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IM - ORIGINAL

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

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Abstract Heart failure is a disease characterized by high prevalence and mortality, and frequent rehospitalizations. The aim of this study is to investigate the prognostic power of combining brain natriuretic peptide (BNP) and congestion status detected by bioelectrical impedance vector analysis (BIVA) in acute heart failure patients. This is an observational, prospective, and a multicentre study. BNP assessment was measured upon hospital arrival, while BIVA analysis was obtained at the time of discharge. Cardiovascular deaths were evaluated at 90 days by a follow up phone call. 292 patients were enrolled. Compared to survivors, BNP was higher in the non-survivors group (mean value 838 vs 515 pg/ml, $p < 0.001$). At discharge, BIVA shows a statistically significant difference in hydration status between survivors and non-survivors [respectively, hydration index (HI) 85 vs 74, $p < 0.001$; reactance (Xc) 26.7 vs 37, $p < 0.001$; resistance (R) 445 vs 503, $p < 0.01$)]. Discharge BIVA shows a prognostic value in predicting cardiovascular death [HI: area under the curve (AUC) 0.715, 95% confidence interval (95% CI) 0.65–0.76; $p < 0.004$; Xc: AUC 0.712, 95% CI 0.655–0.76, $p < 0.007$; *R*: AUC 0.65, 95% CI 0.29–0.706, $p < 0.0247$]. The combination of BIVA with BNP gives a greater prognostic power for cardiovascular mortality [combined receiving operating characteristic (ROC): AUC 0.74; 95% CI 0.68–0.79; $p < 0.001$]. In acute heart failure patients, higher BNP levels upon hospital admission, and congestion detected by BIVA at discharge have a significant predictive value for 90 days cardiovascular mortality. The combined use of admission BNP and BIVA discharge seems to be a useful tool for increasing prognostic power in these patients.

Keywords Acute heart failure · Brain natriuretic peptide · Bioelectrical impedance vector analysis · Prognosis

Introduction

Despite all available therapies and drugs, acute heart failure (AHF) incidence remains unacceptably high worldwide [1]. AHF clinical features are due to the appearance of signs and symptoms of systemic and pulmonary congestion [2]. In heart failure, congestion is, at the same time, a cause and a consequence of worsening cardiovascular function. The activation of the neurohormonal system causes fluid redistribution and accumulation, increases systemic resistance, and reduces capacitance in large veins, with consequent increased after load and preload which cannot be tolerated by the failing heart. These pathophysiological changes lead to clinical decompensation and to brain natriuretic peptide

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(BNP) release as a consequence of the increased ventricular wall tension [2, 3]. For all these reasons, AHF treatment is finalized to stop this progressive hemodynamic course, and as a consequence, decongestion is an important target in the management of these patients [4]. However, approximately, 50% of patients admitted for AHF are discharged with persistent signs or symptoms of congestion [5], and this is of great prognostic significance considering that the ability to maintain a patient free from congestion identifies a population with good survival [6, 7]. The aim of this study is to investigate the ability of BNP and bioelectrical impedance vector analysis (BIVA) to identify patients at risk for 90 days cardiovascular death from hospital discharge.

Materials and methods

This was a prospective observational study in AHF patients presenting to different Emergency Departments (EDs) included into the GREAT Network in Italy, Sant'Andrea University Hospital in Rome, Novara University Hospital, Padova University Hospital, and in two centers in Brazil (Fluminense Federal University Department of Cardiology, and Hospital Unimed Rio, from January 2013 to January 2015.

The inclusion criteria were: ED admission for dyspnea or symptoms linked to AHF, with expected hospitalization. Each patient received standard of care according to European Society of Cardiology guidelines [8], and physicians were blinded to BIVA values. Exclusion criteria were: psychogenic dyspnoea, post-traumatic dyspnoea, pneumothorax, major surgery, coronary artery disease, ascites, edema secondary to venous disease, lymphedema, hypoalbuminemia, body temperature >38 °C, amputation of limbs, burns, patients younger than 18 years, and patients who were unable to give an informed consent. The research protocol was reviewed by the human research Committee from Sant'Andrea Hospital in Rome as coordinating center, and it was consequently approved in all participating centers. Informed written consent was obtained from patients before enrollment. The study protocol conformed to the ethical guidelines of the Declaration of Helsinki. The final diagnosis of AHF was made according to recent guidelines [8]. 90 days after hospital discharge, a telephone call follow up was performed to evaluate the patient's follow-up for cardiovascular death. The aim of this study is to evaluate BIVA and BNP prognostic value in identifying patients who have more risk for subsequent death. On the basis of follow-up results, we divided AHF population into two groups: survivors and non-survivors.

