A health economic evaluation of using N-terminal pro brain natriuretic peptide for the management of acute heart failure: A pilot study in an Indonesian tertiary referral hospital

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Abstract

Heart failure represents a major health problem and economic burden also in development countries such as Indonesia. Based on current guidelines, the use of natriuretic peptides can improve diagnosis, risk stratification, and decrease in hospital length of stay. However, mostly due to the related high costs, many Indonesian physicians currently do not routinely use these biomarkers in their daily clinical practice. By comparing the results of guidance with N-terminal pro brain natriuretic peptide (NT-proBNP) and without NT-proBNP, this pilot study was aimed to determine the clinical effectiveness and costs of using natriuretic peptides in the management of acute heart failure (AHF) patients admitted at National Cardiovascular Center Harapan Kita Hospital, a tertiary referral hospital in Jakarta, Indonesia.

This was a health economic evaluation using a single-blind, randomized controlled trial. AHF patients adjudicated following European Society of Cardiology guidelines were randomly assigned to the 2 groups: NT-proBNP group (group A) and control group (group B). In the group A, NT-proBNP level was obtained at admission and pre-discharge, with the target of achieving a decrease of ≥30%. Randomised patients were followed up to 90 days post-discharge to assess short-term outcomes and costs.

In total, one hundred and twelve patients were enrolled, of whom 56 were randomized in group A and 56 patients in group B. Compared to Group B, in Group A the total costs of patients management resulted to be significantly higher (P<0.05), while no significant difference between the 2 groups was observed for inhospital length of stay, total mortality rate, rehospitalization, and emergency department visits within 90 days post-discharge.

In this pilot study for the management of AHF at an Indonesian National Cardiovascular Center, the routine use of NT-proBNP compared to the non use, at hospital admission and discharge resulted into a significant increase of medical cost without any evident favourable impact on patients outcomes. Larger study in greater Asia Pacific populations should be performed to confirm these preliminary results.

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Introduction

Worldwide prevalence of heart failure is continuously increasing due to the extension in life expectancy leading to an increase in patients morbidity and mortality.[1,2] In the Asia Pacific region including Indonesia, hospitalized patients with acute heart failure (AHF) are of younger age and present more severe clinical condition when compared to United States (US).[3] This suggests a morbidity gap between heart failure patients in Asia Pacific compared to other regions.[3,4]

In addition to the prevalence, various studies indicate a rise of health problems associated with high rates of rehospitalization and death in patients with heart failure.[5] Data from the Acute Decompensated Heart Failure Registry (ADHERE)[6] demonstrated that in Asia Pacific region rehospitalization rates of heart failure patients is 29%, with inhospital and 30 days mortality rates 12%[6] and 17%,[7] respectively. Therefore, a comprehensive efforts to improve management of heart failure patients also in Indonesia is urgently required.

Current international guidelines[8] suggest evidence I-A for using natriuretic peptides (brain natriuretic peptide, BNP, N-terminal pro brain natriuretic peptide, NT-proBNP, or midregional

pro-atrial natriuretic peptide) in the diagnosis of heart failure. Therefore, the role of these biomarkers is well established *e.g.* to differentiate heart failure from other symptoms and diseases,[9] as well as to predict the onset of heart failure, and to stratify the patient's risk. Based on an individual patient meta-analysis, NT-proBNP-guided treatment of heart failure was reported to reduce all-cause mortality in patients aged <75 years and overall reduces heart failure and cardiovascular hospitalization.[10] In developed countries such as in Europe or United States, NT-proBNP is currently widely used.[11,12] Measurement of NT-proBNP was found to be useful to rule-out diagnosis and to predict prognosis of HF patients.[13] However, until now, the role of NT-proBNP to guide management of heart failure has not been applied routinely in Indonesia. Thus, we analysed in this pilot study, the role of NT-proBNP in AHF patients at the tertiary referral hospital, National Cardiovascular Center Harapan Kita (NCCHK), Indonesia in order to evaluate the cost benefit of AHF patients' management in this country.

Materials and Methods

This study was approved by the Institutional Review Board/Health Research Ethic of NCCHK. It was a prospective, randomized, single-blind, single-center, controlled pilot trial conducted between November 2017 and April 2018 at NCCHK. Health economic evaluation was performed alongside clinical trial. Samples size were 108 subjects (54 subjects per each group) which was set according to the difference between two sample proportion formula.

