

# Prognostic value of decreased peripheral congestion detected by Bioelectrical Impedance Vector Analysis (BIVA) in patients hospitalized for acute heart failure: BIVA prognostic value in acute heart failure

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## Abstract

**Objectives:** The objective of this study was to investigate the prognostic role of quantitative reduction of congestion during hospitalization assessed by Bioelectrical Impedance Vector Analysis (BIVA) serial evaluations in patients admitted for acute heart failure (AHF).

**Background:** AHF is a frequent reason for patients to be admitted. Exacerbation of chronic heart failure is linked with a progressive worsening of the disease with increased incidence of death. Fluid overload is the main mechanism underlying acute decompensation in these patients. BIVA is a validated technique able to quantify fluid overload.

**Methods:** a prospective, multicentre, observational study in AHF and no AHF patients in three Emergency Departments centres in Italy. Clinical data and BIVA evaluations were performed at admission (t0) and discharge (tdis). A follow-up phone call was carried out at 90 days.

**Results:** Three hundred and thirty-six patients were enrolled (221 AHF and 115 no AHF patients). We found that clinical signs showed the most powerful prognostic relevance. In particular the presence of rales and lower limb oedema at tdis were linked with events relapse at 90 days. At t0, congestion detected by BIVA was observed only in the AHF group, and significantly decreased at tdis. An increase of resistance variation (dR/H) >11 Ω/m during hospitalization was associated with survival. BIVA showed significant results in predicting total events, both at t0 (area under the curve (AUC) 0.56,  $p < 0.04$ ) and at tdis (AUC 0.57,  $p < 0.03$ ). When combined with clinical signs, BIVA showed a very good predictive value for cardiovascular events at 90 days (AUC 0.97,  $p < 0.0001$ ).

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**Conclusions:** In AHF patients, an accurate physical examination evaluating the presence of rales and lower limbs oedema remains the cornerstone in the management of patients with AHF. A congestion reduction, obtained as a consequence of therapies and detected through BIVA analysis, with an increase of  $dR/H > 11 \Omega/m$  during hospitalization seems to be associated with increased 90 day survival in patients admitted for AHF.

### Keywords

Acute heart failure, congestion, bioelectrical impedance analysis, rehospitalization, death, prognosis

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## Introduction

Acute heart failure (AHF) is a common disease within patients referring to the Emergency Department (ED),<sup>1</sup> and it represents the most frequent cause of hospitalization among patients over the age of 65 years.<sup>2</sup> Despite improvements of care, patients admitted for AHF still have a mortality of 15% and a readmission rate of 30% within 30 to 60 days post discharge.<sup>3</sup> For these reasons, approximately 2.5% of the total healthcare budget in Europe is attributable to AHF.<sup>4</sup> In AHF patients, estimation of fluid overload is important considering that the main mechanism leading to heart failure exacerbation is congestion.<sup>2,5</sup> Congestion is due to the over activation of the renin–angiotensin–aldosterone system, and sympathetic nervous system, as a consequence of arterial under filling, producing sodium and water retention.<sup>5</sup> Diuretic therapy is often empirical being based only on clinical signs and symptoms of congestion. However, recent literature shows that congestion is not always clinically remarkable<sup>2,6,7</sup> and many patients may not present clinical signs or symptoms of congestion (dyspnoea, jugular venous distension, oedema), but already have haemodynamic abnormalities suggestive of heart failure exacerbation (such as elevated left ventricular pressures)<sup>1</sup>. Consequently, during diuretic therapy, monitoring fluid removal is crucial in order to discharge these patients from hospital with an adequate fluid balance status, and to prevent unwanted side effects such as worsening renal function.<sup>8</sup>

Bioelectrical Impedance Vector Analysis (BIVA) is a useful, non-invasive technique to estimate total body fluid content.<sup>6,9–14</sup> In patients referring to the ED for shortness of breath, BIVA is able to discriminate between cardiac and non cardiac origin,<sup>15,16</sup> and fluid retention in AHF patients calculated by BIVA has prognostic value being linked with a significant increased rate of cardiovascular events (death and rehospitalization) at one<sup>9</sup> and at three months.<sup>10</sup> No data are actually available on the usefulness of BIVA variations from admission to discharge in the assessment of prognosis in patients hospitalized for AHF. The aim of our study was to investigate congestion reduction during hospitalization obtained by BIVA serial measurements, and its ability to predict 90 days events in patients hospitalized for AHF.

