD	8,00+0,00	16,00+0,00	0,157
Spirolactone mg, mean + SD	25,00+0,00	25,00+0,00	1
Bisoprolol mg, mean + SD	2,50+0,79	2,35+0,41	0,707
Digoxin mg, mean + SD	0,25+0,00	0,25+0,00	1

studies which ranged from 180 days to 1 year.^{12,13,14,15,}

Our study supports the evidence that the failure in improving the hemodynamic congestion in AHF is associated with an increased risk of rehospitalization within 30 days after hospital discharge. Therefore, we conducted subgroup analysis to search for the treatment regimen to achieve secondary endpoints which included haemodynamic congestion, NT-proBNP reduction > 66%, and PCWP achievement <16 when the patient discharged from the hospital. Patients were grouped into HFmrEF group and HFrEF group.

In HFmrEF patients, treatment regimen of optimal dose of ACEI/ARB, β -blocker, and diuretic was not correlated with improvement in hemodynamic congestion, NT-proBNP reduction of > 66%, and achievement of ePCWP < 16 mmHg at hospital discharge. These results may be caused by the heterogeneous pathophysiologic mechanism in HFpEF and HFmrEF.^{22,23} In the clinical trials and/or daily clinical practice, only a few patients with HFpEF and HFmrEF received ACEI/ARB, β -blocker, and diuretic compared to HFrEF patients.^{24,25,26} There is no effective treatment for reducing morbidity or mortality in HFpEF or HfmrEF patients.²⁷ Neuro-hormonal antagonists (ACEIs, ARBs, MRAs, and β -blockers) have been shown to improve survival in patients with HFrEF and are recommended for the treatment of every patient with HFrEF, unless contraindicated or not tolerated. Initiation and up-titration disease-modifying pharmacological therapy should be done immediately. In case of worsening of chronic HFrEF, every attempt should be made to continue evidence-based, disease-

modifying therapies, in the absence of haemodynamic instability or contra-indications.⁵ In HFrEF patients, treatment regimen of optimal dose of ACEI/ARB, β -blocker, and diuretic was correlated with improvement in hemodynamic congestion, NT-proBNP reduction of > 66%, and achievement of ePCWP < 16 mmHg at hospital discharge. In this study, all patients received β -blocker during hospitalization after they had not shown clinical congestion and had previously received ACEI/ARB and diuretic. β -blocker up-titration also performed during hospitalization. In this study, β -blocker up-titration was faster than the guideline recommendations⁵ or several previous studies.^{28,29,30} Our study supports the evidence that β -blocker initiation and up-titration during hospitalization are save for AHF patients as long as the clinical congestion has been resolved and the patients received optimal dose of ACEI/ARB and diuretics previously.

Our study has several limitations. First, single center study and the small number of samples cannot describe the real world conditions. Second, the short follow-up period makes it possible to provide biased results. Third, there were several confounding factors which were difficult to be managed that could exacerbate AHF and rehospitalization. Our study may be the first study using hemodynamic congestion measured by NT-proBNP level and ePCWP as the predictors of short-term clinical outcomes in AHF patients. We used very strict exclusion criteria to rule out comorbidities which can affect the result.

Table 5. Correlation between treatment regimen and the achievement of secondary endpoints in HFmrEF

		Optimal dose of ACEI/ARB + β -blocker + diuretic			r	P-value
		No	Yes	Total		
NT-proBNP reduction of > 66%	No	2(40%)	2(22,2%)	4(28,6%)	0,185	0,48
	Yes	3(60%)	7(77,8%)	10(71,4%)		
PCWP <16 mmHg	No	2(40%)	3(33,3%)	5(35,7%)	0,067	0,803
	Yes	3(60%)	6(66,7%)	9(64,3%)		
Hemodynamic congestion	No	2(20%)	7(77,8%)	9(64,3%)	0,353	0,158
	Yes	3(60%)	2(22,2%)	5(35,7%)		

ACEI = Angiotensin converting enzyme inhibitor; ARB = Angiotensin receptor blocker; ePCWP = Estimated pulmonary capillary wedge pressure; NT-proBNP = N-terminal pro B-type natriuretic peptide; HFmrEF = Heart failure with midrange ejection fraction

Table 6. Correlation between treatment regimen and the achievement of secondary endpoints in HFrEF