Inclusion criteria were: patients aging between 18-75 years; a primary diagnosis of AHF at the Emergency Department (ED) presentation; use of the national health insurance; willing to be followed for 3 months; willing to sign an informed consent. Exclusion criteria were: severe life-threatening comorbidities with a life expectancy of <2 years; acute pulmonary edema, acute heart failure in the setting of acute coronary syndrome, cardiogenic shock, right heart failure, and hypertensive heart failure; sepsis; liver disease; lung disease with severe radiological findings; mechanical complications of acute myocardial infarction, aortic dissection; congenital heart disease; idiopathic pulmonary hypertension; pulmonary embolism; severe respiratory failure; and severe burns; patients admitted to Intensive Cardiovascular Care Unit (ICVCU);and patients not compliant with therapy and controls. Diagnosis of heart failure at ED based on the Framingham criteria for the diagnosis of heart failure, consists of the concurrent presence of either two major criteria or one major and two minor criteria.[2]

Research subjects were consecutively recruited at NCCHK ED and randomly assigned into 2 groups: NT-proBNP group (group A) was managed based on NT-proBNP testing at admission and before discharge while control group (group B) was not managed based on the NT-proBNP testing.

Subjects assigned to group A had NT-proBNP measured at the ED in order to assess baseline level and prior to discharge to calculate the percent decline from baseline level. In this NT-proBNP group, the decision on whether patient could be discharged or not was determined by cardiologist in charge of the patient based on the clinical assessment then the NT-proBNP level was measured before discharge. Patients in group A were discharged if the NT-proBNP level decreased of ≥30% from baseline. If the target percent decline was not met, intensification of therapy according to the algorithm was performed.[14] On the contrary, patients in the group B were managed based on clinical judgment without the support of the use of NT-proBNP testing. In this control group, the decision on whether patient could be discharged or not was determined solely by cardiologist in charge of the patient based on the clinical assessment. At 90 days of follow-up period after hospital discharge, data on mortality and rehospitalization of the subjects in both groups were recorded. The frequency of visits to the ED and hospitalizations caused by worsening of chronic heart failure, and death were obtained from hospital information system and patients were interviewed over the telephone after 90 days. Data on direct medical costs were obtained from the billing of hospitalization. Direct non-medical and indirect costs were obtained from questionnaires and interviews with patients. We calculated the total cost and analyzed the cost comparison in both groups. The investigation was conducted according to the principles outlined in the Declaration of Helsinki.[15,16]

The research data were processed with Statistical Package for the Social Sciences version 24. Univariat analysis to test normality of data was performed using Kolmogorov-Smirnov test. If the data were normally distributed, the data were described as mean and standard deviation; if the data were not normally distributed, the data were described as median and minimum-maximum range. If the data were normally distributed, an independent T-test for comparing means between two groups was used. If the data distribution was not normal, an U Mann-Whitney test was performed. Comparison of the different proportions between two groups was done by Chi-square test. The significance level in this research is 5% (0.05). We evaluated the cost-efficiency by comparing clinical effectiveness with total cost which consists of direct medical costs, non-medical costs, and indirect costs. If clinical effectiveness of the two groups were equal, the cost comparison of the two groups was performed statistically by independent T-test or U Mann-Whitney test according to the normality of the data. If clinical effectiveness of the two groups were not equal, a cost effectiveness analysis was performed.

Results

A total of consecutive 134 subjects were recruited at the ED and then randomized using a website program (Figure 1). Of the 134 subjects, 22 subjects of which 13 subjects from group A and

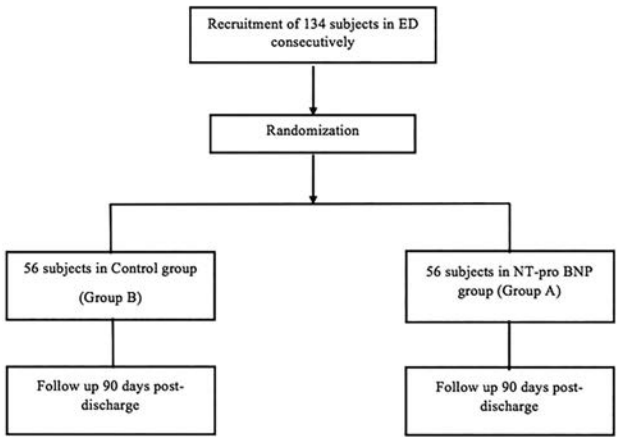

Figure 1. Subject selection and randomization. ED, emergency department. NT-proBNP, N-terminal pro brain natriuretic peptide.