## Methods

### Study population

We conducted a multicentre, prospective cohort study composed of patients presenting to the ED with acute dyspnoea in three teaching hospitals in Italy (Sant'Andrea Hospital, Sapienza University in Rome, as coordinating centre; Padua Hospital University; Novara Hospital, Università degli Studi del Piemonte Orientale). The inclusion criteria were ED admission for dyspnoea due to AHF, with expected hospitalization. The exclusion criteria were: psychogenic dyspnoea, post-traumatic dyspnoea, pneumothorax, major surgery, coronary artery disease, ascites, oedema secondary to venous disease, lymphoedema, hypoalbuminaemia, body temperature  $> 38^{\circ}\text{C}$ , amputation of limbs, burns, patients younger than 18 years, and patients who were unable to give informed consent. Patients enrolled in this study had not been included in other previous studies by our group. Their enrolment followed the same methodological criteria of our previous works on BIVA and AHF.<sup>9</sup>

Three hundred and thirty-six patients were enrolled from September 2011 to September 2012 and constituted the study population. At admission in the ED, BIVA evaluations were performed before starting any treatment. The attending ED physician made the initial symptom-based diagnosis and proceeded to baseline data collection; he was blinded to BIVA values. The research protocol was reviewed by the human research Committee from Sant'Andrea Hospital in Rome as coordinating centre and it was consequently approved in all participating centres. Informed written consent was obtained from patients before enrolment. The study protocol conformed to the ethical guidelines of the Declaration of Helsinki.

### Clinical evaluation and follow-up

Trained investigators collected BIVA measurements at admission ( $t_0$ ), and before discharge ( $t_{dis}$ ). Data collection included: clinical history, vital parameters, blood analysis values (creatinine, blood urea nitrogen, glycaemia, blood sodium level, blood potassium level, liver function tests, arterial blood gas analysis, complete blood count, and

biomarkers), echocardiography and cardiac catheterization as available, as well as the hospital course. In order to avoid diagnosis bias, two cardiologists, on the basis of current guidelines,<sup>17</sup> independently reviewed all medical records of the patients and classified the dyspnoea due to heart failure or due to other causes. Follow-up data were recorded at the end of 90 days from discharge by telephone interview with patients, or a relative, or the family practitioner. We considered as adverse medical outcome readmission after hospitalization or death. According to the final diagnosis, patients were divided into two groups: AHF and no AHF.

### BIVA measurement

For BIVA assessment, we used a bioelectrical impedance analyser, single 50 kHz frequency (EFG, Akern, Florence, Italy).

The BIVA measurement assessed at patients' ED arrival and discharge 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  $\mu$ A and an operating frequency of 50 kHz. The results were visualized in two ways: as a bi-variate impedance vector or as a BIVA-derived hydration percentage. The first method includes a direct impedance plot which measures resistance (R) and reactance (Xc), as a bi-variate vector in a nomogram (R/Xc graph).<sup>18</sup> Reference values,<sup>18,19</sup> stratified for classes of age, body mass index 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.<sup>19,20</sup> 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 the Hydration Index.<sup>9</sup> This value is calculated by an independently determined equation that uses the two components of BIVA, R and Xc. Hydration Index normal value is between 72.7% and 74.3%, corresponding to the 50th percentile.<sup>8–12,21</sup>

At ED arrival, R and Xc were recorded for each patient, normalized by the subject's height and graphically expressed on the R-Xc plane; furthermore, the Hydration Index was also assessed.

### Statistical analysis

Continuous variables were expressed as mean  $\pm$  SD if normally distributed, or median (interquartile range) if not normally distributed, unless otherwise specified, and the appropriate parametric (*t*-test) or non-parametric (Mann-Whitney) test was used to assess significance of the