BIVA evaluation

We used a bioelectrical impedance analyzer, a single 50 kHz frequency (EFG, Akern, Florence, Italy). The BIVA measurement assessed at the time of patients' discharges from the hospital was performed at bedside, with the patient supine, without metal contacts and with inferior limbs abducted at 45° and superior limbs abducted at 30° to avoid skin contacts. Four skin electrodes were applied (two on the wrist and two on the ipsilateral ankle) maintaining a minimal inter-electrode distance of 5 cm. The device uses an alternating current flux of 800 μA and an operating frequency of 50 kHz. The results were visualized in two ways: as a bivariate impedance vector, or as a BIVA-derived hydration percentage. The first method includes a direct impedance plot that measures resistance (*R*) and reactance (Xc), as a bivariate vector in a nomogram (*R*/Xc graph) [9]. Reference values [10, 11], stratified for classes of age, BMI, and gender are plotted as tolerance ellipses in the same coordinate system. Reference intervals are plotted as three tolerance ellipses, and are distinguished corresponding to the 50th, 75th, and 95th vector percentile of the healthy reference population [11, 12]. The major axis of this ellipse indexes hydration status, and the minor axis reflects tissue mass. The second method expresses the state of hydration as a percentage called hydration index (HI) [12]. This value is calculated by an independently determined equation that uses the two components of BIVA, R and Xc. HI normal value is between 72.7 and 74.3%, corresponding to the 50th percentile [12, 13]. At discharge, *R* and Xc were recorded for each patient, normalized by the subject's height and graphically expressed on the *R*–Xc plane; furthermore, HI was also assessed.

BNP assessment

A blood sample for BNP was performed for all patients upon arrival in the ED through an EDTA anticoagulated whole blood test tube. The sample was then sent to the central laboratory where a quantitative chemiluminescent immunoassay (Architect BNP by Abbott®) was used to measure BNP in plasma.

hs-cTnI assay

Samples of peripheral venous blood were drawn in each patient, in 10 cc heparinized tubes, and then sent to our central hospital laboratory as hs-cTnI was measured. Indeed, a routine screening diagnostic test was performed in real time for the detection of an acute coronary syndrome. The ARCHITECT STAT High Sensitive Troponin-I assay (Abbott Laboratories, Abbott Park, Illinois, USA) is

a chemiluminescent microparticle immunoassay for the in vitro quantitative determination of cardiac troponin I, and can be used with the Abbott ARCHITECT i2000SR and i1000SR analysers [14]. Results are available within 16 min. ARCHITECT STAT High Sensitive Troponin-I assay can detect troponin I in 96% of the reference population, and has a recommended 99th percentile cut-off of 26.2 pg/ml. The manufacturer's instructions for use also state a 99th percentile cut-off of 34.2 pg/ml for men and 15.6 pg/ml for women [15].

Statistical analysis

Continuous variables were expressed as mean ± SD if normally distributed, or median (interquartile range—IQR) if not normally distributed, unless otherwise specified, and the appropriate parametric (*t* test) or nonparametric (Mann–Whitney) test was used to assess significance of the differences between subgroups. Categorical variables were displayed as frequencies and compared using the χ^2 test. All of the tests were two-sided and statistical significance was set at $p < 0.05$. BIVA data were analyzed as *R*/Xc graph using BIVA software by Piccoli A. and Pastori G. Univariate analysis was performed to evaluate the predictive performance of BIVA variables and of clinical signs and odds ratio (OR) and 95% confidence intervals (95% CI) were calculated. Multivariate survivor analysis was performed with Cox analysis. Receiver operating characteristics (ROC) curves analysis was performed to identify the prognostic value of clinical variables and BIVA variables alone or in combination. All data were first analyzed for normality of distribution using the Kolmogorov–Smirnov test of normality. Statistical analysis was performed using the Statistical Package for Social Science (SPSS), release 15.0.

