The Added Value of Bioimpedance Analysis to NT-proBNP in Predicting Short-term outcome in Acute Heart Failure Patients

Putri Annisa Kamila1*, Mohammad Saifur Rohman1,2, Setyasih Anjarwani2, Djanggan Sargowo2, Anna Fuji Rahimah2, Indra Prasetya2, Muhammad Rizki Fadlan1, Salvatore Di Somma3

1 Brawijaya Cardiovascular Research Center, Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia
2 Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Brawijaya – dr. Saiful Anwar General Hospital, Malang, Indonesia.
3 University La Sapienza Rome, Sant’Andrea Hospital, President GREAT Network Italy, Rome, Italy

ARTICLE INFO

Keywords:
Acute Heart Failure;
NT-proBNP;
Bioimpedance Analysis;
Total Body Water

ABSTRACT

Background: Acute heart failure (AHF) is a significant clinical problem, which has a high prevalence, mortality, and rehospitalization. Congestion is critical in the pathogenesis of AHF, which is also a predictor of mortality and rehospitalization in patients with AHF.

Objective: Knowing the effect of adding a %Total body water (TBW) test detected by Bioimpedance Analysis to NT-proBNP as a short-term clinical outside predictor of patients with acute heart failure

Method: This research is an analytical observational study using prospective cohort methods. The research was conducted at Dr. Saiful Anwar Malang Hospital in January 2018-July 2019 with research subjects taken consecutively against all AHF patients hospitalized at RSUD dr. Saiful Anwar Malang. The data were taken in the form of NT-proBNP value during mission and %TBW before the patient leaves the hospital detected with NICaS examination. 90 days follow-up was conducted via phone calls to the patients, to evaluate the patient's follow-up for cardiovascular death and rehospitalization.

Results: This study involved 65 subjects who were on average 61 years old and the majority male. Non-survivor patients had a higher NYHA class, NT-proBNP, and %TBW pre-discharge than the survivor group. Based on a statistical analysis we found that the ROC curve shows NT-proBNP is a good predictor of mortality (HR: AUC 0.74; 95%CI 0.59-0.90) and rehospitalization (HI: AUC 0.88; 95%CI 0.78-0.97). Similarly, %TBW pre-discharge shows good predictors of mortality (HI: AUC 0.72, 95%CI 0.56-0.87) and rehospitalization (HI: AUC 0.83, 95%CI 0.73-0.94). The addition of the %TBW pre-discharge parameter to NT-proBNP results in the best predictor numbers among the three for both mortality (HI: AUC 0.84; 95%CI 0.72-0.96) and rehospitalization (HI: AUC 0.92; 95%CI 0.85-1.00).

Conclusion: The addition of pre-discharge %TBW examination detected by a bioimpedance analysis tool to NT-pro BNP at admission, increases the predicted value of short-term clinical outpatient in the form of mortality and rehospitalization of patients with acute heart failure.

1. Introduction

Acute heart failure (AHF) is a serious clinical problem that has led the patient to seek acute care and requiring urgent diagnosis, facilitating a treatment decision that is appropriate to the particular AHF mechanism.1 Furthermore, in-hospital mortality rates are higher after discharge, ranging from 4% to 8%, are estimated to be 8-15% by 3 months, and are followed by regular rehospitalizations (30-38 percent at 3 months).2,3

The presence of signs and symptoms of systemic and pulmonary congestion is the product of AHF clinical features.4 The main feature in the pathogenesis of AHF is congestion or fluid overload, and it is present in most patients admitted to this disease. Its severity was related to the prognosis of acute heart failure patients.5 Moreover, congestion is both a cause and an effect of worsening cardiovascular function in heart failure. As a result of elevated ventricular wall tension, these pathophysiological alterations relate to clinical deterioration and brain natriuretic peptide (BNP) secretion.6 For all these concerns, in order to avoid this progressive hemodynamic pathway, AHF therapy is undertaken and, as a result, decongestion is an important priority in the care of these patients.7 Nearly half of hospitalized AHF patients, however, are discharged with chronic congestion signs and symptoms, and this is of considerable prognostic importance because the capacity to keep patient congestion-free will define a good survival population.8 The objective of this study is to investigate the additional prognostic power of combining congestion status detected by bioimpedance analysis (BIA) to standardized NT-proBNP.