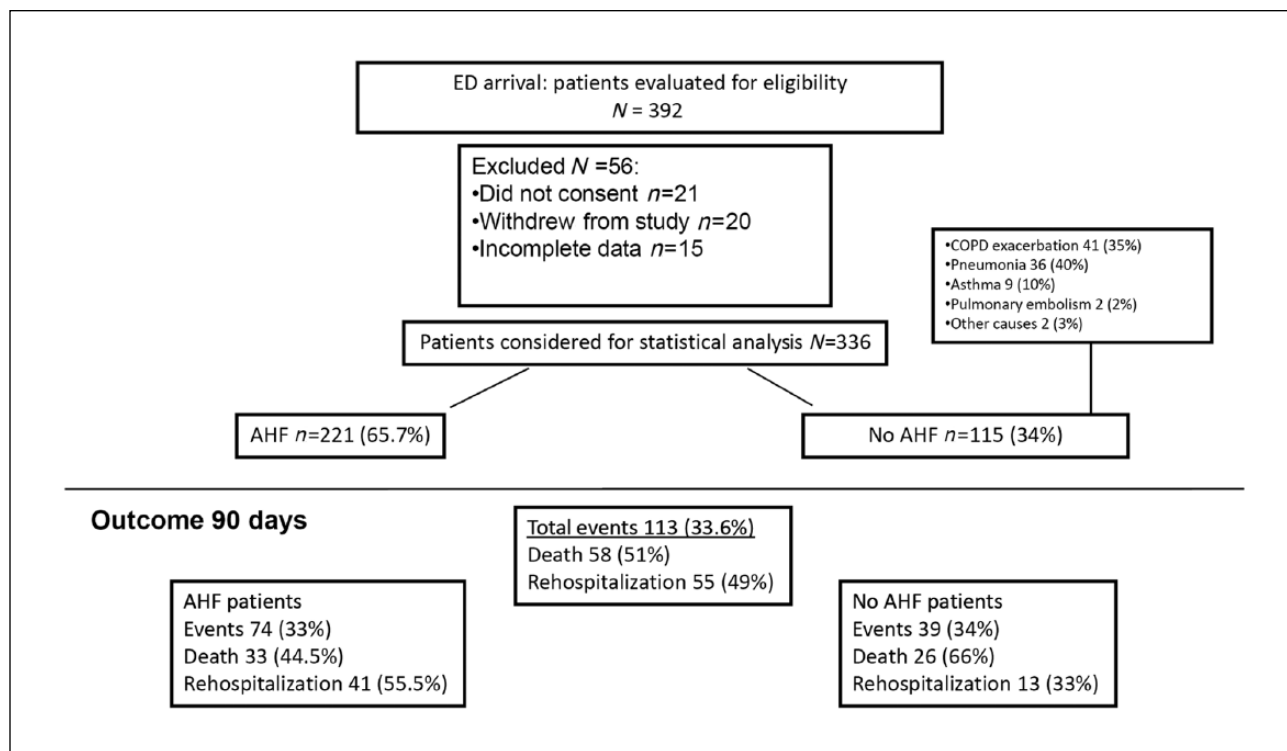
differences between subgroups. Categorical variables were displayed as frequencies and compared using the  $\chi^2$  test. All of the tests were two-sided and statistical significance was set at  $p < 0.05$ . BIVA data were analysed as R/Xc graph using BIVA software by A Piccoli and G Pastori. We performed the Hotelling's  $T^2$  test for paired data (discharge–admission). The survival to outcomes was evaluated according to the Kaplan–Meier method and tested with Log-rank test. Survival curves were created as a function of the median of differences of R/H and Xc/H at discharge. 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 analysed for normality of distribution using the Kolmogorov–Smirnov test of normality. Statistical analysis was performed by using the Statistical Package for Social Science (SPSS), release 15.0.

### Results

We enrolled 392 consecutive patients referring to the ED for shortness of breath (Figure 1). Complete statistical analysis was performed in 336 patients since 21 did not consent, 20 withdrew the consent after agreeing and 15 were excluded for incomplete data. The most frequent leading causes in no AHF patients were: chronic obstructive pulmonary disease exacerbation, pneumonia, asthma, pulmonary embolism, and sepsis. Patients' characteristics are shown in Table 1. Patients with final diagnosis of AHF were significantly older than no AHF. Also, in the AHF group, patients showed lower estimated glomerular filtration rate, more clinical and radiological signs of congestion and higher Brain Natriuretic Peptide (BNP) values.