		Optimal dose of ACEI/ARB + β -blocker + diuretic			r	P-value
		No	Yes	Total		
NT-proBNP reduction of > 66%	No	5(100%)	3(21,4%)	8(42,1%)	0,574	0,02
	Yes	0(0%)	11(78,6%)	11(57,9%)		
PCWP <16 mmHg	No	5(100%)	5(35,7%)	10(52,6%)	0,493	0,013
	Yes	0(0%)	9(64,3%)	9(47,4%)		
Hemodynamic congestion	No	0(0%)	8(57,1%)	8(42,1%)	0,454	0,026
	Yes	5(100%)	6(42,9%)	11(57,9%)		

ACEI = Angiotensin converting enzyme inhibitor; ARB = Angiotensin receptor blocker; ePCWP = Estimated pulmonary capillary wedge pressure; NT-proBNP = N-terminal pro B-type natriuretic peptide; HFmrEF = Heart failure with reduced ejection fraction

Conclusion

Hemodynamic congestion assessed using NT-proBNP level and ePCWP at hospital discharge increased 30 day rehospitalization in AHF patients. Hemodynamic congestion can be considered as a therapeutic target in AHF patients during hospitalization. In HFrEF, improvements of hemodynamic congestion can be achieved by giving the treatment regimen of optimal dose of ACEI/ARB, β -blocker, and diuretic.

Ethical Clearance

This study had approved by Ethical Committee on Health Research of dr. Saiful Anwar General Hospital Malang with reference number: 400/02/K.3/302/2018.

Publication approval

The publication of this article has been approved by every party.

Conflict of Interest

None.

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List of Abbreviations

ACEI = Angiotensin converting enzyme inhibitor
 ARB = Angiotensin receptor blocker
 AHF = Acute heart failure
 AUC = Area under the curve
 CRT = Cardiac resynchronization therapy
 CKD = Chronic kidney disease
 COPD = Chronic obstructive pulmonary disease
 ePCWP = Estimated pulmonary capillary wedge pressure

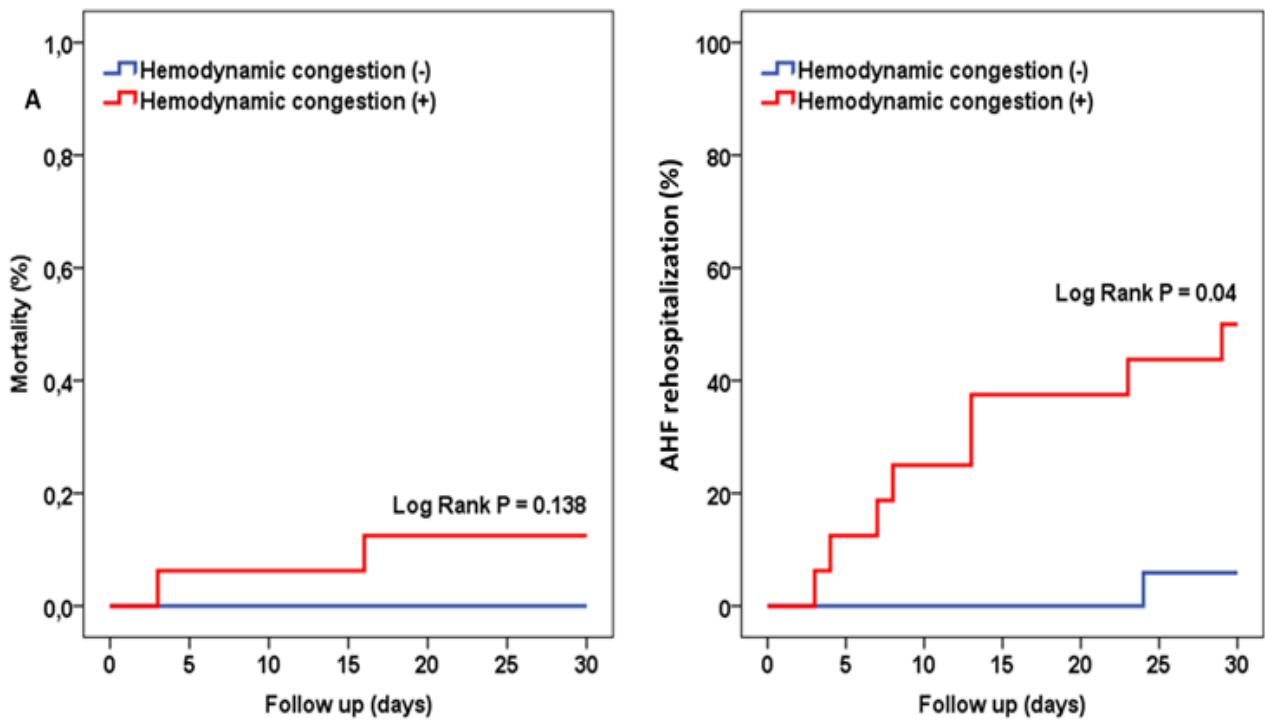


Figure 1. Kaplan-Meier Curve of 30 day cardiovascular mortality (A) and AHF rehospitalization (B)