2. Method

2.1 Study Design

*Corresponding author at: Brawijaya Cardiovascular Research Center, Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia
E-mail address: putriannisamd@gmail.com (P.A. Kamila).

https://doi.org/10.21776/ub.hsj.2021.002.01.06
Receive 25 January 2021; Received in revised form 1 February 2021; Accepted 15 February 2021
Available online 28 February 2021
2214-5400/ ©UB Press. All rights reserved.
This is an observational analytic, with cohort prospective study. The sample of this study were patients with acute heart failure (AHF) presenting and admitted to Saiful Anwar General Hospital Malang. The inclusion criteria were: patients with age > 40 years old, who admitted with dyspnea due to AHF or symptoms linked to AHF, with hospitalization predicted. According to European Society of Cardiology standards, each patient got routine treatment and BIA values were blinded to the physicians. Exclusion criteria were pregnancy, patient with malignancy or terminally ill with life expectancy less than 6 months, and patients who were discharged without beta-blockers or ACE inhibitor. The final diagnosis of AHF was made according to the recent guideline. Upon arrival at the ED, a blood examination for NT-proBNP was carried out for every patient. After that, the sample was sent to the central laboratory and was analyzed with a sandwich-type electrochemiluminescence sensor. We used a bioelectrical impedance analyzer, to analyze the percentage of total body water (TBW) of the patients, at the time before discharge (pre-discharge). TBW was measured non-invasively using NICA (Non-Invasive Cardiac System, Ni Medical Ltd., Singapore), bedside at supine position. Without contact with metal and with abducted inferior limbs at 45 degrees and with abducted superior limbs at 30 degrees to prevent contact with the flesh. A phone call follow-up was conducted 90 days after hospital discharge to assess the follow-up of the patient for coronary mortality and rehospitalization.

### 4. Discussion

Both BIA and BNP are presently used as valid methods for managing patients with AHF.\(^9,10\) Two facets of the same pathophysiological pathway are reflected: BNP is released due to elevated clinical congestion.

#### Table 2. Patients condition and treatment at pre-discharge

| Variable          | Non Survivor | Survivor | p     |
|-------------------|--------------|----------|-------|
| & n=12            | & n=53       |          |       |
| Dioxide (%)       | 0%           | 0%       | -     |
| Ortopnea (%)      | 0%           | 0%       | -     |
| PND (%)           | 0%           | 0%       | -     |
| GCS, mean ± SD    | 15.0±0.00    | 15.0±0.00| 1     |
| SBP mmHg, mean ± SD | 122.40±14.72 | 120.22±12.81 | 0.52 |
| DBP mmHg, mean ± SD | 72.35±12.83 | 70.49±8.20 | 0.68 |
| MAP mmHg, mean ± SD | 89.62±11.41 | 85.19±7.35 | 0.15 |
| HR x/minute, mean ± SD | 76.7±2.38 | 76.94±6.22 | 0.94 |
| RR x/minute, mean ± SD | 19.71±1.06 | 19.36±0.93 | 0.25 |
| S3 (%)           | 0%           | 0%       | -     |
| Asctes (%)        | 0%           | 0%       | -     |
| Hepatomegaly (%)  | 0%           | 0%       | -     |
| Leg Edema (%)     | 0%           | 0%       | -     |