BIVA variations at different times in the total population and in the two groups are shown in Table 2. In AHF patients mean Hydration Index at arrival was 82.8  $\pm$  6%, while in no AHF it was 75.7  $\pm$  4% ( $p < 0.001$ ). In the AHF group, Hydration Index and R changed significantly from admission to discharge: Hydration Index showed a significant decrease from 82.8  $\pm$  6% to 78.5  $\pm$  6% ( $p < 0.001$ ), while in the no AHF group, the Hydration Index moved from 75.7  $\pm$  4% to 75.9  $\pm$  4% ( $p = 0.7$ ). These data are also described in Figure 2. Cox regression analysis obtained for dR/H (R at discharge – R at admission) showed that dR/H was associated with better prognosis (Hydration Index 0.417,  $p < 0.01$ ).

Figure 3 shows BIVA vector variations (t0–tdis) by Hotelling's  $T^2$  test in the two groups: in AHF patients (red ellipse) the vector showed a significant lengthening during hospitalization, which excludes the null vector ( $T^2 < 0.05$ ) suggesting a reduction in congestive status. In no AHF



**Figure 1.** Dyspnoeic patients' enrolment at Emergency Department arrival. In the lower part of the figure AHF) and no AHF outcomes are described.

ED: Emergency Department; COPD: chronic obstructive pulmonary disease; AHF: acute heart failure.

**Table 1.** Patient's characteristics.

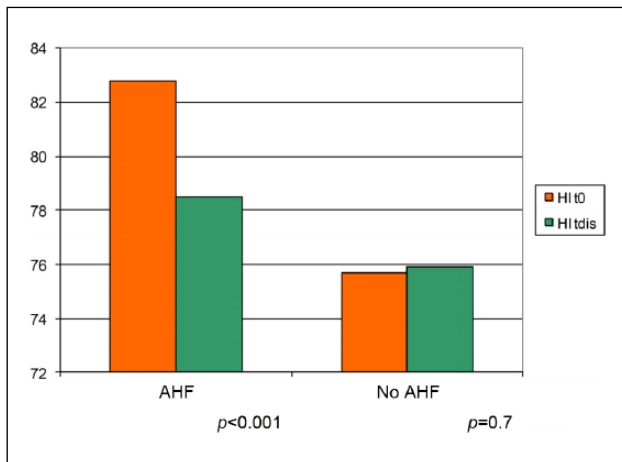
	Total population	AHF	No AHF	p value
N	336	221	115	
Sex, N (%)	F 183 (55) M 153 (45)	F 129 (58) M 92 (41)	F 54 (47) M 61 (53)	
Age, mean SD	78 10	79 8	76 12	<0.001
Systolic blood pressure, mean SD	139 26	140 27	138 25	0.5
Diastolic blood pressure, mean SD	75 15	77.4 16	76 14	0.5
Heart rate, mean SD	88 21	87 22	92 18	<0.05
<b>Medical history</b>				
History of heart failure, N (%)	167 (49.7)	150 (68)	17 (14.7)	<0.001
Myocardial infarction, N (%)	67 (20)	55 (25)	12 (10)	<0.01
Coronary artery disease, N (%)	108 (32)	90 (41)	18 (15)	<0.001
<b>Physical exam</b>				
Cardiac asthma, N (%)	20 (6)	17 (8)	3 (2.6)	0.12
Jugular distension, N (%)	151 (45)	130 (59)	21 (18)	<0.001
Oedema, N (%)	227 (67)	177 (80)	50 (43)	<0.001
Orthopnoea, N (%)	113 (33)	93 (42)	20 (17)	<0.001
Rales, N (%)	233 (69)	179 (81)	54 (47)	<0.001
<b>Radiology</b>				
Chest X-ray, N (%)	224 (66)	178 (80.5)	46 (40)	<0.001
<b>Laboratory</b>				
BNP, mean SD	658 896	859 985	229 433	<0.001
Estimated glomerular filtration rate, mean SD	58.7 28	54.8 26	67 29	<0.001
Na, mean SD	137.6 4.9	137.5 5	137.8 4	1

AHF: acute heart failure; F: female; M: male; BNP: Brain Natriuretic Peptide.