Results

292 AHF patients were included into the study. The patients' characteristics are shown in Table 1. At 90 days, 36 patients had died (12%). The age, the presence of rales, levels of Hs Troponin I, BNP, and BIVA variables, show statistically significant differences between survivors and non-survivors. BNP levels are higher in the non-survivor group than in survivors (respectively, 838 vs 512 pg/ml, $p < 0.01$). BIVA values performed at discharge, show a significant presence of congestion in patients who die [median values in non-survivors vs survivors, respectively, HI 85–74% ($p < 0.001$), *R* 445–503 Ohm/m ($p < 0.01$), Xc 26.7–37 Ohm/m ($p < 0.0001$)]. As shown in Table 2, at univariate analysis, BIVA and BNP are significantly associated with 90 days mortality. At multiple regression analysis, only age and BNP maintain statical significance (Table 2). ROC analysis shows that BIVA is a predictor of death [(HI:AUC 0.71, 95% CI 0.65–0.76, $p < 0.004$); (Xc: AUC 0.71, 95% CI 0.655–0.76, $p < 0.007$); (*R*: AUC 0.65, 95% CI 0.29–0.706, $p < 0.02$)], while BNP does not reach statistical significance (AUC 0.55, 95% CI 0.497–0.615, $p = 0.42$), as shown in

Table 1 Patients' characteristics

Variables	Non-survivors (36/292 pts) 12.3%	Survivors (256/292 pts) 87.6%	*p*
Age years (median)	83.50 (76.50–87.50)	76.00 (65.00–83.00)	**0.0002**
Gender M/F	16/20	119/137	0.85
Rales y/n	30/6	148/108	**0.003**
Edema y/n	28/8	164/91	0.13
JVD y/n	20/16	109/146	0.15
SBP mmHg (median)	132.50 (120.00–147.50)	127.50 (110.00–150.00)	0.76
DBP mmHg (median)	75.00 (62.50–80.00)	70.00 (65.00–80.00)	0.81
HR bpm (median)	83.50 (70.00–95.50)	78.00 (68.00–90.00)	0.13
BNP pg/ml (median)	838.50 (371.00–1295.00)	512.50 (282.50–956.50)	**0.01**
Hydration index % (median)	85.00 (74.02–87.95)	74.00 (73.42–81.15)	**0.001**
R Ohm/m (median)	445.30 (360.80–521.97)	503.60 (433.15–566.55)	**0.01**
Xc Ohm/m (median)	26.70 (20.75–37.15)	37.00 (30.20–47.40)	**0.0001**
Creatinine m g/dl (median)	1.40 (1.01–2.21)	1.19 (0.90–1.60)	0.058
Na mmol/L (median)	138.00 (131.50–142.00)	138.00 (135.00–140.00)	0.83
Tpl pg/ml (median)	0.076 (0.030–0.19)	0.030 (0.020–0.080)	**0.0007**

Variables are presented as median (interquartile range)

Variables statistically significant between non-survivor and survivor group are indicated in bold (age, rales, BNP, HI, *R*, Xc, TpI)

y/n yes/no, *JVD* jugular vein distension, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *mmHg* millimeters of mercury, *HR* heart rate, *bpm* beats per minute, *pg/ml* picograms per millimeter, *BNP* brain natriuretic peptide, % percentage, *R* resistance, *Xc* reactance, *Ohm/m* Ohm meter, *Na* sodium, *mmol/l* millimoles per liter, *TpI* Troponin I