#### Table 1. Baseline characteristics of patients with 90 days mortality.

| Variable          | Non Survivor | Survivor | p     |
|-------------------|--------------|----------|-------|
| & n=12            | & n=53       |          |       |
| Age (years), mean ± SD | 60.6±11.8   | 61.6±12.1 | 0.79  |
| Male (%)          | 66.5±8.5     | 68.9±8.7 | 0.60  |
| Orthopnea (%)     | 93.3%(11/12) | 94.9%(50/53) | 0.27  |
| PND (%)           | 66.7%(8/12)  | 69.8%(37/53) | 0.83  |
| NYHA IV           | 71.4%        | 35.3%    | 0.03  |
| SBP mmHg, mean ± SD | 136.4±26.4  | 141.8±33.2 | 0.60  |
| DBP mmHg, mean ± SD | 83.66±19.9  | 84.05±14.6 | 0.93  |
| MAP mmHg, mean ± SD | 101.2±20.8  | 103.3±19.8 | 0.74  |
| SaO2 %, mean ± SD | 97.3±1.6     | 97.0±1.4  | 0.65  |
| JVP cmH2O, mean ± SD | 9.2±1.0     | 9.1±0.96  | 0.70  |
| Rales %           | 57.8%        | 15.7%    | 0.005 |
| S3 (%)           | 20.0%        | 28.8%    | 0.78  |
| Leg Edema (%)     | 12(80.0%)    | 41 (87.2%) | 0.78  |
| Atrial fibrillation (%) | 20.0%(3)   | 12.8%(6)  | 0.78  |
| CTR %, mean ± SD | 72.94±5.95   | 69.71±4.82 | 0.31  |
| Alveolar congestion (%) | 33.3%     | 29.8%    | 0.91  |
| Pleural Effusion (%) | 20%         | 28.9%    | 0.78  |
| EF biplane %, mean ± SD | 41.4±11.2   | 40.0±13.3 | 0.72  |
| %TBW discharge    | 80.9±11.4    | 57.1±14.6 | 0.000 |
| NT-proBNP on admission pg/ml, mean ± SD | 14210±1237 | 5075±740 | 0.015 |
| Sodium            | 138.4±3.9    | 138.2±4.0 | 0.88  |
| Potassium         | 3.9±0.4      | 4.0±0.7  | 0.63  |
| Creatinin mg/dl, (>1.6 mg/dl (%)) | 57% | 21.6% | 0.024 |
| eGFR (ml/minutes/1.73 m2, mean ± SD) | 73.6±17.7 | 72.5±25.8 | 0.89 |
| Hemoglobin g/dl, mean + SD | 12.5±2.0 | 13.6±1.7 | 0.37 |

differences in medical therapy during hospitalization between survivors and non-survivors. All patients were discharged without any sign of clinical congestion.

From the univariate analysis, NYHA, serum creatinine, rales, percentage TBW at discharge, and NT-proBNP admission are significantly associated with 90 days mortality and rehospitalization. At multiple regression analysis, only NT-proBNP admission and percentage TBW predischarge maintain statistical significance (Table 3). ROC analysis shows that percentage TBW pre-discharge is a predictor of death and rehospitalization (respectively, AUC : 0.72, 95% CI 0.56 – 0.875 p<0.001 and AUC: 0.83, 95% CI 0.726 – 0.940 p<0.001). NT-proBNP also shown to be a predictor of death and rehospitalization from ROC analysis (respectively AUC: 0.74, 95% CI 0.586 – 0.893, p< 0.001 and AUC: 0.88, 95% CI 0.784 – 0.972 p< 0.001). However, combining percentage of TBW predischarge to NT-proBNP admission show the best prognostic value for mortality and rehospitalization (respectively, AUC: 0.84, 95% CI 0.72 – 0.96 p<0.001 and AUC: 0.92, 95% CI 0.85 - 1.00 p<0.001). The combination of these two shows better prognostic power compared to each parameter alone.

#### 2.2 Statistical Analysis

Data were analyzed with SPSS 22 Software. Univariate analysis was performed for baseline characteristics. A bivariate analysis was performed for baseline characteristics. A univariate analysis shows that percentage TBW pre-discharge is a predictor of 90 days mortality and rehospitalization. At multiple regression analysis, only NT-proBNP admission and percentage TBW predischarge maintain statistical significance (Table 3). ROC analysis shows that percentage TBW pre-discharge is a predictor of death and rehospitalization (respectively, AUC : 0.72, 95% CI 0.56 – 0.875 p<0.001 and AUC: 0.83, 95% CI 0.726 – 0.940 p<0.001). NT-proBNP also shown to be a predictor of death and rehospitalization from ROC analysis (respectively AUC: 0.74, 95% CI 0.586 – 0.893, p< 0.001 and AUC: 0.88, 95% CI 0.784 – 0.972 p< 0.001). However, combining percentage of TBW predischarge to NT-proBNP admission show the best prognostic value for mortality and rehospitalization (respectively, AUC: 0.84, 95% CI 0.72 – 0.96 p<0.001 and AUC: 0.92, 95% CI 0.85 - 1.00 p<0.001). The combination of these two shows better prognostic power compared to each parameter alone.
percentage TBW at discharge, and NT-proBNP admission are significantly associated with 90 days mortality and rehospitalization. At multiple regression analysis, only NT-proBNP admission and percentage TBW predischarge maintain statistical significance (Table. 3). ROC analysis shows that percentage TBW pre-discharge is a predictor of death and rehospitalization (respectively, AUC : 0.72, 95% CI 0.56 – 0.87.5 p<0.001 and AUC: 0.83, 95% CI 0.726 – 0.940 p<0.001). NT-proBNP also shown to be a predictor of death and rehospitalization from ROC analysis (respectively AUC: 0.74, 95% CI 0.586 – 0.893, p< 0.001 and AUC: 0.88, 95% CI 0.784 – 0.972 p< 0.001). However, combining percentage of TBW predischarge to NT-proBNP admission show the best prognostic value for mortality and rehospitalization (respectively, AUC : 0.84, 95% CI 0.72 – 0.96 p<0.001 and AUC: 0.92, 95% CI 0.85 - 1.00 p<0.001). The combination of these two shows better prognostic power compared to each parameter alone.