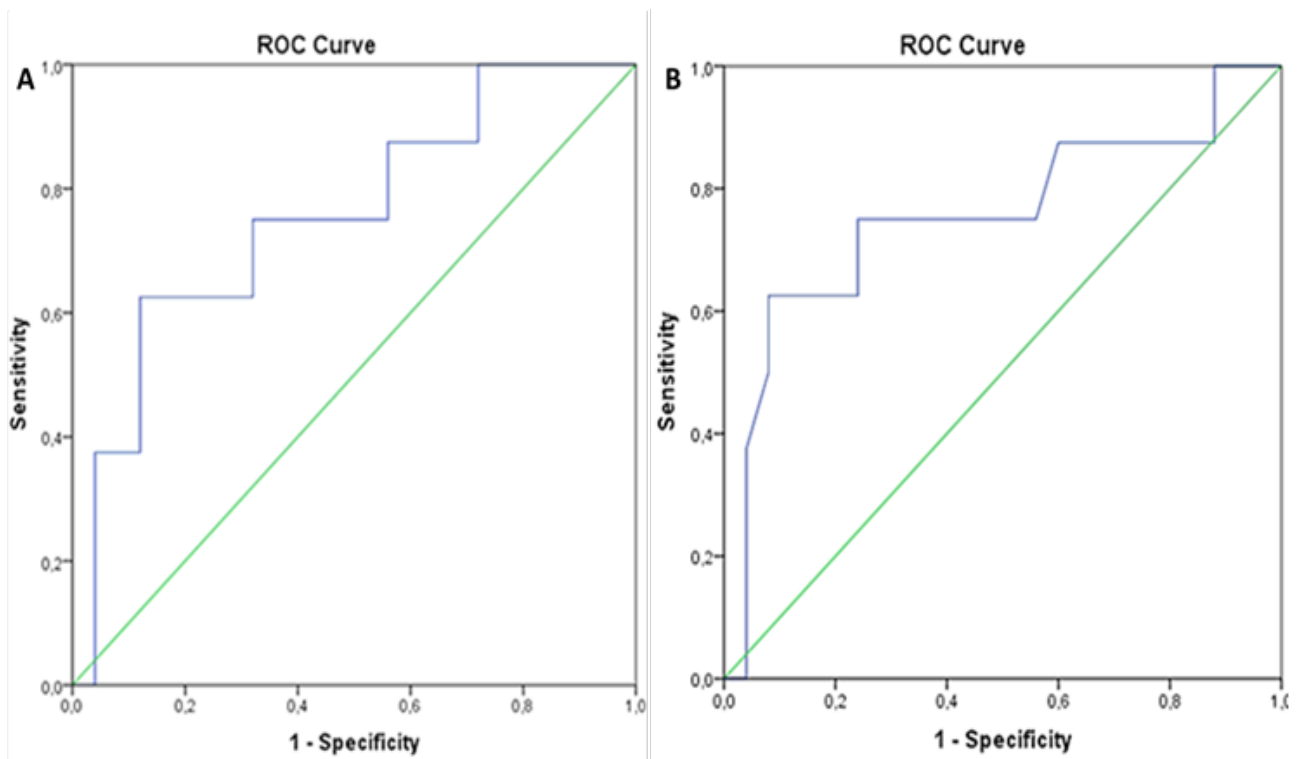


Figure 2. Receiver operating characteristic (ROC) to determine the NT-proBNP cut off. Single NT-proBNP value at hospital discharge (A) and NT-proBNP reduction during in-hospital treatment (B)

ER = Emergency room
 ESC = European society of cardiology
 HFmrEF = Heart failure with midrange ejection fraction
 HFrEF = Heart failure with reduced ejection fraction
 ICD = Implantable cardioverter defibrillator
 MRA = Mineralocorticoid receptor antagonist
 NT-proBNP = N-terminal pro B-type natriuretic peptide
 NYHA = New York heart association
 PCWP = Pulmonary capillary wedge pressure
 RISKESDAS = Riset kesehatan dasar
 ROC = Receiver operating characteristic
 TIA = Transient ischemic attack

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