9 subjects from group B, were excluded from the per protocol analysis because considered protocol-violators. Of these 22 subjects, 2 patients died in hospital, 1 patient was diagnosed with pulmonary tuberculosis, 2 patients deteriorated and were transferred to ICVCU, 1 patients was diagnosed with chronic kidney disease in hospital, 1 patient was diagnosed as having a *Grown up Congenital Heart Disease* in hospital, 2 patient resigned from the study, 1 patient discharged by his own request, 2 patients suffered ischemic stroke, 1 patient was diagnosed acute coronary syndrome in hospital, 1 patient was diagnosed with a malignancy in hospital, 6 patients were not compliant, and 2 patients were not reachable by phone. Thus, there were a total of 112 patients enrolled in the study, consisting of 56 patients in group B and 56 patients in group A, were included in the per protocol analysis.

Characteristics of the subject

Demographic characteristics and medical and comorbid characteristics can be seen in Tables 1 and 2. Characteristics of physical examination and diagnostic test and characteristics of hospital care can be seen in Tables S1 and S2 (in the Appendix).

Table 1. Demographic characteristics.

Variables	All Subjects (n=112)	NT-pro BNP group A (n=56)	Control Group B (n=56)	Value of P*
Age (years)	59.5 (19-75)°	57.4 ± 9.94#	60.0 (19-75)	0.850
Gender				0.589
Male [n(%)]	96 (85.7)	49 (87.5)	47 (83.9)	
Women [n(%)]	16 (14.3)	7 (12.5)	9 (16.1)	
Education				0.362
No school [n(%)]	2 (1.7)	0 (0.0)	2 (3.6)	
Elementary school not completed [n (%)]	8 (7.1)	4 (7.1)	4 (7.1)	
Elementary School [n(%)]	7 (6.2)	5 (8.9)	2 (3.6)	
Junior High School [n(%)]	9 (8.0)	2 (3.6)	7 (12.5)	
Senior High School [n(%)]	42 (37.5)	22 (39.3)	20 (35.7)	
Diploma [n(%)]	8 (7.1)	4 (7.1)	4 (7.1)	
Bachelor [n(%)]	26 (23.2)	15 (26.8)	11 (19.6)	
Master [n(%)]	8 (7.1)	4 (7.1)	4 (7,1)	
Doctoral [n(%)]	2 (1.7)	0 (0.0)	2 (3.6)	
Working status				0.102
Working [n(%)]	44 (39.2)	21 (37.5)	23 (41.1)	
Economic and Social Status				
Income per month Rp.0-1.500.000 [n(%)]	42 (37.5)	23 (41.1)	19 (33.9)	0.360
Emotional Support [n(%)]	103 (92)	51 (91.1)	52 (92.9)	0.782

NT-proBNP, N-terminal pro brain natriuretic peptide; Rp, Indonesian Rupiah. *Based on U Mann-Whitney test, Chi-Square test, or independent T test (according to data type and distribution), statistically significant when P value <0.05. °Median; range in parentheses (applies to similar values). #Average ± standard deviation (applies to similar values).

Table 2. Medical and comorbid characteristics.

Variables	All Subjects (n=112)	Group A (n=56)	Group B (n=56)	Value of P*
Comorbids				
CAP [n(%)]	18 (16.1)	11 (19.6)	7 (12.5)	0.303
Diabetes Mellitus [n(%)]	57 (50.9)	29 (51.8)	28 (50.0)	0.850
Hypertension [n(%)]	60 (53.6)	28 (51.8)	31 (55.4)	0.581
Smoking history [n(%)]	56 (50.0)	28 (50.0)	28 (50.0)	1.000
Atrial fibrillation [n(%)]	44 (38.9)	21 (37.5)	23 (41.1)	0.102
CRT [n(%)]	2 (3.6)	1 (1.8)	1 (1.8)	0.752
Medical characteristics				
History of hospitalization because of HF [n(%)]	53 (47.3)	26 (46.4)	27 (48.2)	0.850
NYHA Functional Class [n(%)]				0.123
Class III [n(%)]	94 (84.0)	50 (89.2)	44 (78.6)	
Class IV [n(%)]	18 (16.0)	6 (10.8)	12 (21.4)	
Treatment before admission to ED [n (%)]				
ACE inhibitor [n(%)]	44 (39.2)	23 (41.0)	21 (37.5)	0.237
Beta blocker [n(%)]	48 (42.9)	26 (46.4)	22 (39.3)	0.445
ARB [n(%)]	28 (25)	13 (23.2)	15 (26.8)	0.245
Diuretics [n(%)]	65 (58.0)	35 (62.5)	30 (53.6)	0.338
Etiology of heart failure				0.132
Coronary heart disease [n(%)]	89 (79.5)	47 (83.9)	42 (75.0)	
Hypertensive heart disease [n(%)]	15 (13.4)	4 (7.1)	11 (19.6)	
Cardiomyopathy [n(%)]	8 (7.1)	5 (8.9)	3 (5.4)	