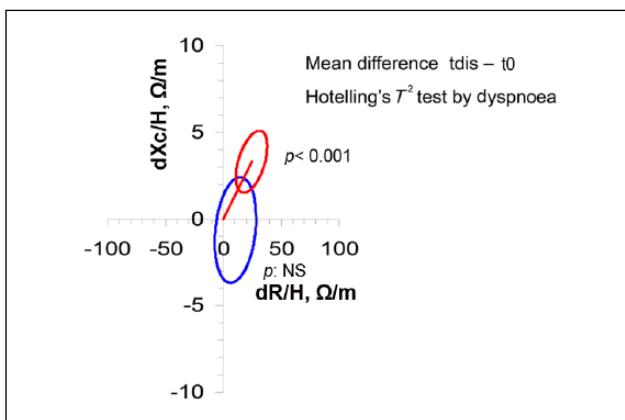
**Table 2.** BIVA values at admission and at discharge.

	BIVA admission	BIVA discharge	p value
<b>Total population (N = 336)</b>			
Hydration Index	79.5 ± 6.5	77.7 ± 6	<0.001
R/H (Ω/m)	470.5 ± 120.5	496 ± 111	<0.005
Xc/H (Ω/m)	36 ± 13.8	38 ± 13	=0.05
<b>AHF group (n = 221)</b>			
Hydration Index	82.8 ± 6	78.5 ± 6	<0.001
R/H (Ω/m)	448.4 ± 113	485 ± 109	<0.001
Xc/H (Ω/m)	34 ± 12	36 ± 13	=0.09
<b>No AHF group (n = 115)</b>			
Hydration Index	75.7 ± 4	75.9 ± 4.4	=0.7
R/H (Ω/m)	512 ± 123	521 ± 113	=0.56
Xc/H (Ω/m)	43.2 ± 14	42 ± 12	=0.48

BIVA: Bioelectrical Impedance Vector Analysis; AHF: acute heart failure.



**Figure 2.** Hydration Index at arrival (t0) and at discharge (tdis) in AHF group and no AHF group.  
HI: Hydration Index; AHF: acute heart failure.

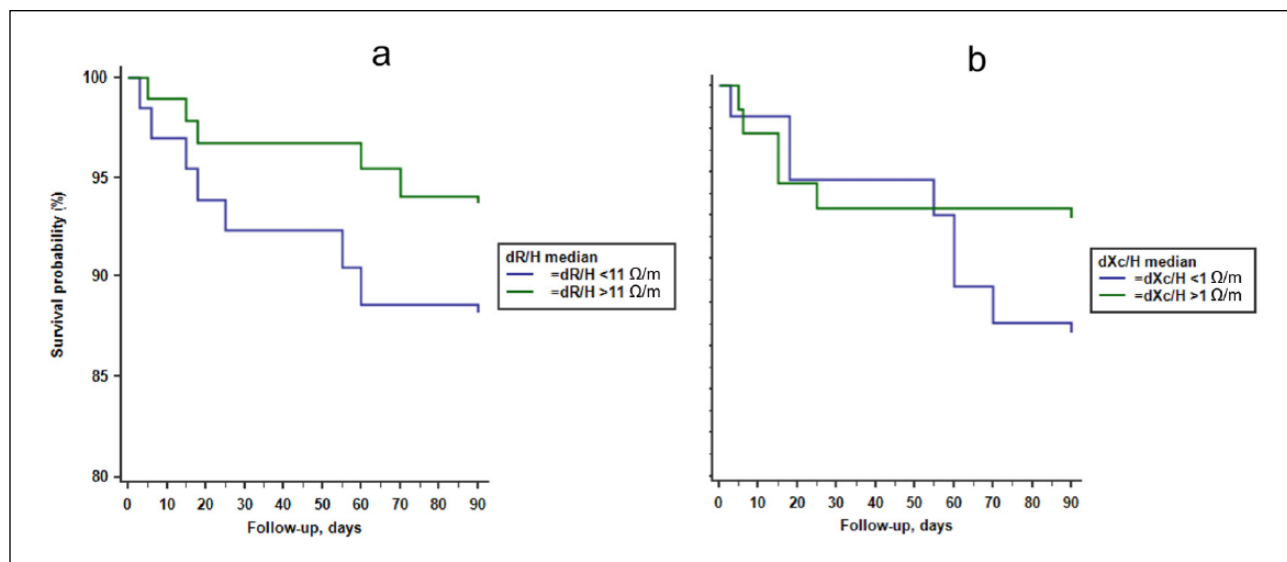


**Figure 3.** BIVA vector variations (t0–tdis) evaluated by Hotelling's  $T^2$  test in the two different groups: in AHF patients (red ellipse) vector showed a significant lengthening during hospitalization. In no AHF patients (blue ellipse) there was not a significant vector displacement.