4. Discussion

Both BIA and BNP are presently used as valid methods for managing patients with AHF.9,10 Two facets of the same

| Table. 3. Multivariate Analysis | OR   | Sig   |
|-------------------------------|------|-------|
| TBW % pre-discharge           | 4.230| 0.049 |
| NT-proBNP admission           | 5.817| 0.010 |
| NT-proBNP admission + TBW % pre-discharge | 10.23 | 0.005 |
| NYHA Class IV                 | 1.2  | 0.213 |
| Rales                         | 1.2  | 0.499 |
| Creatinine Serum              | 2.09 | 0.899 |

From the univariate analysis, NYHA, serum creatinine, rales, and differences in medical therapy during hospitalization between survivors and non-survivors. All patients were discharged without any sign of clinical congestion.

Table 1. Baseline characteristics of patients with 90 days mortality.

![Figure 1](A) ROC curve of NT-proBNP at admission to 90 days mortality. (B) ROC curve of NT-proBNP at admission to 90 days rehospitalization

![Figure 2](A) ROC curve of pre-discharge %TBW to 90 days mortality. (B). ROC curve of pre-discharge %TBW to 90 days rehospitalization
pathophysiological pathway are reflected: BNP is released due to elevated ventricular filling pressure and wall tension, while BIA variables reflect changes in body hydration of the failing cardiovascular system. BNP alone, however, may not indicate pathophysiological congestion mechanisms, and other congestion indicators can be useful in determining congestion and risk stratification in patients with HF. BIA is a quick and easy tool for the evaluation of body peripheral hydration status among emerging strategies, offering prognostic information in HF patients.

A recent study has shown that bioimpedance analysis expressed in hydration status or total body water was related to NT-proBNP and CVP. In a recent analysis of the literature, Oremus et al. indicate that NT-proBNP in both decompensated and chronic healthy HF populations is correlated with all-cause mortality and composite outcome. There is, however, insufficient evidence in the literature that NT-proBNP contributes incremental importance to other prognostic variables in the short and long-term estimation of all-cause and cardiovascular mortality. Instead, when used in conjunction with BIA, NT-proBNP was more predictive of death and rehospitalization in our study. As for BIA variables at discharge, our analysis shows that with a chronic state of congestion, certain HF patients are discharged. Their detection is important since these patients are those at increased risk of death and rehospitalization for 90 days.

The role of BIA in detecting congestion and latent fluid overload, Valle et al. showed that it has better diagnostic sensitivity compared to other parameters such as fluid balance, and it also demonstrates an emerging role in the prognostic significance. A previous study by Santarelli et al. indicates that the elimination of congestion observed by BIA during hospitalization of AHF patients is correlated with an improvement in the outcome of patients. Donner Alves et al., who identify incremental improvements in hydration status during diuretic treatment in hospitalized AHF patients, demonstrate the same outcome. Instead, BIA prognostic significance before discharge was measured in this study. It was performed taking into account that clinical symptoms of congestion are frequently absent at this point as a result of diuretic treatment, and clinical judgment may not be accurate.

This study offers valuable knowledge from this point of view that BIA analysis is beneficial as it facilitates the detection of certain patients that have subclinical congestion, and this could aid doctors in determining the discharge of the patient. Moreover, our findings support the effectiveness of BNP in the risk stratification of patients who presented to ED with AHF, but the most crucial and newest element is obtained from the combined use of NT-proBNP and BIA.

The previous study shows NT-proBNP and BIA can be very helpful in the diagnosis, but also the clinical care of patients with AHF. This research expands these results, showing that they would have a poorer result when AHF patients are discharged with a chronic congestive state, even if clinically latent.

The limitations of this study are the sample size due to only a single center was involved in our study and the period of follow-up was quite short to rule-out biases.

**Conclusion**

Our study shows that in AHF patients, adding hydration status, measured as a percentage of total body water by bioimpedance analysis device before hospital discharge, to admission NT-proBNP increases short-term prediction for mortality and rehospitalization in acute heart failure patients.