CAP, community acquired pneumonia; CRT, cardiac resynchronization therapy; HF, heart failure; NYHA, New York Heart Association; ED, emergency department; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker. *Based on U Mann-Whitney, Chi-Square test, or independent T test (according to data type and distribution), significant when P value <0.05.

Comparison of N-terminal pro brain natriuretic peptide levels at admission and before discharge

The level of NT-proBNP at admission and before discharge in the Group A can be seen in Table S3 (in the Appendix).

In the group A, NT-proBNP levels was reduced of more than 30% from baseline in almost all subjects. Only one subject had decreased level of NT-proBNP less than 30%, then the therapy was optimized by increasing the dose of intravenous diuretic. NT-proBNP testing was recheck in the next day and NT-proBNP level finally decrease more than 30% from baseline. This subject was allowed to discharge. The percentage changes of NT-proBNP level in the Group A are shown in Table 3.

Assessment of clinical effectiveness

The parameters used to assess clinical effectiveness in this study were short-term outcomes of in hospital length of stay, rehospitalizations and visits to ED caused by worsening of heart failure, and death within 90 days post-discharge. These parameters were then compared between the two patient groups using Chi-Square test. The short-term outcomes of two groups are shown in Table 4.

Cost analysis

There are two components of cost that researcher calculated: the cost of hospitalization and the cost of rehospitalization (including visit to ED). Each of these costs was divided into three components: direct medical costs, direct non-medical cost, and indirect costs. Direct medical costs were divided into 4 components: laboratory test cost, radiology test cost, service cost, and room cost. The service cost consists of doctor visit fee, doctor consultation fee, medical treatment fee, and drug cost. Direct non-medical costs consist of patient and family transportation costs, accommodation cost, and consumption cost. Indirect costs were loss of patient and family income due to hospitalization.

The analysis used in this study was a partial health economic evaluation which compare total cost between group A and B. Comparative cost analysis was performed between the two groups using U Mann-Whitney test because the data were not normally distributed. The comparison of cost components between the NT-proBNP and control group are shown in Table 5.

Discussion

This randomized controlled trial was conducted in AHF patients who were hospitalized at NCCHK between November 2017 and April 2018. It was intended as supportive health economic information for the implementation of a new management method using biomarkers in Indonesia. The novelty of this research is the use of a societal economic perspective in cost calculation, where previous studies used the hospital and third party perspectives.[17-19]

Table 3. Changes in N-terminal pro brain natriuretic peptide (NT-proBNP) levels by cut-off of ≥ 30% decrease respect to baseline.

Variables	Number of subjects (n=56)
Decrease in NT-pro BNP before discharge ≥30% [n(%)]	55 (98.2%)
Decrease in NT-pro BNP before discharge <30% [n(%)]	1 (1.7%)
Increase in NT-pro BNP before discharge >30% [n(%)]	0

Table 4. Short-term outcomes.

Variables	Group A (n=56)	Group B (n=56)	Value of P
Length of stay (days)*	7 (3-21)	6 (3-20)	0.276
Visit to ED and rehospitalization rate within 90 days post discharge [n of patients (%)]	18 (32.1)	19 (33.9)	0.841
Death within 90 days post discharge [n of patients (%)]	1 (1.7)	1 (1,7)	1.0
Death, visit to ED, and rehospitalization rate within 90 days post discharge [n of patients(%)]	19 (33.9)	20 (35.7)	0.841

ED, emergency department. *Median; range in parentheses.