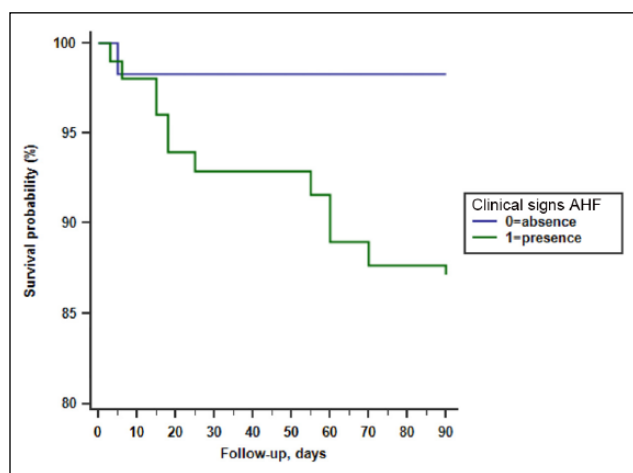
patients (blue ellipse), there was not a significant vector displacement. Indeed, in no AHF group did the vector migrate close to the null vector ( $T^2$ : NS). The Kaplan–Meier survival curve for the AHF group is shown in Figure 4. During hospitalization an increase of R from admission to discharge ( $dR/H$ ) > 11 Ω/m is significantly related to higher survival at 90 days ( $p < 0.03$ ) as shown in Figure 4(a). We did not find significant results ( $p = 0.24$ ) about  $dXc/H$  (Figure 4(b)). We performed Kaplan–Meier curves considering the presence or absence of clinical signs of AHF (jugular vein distension, rales, lower limb oedema) and built a binomial score (1=presence, 0=absence of at least one of the three signs). Figure 5 shows that patients discharged with no signs of congestion had a higher survival on follow-up in comparison with those with clinical signs ( $p < 0.002$ ).

In the univariate analysis to compare BIVA with clinical signs prognostic value, we found that the presence of clinical signs of congestion at discharge, but not BIVA variables, had significant 90 days prognostic value both for death (i) and for rehospitalization (ii), and for total events (iii) (lower limb oedema: (i) OR 4.33 (95% CI 2.29–8.20),  $p < 0.001$ ; (ii) OR 3.07 (95% CI 1.62–5.81),  $p < 0.0005$ ; (iii) OR 5.41 (95% CI 3.25–8.98),  $p < 0.0001$ ; rales: (i) OR 26.88 (95% CI 12.30–58.71),  $p < 0.0001$ ; (ii) OR 3.87 (95% CI 2.09–7.14),  $p < 0.0001$ ; (iii) OR 38.25 (95% CI 19.04–76.85),  $p < 0.0001$ ; jugular vein distension: (i) OR 14.23 (95% CI 6.07–33.35),  $p < 0.0001$ ; (ii) OR 1.22 (95% CI 0.47–3.15),  $p = 0.67$ ; (iii) OR 21.74 (95% CI 6.43–73.45),  $p < 0.0001$ ), as shown in Figure 6(a).

At ROC analysis, Xc, obtained through BIVA, at both t0 (area under the curve (AUC) 0.56,  $p = 0.04$ ) and tdis (AUC 0.57,  $p = 0.03$ ), resulted in being of value in predicting events. For death, Hydration Index >81.7% and Xc <32 Ω/m, when measured by mean of BIVA at t0, showed significant AUC 0.61 ( $p < 0.01$ ). Clinical signs showed statistical predictive power for total events, death and rehospitalization; the best result was obtained analysing rales



**Figure 4.** (a) Kaplan–Meier survival curves as a function of the median of differences of R/H at discharge. (b) Kaplan–Meier survival curves as a function of the median of differences of Xc/H at discharge.



**Figure 5.** Kaplan–Meier survival curves as a function of the presence (1) or absence (0) of clinical signs of congestion. AHF: acute heart failure.

incidence (AUC 0.83,  $p < 0.0001$ ). When compared with BIVA variables, we obtained that the clinical signs evaluated at  $t_0$  and  $t_{dis}$  presented higher probability in predicting total events and for death at 90 days (Figure 6(a)). But when clinical signs were combined with BIVA variables for the prediction of total events, the ROC curve showed a higher predictive power with an AUC 0.97,  $p < 0.0001$  (Figure 6(b)).