**Declarations**

7.1. Ethics Approval and Consent to participate
Patient has provided informed consent prior to involve in the study.

7.2. Consent for publication
Not applicable.

7.3. Availability of data and materials
Data used in our study were presented in the main text.

7.4. Competing interests
Not applicable.

7.5. Funding source
Not applicable.

7.6. Authors contributions
Idea/concept: PAK. Control/supervision: DS, MSR, SA, IP, SDS. Literature review: PAK. Writing the article: PAK, MRF. Critical review: DS, MSR, SA, IP, SDS. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

7.7. Acknowledgements
We thank to Brawijaya Cardiovascular Research Center.
References

1. Ural D, Çavuşoğlu Y, Eren M, et al. Diagnosis and management of acute heart failure. 2016;15:860.

2. Moser DK, Frazier SK, Worrall-Carter L, et al. Symptom variability, not severity, predicts rehospitalization and mortality in patients with heart failure. 2011;10:124-9.

3. Adams Jr KF, Fonarow GC, Emerman CL, et al. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). 2005;149:209-16.

4. Colombo PC, Doran AC, Onat D, et al. Venous congestion, endothelial and neurohormonal activation in acute decompensated heart failure: cause or effect? 2015;12:215-22.

5. Tubaro M, Vranckx P, Price S, Bonnefoy E, Vrints C. The ESC textbook of intensive and acute cardiovascular care: Oxford University Press, USA; 2021.

6. Oremus M, McKelvie R, Don-Wauchope A, et al. A systematic review of BNP and NT-proBNP in the management of heart failure: overview and methods. 2014;19:413-9.

7. Shakar SF, Lindenfeld JJ. Treatment approaches to congestion relief in acute decompensated hf: insights After DOSE-AHF and CARRESS-HF. 2014;16:330.

8. Gheorghiade M, Filippatos G, De Luca L, Burnett JJ. Congestion in acute heart failure syndromes: an essential target of evaluation and treatment. 2006;119:S3-S10.

9. Valle R, Aspromonte N, Milani L, et al. Optimizing fluid management in patients with acute decompensated heart failure (ADHF): the emerging role of combined measurement of body hydration status and brain natriuretic peptide (BNP) levels. 2011;16:519-29.

10. Di Somma S, Navarin S, Giordano S, et al. The emerging role of biomarkers and bio-impedance in evaluating hydration status in patients with acute heart failure. 2012;50:2093-105.

11. Di Somma S, Lukaski H, Codognotto M, et al. Consensus paper on the use of BIVA (Bioelectrical Impedance Vector Analysis) in medicine for the management of body hydration. 2011;7:6-14.

12. Massari F, Iacoviello M, Scicchitano P, et al. Accuracy of bioimpedance vector analysis and brain natriuretic peptide in detection of peripheral edema in acute and chronic heart failure. 2016;45:319-26.

13. Massari F, Scicchitano P, Iacoviello M, et al. Multiparametric approach to congestion for predicting long-term survival in heart failure. 2020;75:47-52.

14. Di Somma S, Lalle I, Magrini L, et al. Additive diagnostic and prognostic value of bioelectrical impedance vector analysis (BIVA) to brain natriuretic peptide ‘grey-zone’in patients with acute heart failure in the emergency department. 2014;3:167-75.

15. Kociol RD, McNulty SE, Hernandez AF, et al. Markers of decongestion, dyspnea relief, and clinical outcomes among patients hospitalized with acute heart failure. 2013;6:240-5.

16. Lucas C, Johnson W, Hamilton MA, et al. Freedom from congestion predicts good survival despite previous class IV symptoms of heart failure. 2000;140:840-7.

17. De Berardinis B, Magrini L, Zampini G, et al. Usefulness of combining galectin-3 and BIVA assessments in predicting short-and long-term events in patients admitted for acute heart failure. 2014;2014.

18. Santarelli S, Russo V, Lalle I, et al. Usefulness of combining admission brain natriuretic peptide (BNP) plus hospital discharge bioelectrical impedance vector analysis (BIVA) in predicting 90 days cardiovascular mortality in patients with acute heart failure. 2017;12:445-51.

19. Alves FD, Souza GC, Aliti GB, Rabelo-Silva ER, Clausell N, Biolo AJN. Dynamic changes in bioelectrical impedance vector analysis and phase angle in acute decompensated heart failure. 2015;31:84-9.