Table 2 Univariate and multiple regression analysis

Univariable model result variables	*B*	OR (95% CI)	*p*
Age	0.061 ± 0.019	1.06 (1.02–1.10)	**0.001**
Gender	−0.082 ± 0.358	0.92 (0.45–1.85)	0.81
DBP	−0.005 ± 0.013	0.99 (0.96–1 02)	0.65
SBP	−0.0007 ± 0.006	0.99 (0.98–1.01)	0.91
HR	0.010 ± 0.008	1.01 (0.99–1.02)	0.18
Na	0.007 ± 0.037	1.00 (0.93–1.08)	0.83
Tpl	0.238 ± 0.127	1.26 (0.98–1.62)	0.06
BNP	0.0004 ± 0.0001	1.00 (1.00–1.00)	**0.005**
Creatinine	0.127 ± 0.136	1.13 (0.87–1.48)	0.34
Hydration index	0.120 ± 0.028	1.12 (1.06–1.19)	**<0.0001**
R	−0.004 ± 0.001	0.99 (0.99–0.99)	**0.01**
Xc	0.063 ± 0.017	0.93 (0 90–0.97)	**0.0004**
JVD	0.515 ± 0.358	1.67 (0.82–3.38)	0.15
Leg edema	0.663 ± 0.421	1.94 (0.84–4.43)	0.11
Rales	1.294 ± 0.464	3.64 (1.46–9.07)	**0.005**

Multiple regression Variables	*B*	SE	*p*	OR (95% CI)
Age	0.057983	0.023727	**0.01**	1.05 (1.01–1.11)
BNP	0.00044843	0.00019086	**0.01**	1.00 (1.00–1.00)
Hydration index	0.10045	0.064278	0.1181	1.10 (0.97–1.25)
R	−0.0018949	0.0023390	0.4179	0.99 (0.99–1.00)
Xc	0.0041397	0.032232	0.8978	1.00 (0.94–1.06)
Rales	0.48071	0.52555	0.3604	1.61 (0.57–4.53)
Constant	−14.5207			

Statistically significant variables at univariable analysis (age, BNP, HI, *R*, Xc, rales) and multiple regression (age, BNP) are shown in bold

JVD Jugular vein distension, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HR* heart rate, *BNP* brain natriuretic peptide, *R* resistance, *Xc* reactance, *Na* sodium, *TpI* Troponin I

Fig. 1. However, combining BIVA (expressed as hydration index) with BNP (Fig. 2), we obtain the best prognostic value (AUC 0.73, 95% CI 0.682–0.788, $p < 0.0001$).

Discussion

BIVA and BNP are currently considered both valid instruments in the management of AHF patients [16–20]. They reflect two aspects of the same pathophysiological mechanism: BNP is released as a result of the increased ventricular filling pressure and ventricle's wall tension, while BIVA variables reflect the body hydration changes in the failing cardiovascular system [3, 18]. For these reasons, it is currently well known that in AHF patients, BIVA, BNP, NYHA functional classes and central venous pressure are strongly related [16, 20].

In our study, 90 days non-survivor AHF patients have higher BNP values upon ED arrival, suggesting that BNP at the moment of patient presentation could be very useful in the risk stratification for these patients. The prognostic validity of wBNP measurement has been previously evaluated. Nishii et al. report that high levels of BNP are predictor of long term risk in patients with non ischemic dilated cardiomyopathy [21]. In the Italian Red Study [22], BNP serial evaluation (at admission, at 24 h, and at discharge), were performed in 247 AHF patients. At admission, similar to our results, BNP median value was 822 pg/ml. A reduction of BNP levels during hospitalization, demonstrates a strong negative prognostic value for future cardiovascular outcomes. In addition, from a study subanalysis, it was shown that serial BNP evaluation after discharge in chronic AHF elderly patients is useful in the prediction of 30 days post discharge events [22]. In particular, the gradual and continuous decrease of BNP after hospital discharge in that study is associated with a lower incidence of adverse events.

Oremus et al. in a recent review of the literature [3] show that BNP is associated with all-cause mortality and composite outcomes in both decompensated and chronic stable HF population. Nevertheless, in the literature there is limited evidence that BNP adds incremental value to other