Table 5. Comparison of cost components between the N-terminal pro brain natriuretic peptide (NT-proBNP) and control group.

Variables	Control Group (n=56)	NT-pro BNP group (n=56)	Value of P
Hospitalization costs (Rp)	7,252,661 (3,946,766-37,468,915)*	8,900,023 (4,423,746-25,353,323)	0.033
1. Direct medical cost (Rp)	6,588,540 (3,866,766-37,218,915)	8,212,689 (3,623,746-24,553,323)	0.010
Radiology (Rp)	160,000 (0-1,020,000)	160,000 (0-860,000)	0.981
Room (Rp)	3,000,000 (800,000-13,500,000)	3,625,000 (1,500,000-10,000,000)	0.189
Laboratory (Rp)	1,185,000 (365,000-4,325,000)	1,896,500 (1,175,000-6,206,000)	0.000
Service (Rp)	2,440,782 (1,106,059-19,638,915)	2,612,549 (1,322,830-11,188,322)	0.091
2. Direct non-medical costs (Rp)	435,000 (80,000-3,000,000)	410,000 (80,000-1,400,000)	0.381
3. Indirect cost (Rp)	0 (0-2,000,000)	0 (0-3,400,000)	0.388
Costs due to rehospitalization and visit to ED (Rp)	18,712,536 (11,309,565-53,281,328)	22,751,630 (9,002,122-41,036,827)	0.749
1. Direct medical costs due to rehospitalization and visit to ED (Rp)	0 (0-52,751,328)	0 (0-39,636,827)	0.754
2. Direct non-medical costs due to rehospitalization and visit to ED (Rp)	0 (0-6,000,000)	0 (0-1,400,000)	0.887
3. Indirect costs of rehospitalization and visit to ED (Rp)	0 (0-2,000,000)	0 (0-3,400,000)	0.514
Total cost in 90 days (Rp)	8,886,083 (4,137,608-91,280,243)	10,271,610 (5,327,830-61,594,110)	0.254

Rp, Indonesian Rupiah.*Median; range in parentheses (applies to similar values).

Basic characteristics

In this study, patients were divided into two groups, the NT-proBNP group (group A) and the control group (group B). Both groups had the same demographic characteristics. Subjects in this study were mostly male (85.7%). The median age was 59.5 years. The basic characteristics of the subjects in this study are similar to those of previous studies.[11]

Comorbidities and medical characteristics of both groups were comparable. Confounding factors such as history of hospitalization, New York Heart Association (NYHA) functional class, and pharmacological treatment of heart failure were comparable between the two groups. Comorbidities that were predictors of rehospitalization such as hyponatremia and renal insufficiency were similar in the 2 groups. Several potential confounding factors were identified from the beginning, such as age, education level, low economic status, hyponatremia, diabetes mellitus, renal insufficiency, and and they were also similar in the 2 groups.

Characteristic of hospital care

In this study, patients in group A were discharged based of NT-proBNP level reduced of ≥30% compared from baseline. All subjects in group A met the target percent decline of NT-proBNP levels at discharge. This is accordance with study by Di Somma *et al.*,[20] that suggests the in hospital use of NT-proBNP monitoring starting after 24 hours of a conventional treatment until discharge in order to obtain a *humoral* stabilization of these patients. In this study, we did not evaluate the time-dependent course of patients attaining target from admission until discharge. Previous study by Stienen *et al*.[21] showed that a target ≥30% NT-proBNP reduction is gradually attained before discharge and rebound NT-proBNP increases to levels off-target occur in up to 33% of heart failure patients who initially attained target early during admission. In our pilot study, decrease of NT-proBNP level ≥30% at discharge was used solely as a parameter to determine whether the patients could be discharged or not and a predictor for short-term outcomes. Beyond NT-proBNP, Stojcevski *et al.*[22] had suggested to assess hemoglobin and NT-proBNP level together in order to detect the patients with higher risk of future death and rehospitalisation. In AHF patients, discharge anaemia is a strong predictor for short and long-term rehospitalisation. Santarelli *et al.*[23] also suggest to use combination of BNP and Bioelectrical Impedance Vector Analysis for detecting hydration status before discharge, to identify patients at high risk of death in the next 90 days after hospital discharge.