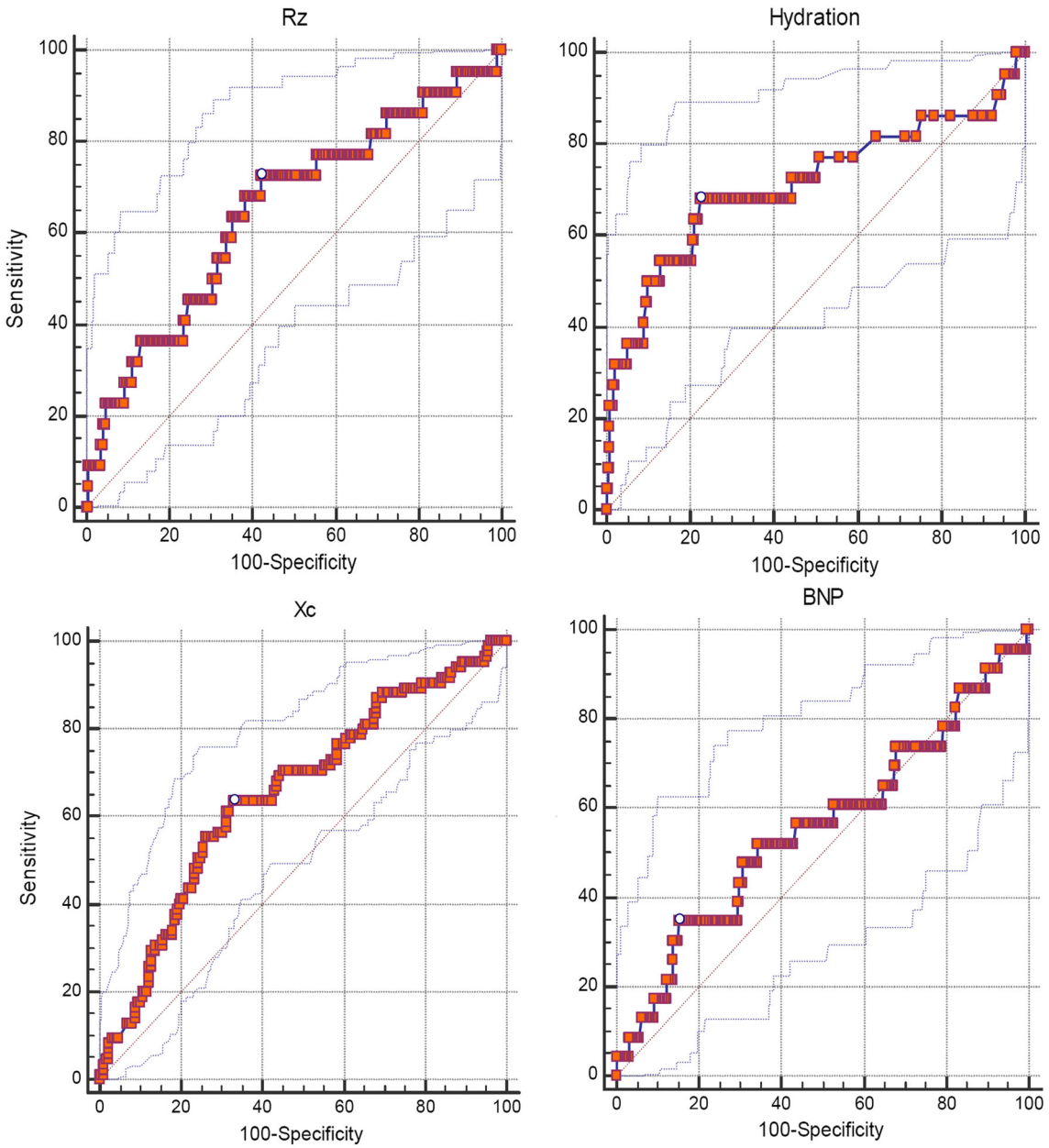

Fig. 1 BNP and BIVA ROC curves for the predication of death at 90 days. *R*: AUC 0.65, 95% CI 0.29–0.706, $p < 0.0247$; Xc: AUC 0.712, 95% CI 0.655–0.76, $p < 0.007$; HI: AUC 0.715, 95% CI 0.65–0.76, $p < 0.004$; BNP: AUC 0.557, 95% CI 0.497–0.615, $p = 0.42$

prognostic factors in predicting all-cause and cardiovascular mortality in the short and long terms. Instead, in our study BNP is been more predictive of death when used in combination with BIVA (Fig. 2).