The median length of stay of all the subjects was 6 days. This is in accordance with data from ADHERE-International cohort, which showed the median length of stay of heart failure patients was 6 days.[3] The length of stay of the subjects in the NT-proBNP group was slightly longer than the control group (7 days *vs* 6 days) even though the difference is not statistically significant. One of the possible explanations for this lack of difference is the similarity of therapy in two groups.

Assessment of clinical effectiveness

The total amount of visits to ED and rehospitalization rate in this study population was 33.0% in the 90 days post-discharge follow-up. This result is similar to that from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) study, which showed the rate of rehospitalization in patients with heart failure was 30% at 60 to 90 days post discharge.[9] In the comparative analysis of the two groups, the result shows a similar median length of hospital stay and similar proportion of rehospitalizations, visits to ED, and death within 90 days post-discharge in both groups. This appears to be differ respect to previous studies; in fact Di Somma *et al.*[24] showed that serial measurements of natriuretic peptides levels seem to be useful for a better evaluation of clinical improvement during hospitalization. The different of our results with the Di Somma study could also be due to the different biomarker used since we used in this study NTproBNP, while Di Somma et at used BNP in their Italia Red study.[24] Meta-analysis have also shown that management with NT-proBNP guidance can decrease rehospitalization, one of the underlying reasoning possibly being the more intensive medical therapy in the NT-proBNP group compared with the control group.[12] In our pilot study, the intensity of therapy in both groups was comparable and this could provide a reason for the discrepant results from our study results respect to previous published papers.

Cost analysis

The cost analysis result showed that hospitalization cost was higher in group A than in group B. A cost comparison analysis was conducted to observe the difference of each cost component. Comparison of total cost between NT-proBNP and control group showed that there was no statistically significant difference (Indonesian Rupiah, Rp 10,271,610 compared to Rp 8,886,083, P=0.254). This was due to the same number of visits to the ED and rehospitalizations in the NT-proBNP and control groups.

Hospitalization cost showed a significant difference between two groups, being the hospitalization cost in NT-proBNP group higher than in the control group (Rp 8,900,023 compared to Rp.7,252,661, P<0.05). Cost component which was significantly different between the NT-proBNP group and the control group was represented by the direct medical costs. The direct medical costs of the NT-pro BNP group were higher than those of the control group (Rp 6,588,540 compared to Rp 8,212,689, P<0.05). The cost driver of direct medical costs that was significantly different between the two groups was the laboratory cost. Median laboratory costs were higher in the NT-pro BNP group than in the control group (Rp 1,185,000 compared to Rp 1,896,500, P<0.05). Laboratory costs in the NT-proBNP group were higher because of the price of NT-proBNP testing at NCCHK (Rp. 270,000/single test) and performed at least 2 times in each subject of Group A. The standard management at NCCHK does not currently include NT-proBNP or other HF biomarkers testing in AHF patients. Use of NT-proBNP, although initially expensive would be expected to improve clinical outcomes in AHF patients. In our pilot study, the expected improved outcomes with the use of NT-proBNP were not observed probably because at NCCHK the standard management of AHF patients without biomarkers use was comparable to the NT-proBNP-guided management. The results from this pilot analysis seem to reject the hypothesis that management with NT-proBNP guidance in Indonesia is more economically efficient than the standard management, as previously found in an European study.[25] There are several limitations of this study. Patients were from single health care facility (NCCHK) which is a tertiary referral hospital and a teaching hospital. The results may therefore not be generalized to other health services in Indonesia. Some of the data regarding direct non-medical cost and indirect costs were obtained from questionnaires filled out by the patients before discharge. This can lead to misperceptions by research subjects so that the data obtained may be inappropriate. Serial examination of lab parameters and echocardiography routinely at discharge, including close monitoring of NT-proBNP level, could not be done due to limitation in insurance coverage. The use of NT-proBNP was not driven taking into account the caveats of this biomarkers such as renal dysfunction or obesity or the presence of atrial fibrillation.

Conclusions

In this pilot study on the standard management of AHF in tertiary referral hospital in Indonesia, the use of NT-proBNP guidance was not economically more efficient than the no use of the biomarker. On the other side the direct medical costs for the management of AHF patients, based on NT-proBNP, resulted to be higher than the control group, with the cost driver being the laboratory cost. These results could not be generalized to other hospitals with different characteristics from NCCHK, which is a tertiary referral hospital. Additional studies in a larger cohort of patients comparing data from Indonesia to other Asia Pacific countries should be performed in order to confirm our preliminary results.

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