As for BIVA variables at discharge, our study confirms that some HF patients are discharged with a persistent state of congestion. Their identification becomes crucial because these patients are those with a higher risk for 90 days mortality [6, 7]. In the DOSE-AHF trial, there exists a correlation between weight loss, net fluid loss and 60th days death or rehospitalization [4]. In detecting congestion and latent fluid overload, BIVA has greater diagnostic sensitivity than other techniques (including fluid balance), and it also shows an emerging role for its prognostic value [16]. Previous data from our group demonstrates that the reduction of congestion detected by BIVA, during AHF patients hospitalization, is linked with an improvement in patients' outcome [17, 20, 23]. In particular, we demonstrate that BIVA values at arrival in the ED are very useful in identifying patients at high risk for death and hospitalization at short and long term [20]. The same result is shown by Donner Alves et al. who describe the progressive changes in hydration status during diuretic therapy in AHF hospitalized patients [24]. Instead, in this study, we evaluate BIVA prognostic relevance before discharge; this

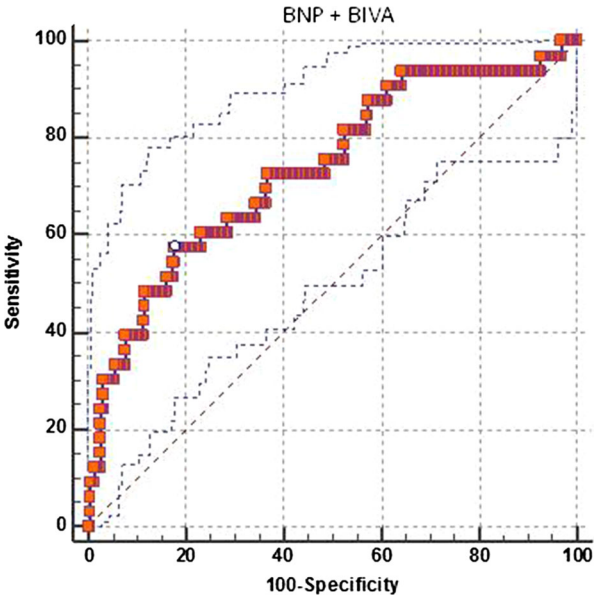

Fig. 2 Combined ROC for BNP and BIVA for the predication of death at 90 days: AUC 0.737, 95% CI 0.682–0.788, $p < 00.001$

was done assuming that at this moment, clinical signs of congestion are often missing as a consequence of diuretic therapy, and clinical judgment may not be reliable. In this perspective, this study adds important information: BIVA analysis is important because it allows identification of those patients who have subclinical congestion, and this could help physician in the decision of patient's discharge.

In addition, our data confirm the utility of BNP in the risk stratification of AHF patients arriving to the ED, but the most important and newest aspect is derived from the combined use of BNP and BIVA.

In a previous study from our group, we find that BNP and BIVA may be very helpful in the diagnosis, but also during the therapeutic management of AHF patients, maintaining an optimal hydration status through the correct use of diuretics [13]. This study extends these findings demonstrating that when AHF patients are discharged with a persistent congestive state, even if clinically latent, they will have a worse outcome.

The most important limitation of this study is the lack of information about the type of heart failure (with preserved ejection fraction or not), and the likely presence of comorbidities due to the population's median age that makes the sample inhomogeneous.

Conclusion

Our study shows that in AHF patients, a high BNP level at admission allows accurate risk stratification. Moreover, at the time of discharge, it is necessary to achieve an optimal hydration status detected by BIVA. The achievement of normal hydration detected by noninvasive assessment of body fluid content by BIVA at discharge, should be one of the major targets in the management of AHF patients to improve their life expectancy. The combined use of BIVA and BNP in AHF patients should be a complementary instrument in the management of AHF patients, to identify patients at high risk of death in the next 90 days after hospital discharge.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests (financial, political, personal, religious, ideological, academic, intellectual, or any other) to declare in relation to this manuscript.

Statement of human and animal rights The research protocol was reviewed by the human research Committee from Sant'Andrea Hospital in Rome as coordinating center and it was consequently approved in all participating centers. The study protocol was conform to the ethical guidelines of Declaration of Helsinki.

Informed consent Informed written consent was obtained from patients before enrollment.

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