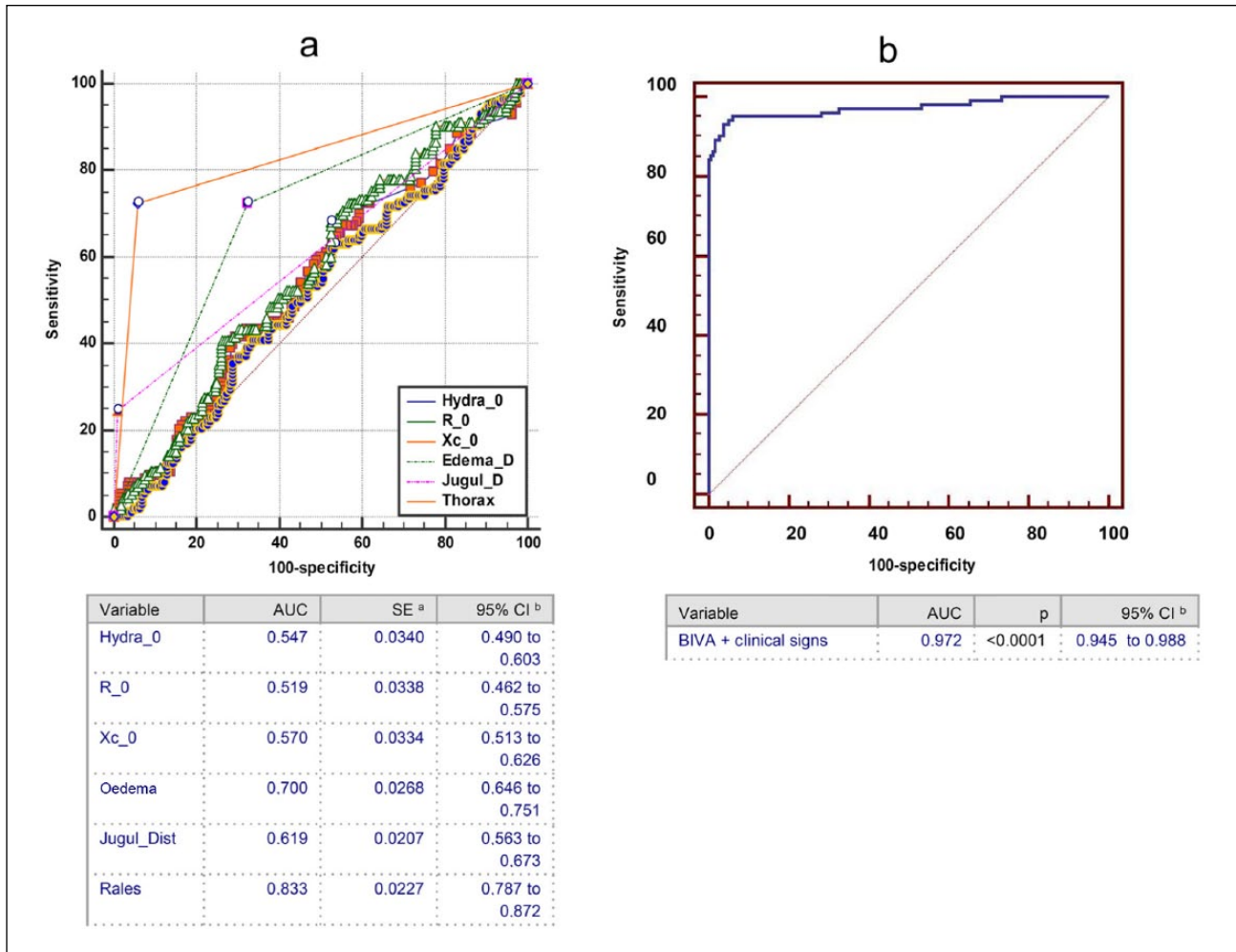
## Discussion

Congestion symptoms are the most common reason for hospitalization among AHF patients,<sup>2,3</sup> and their persistence at

discharge is associated with mortality and readmission.<sup>22</sup> Consequently, resolution of orthopnoea, jugular venous distension  $< 8 \text{ cmH}_2\text{O}$  and the absence of pitting oedema are reasonable clinical targets, and the major goal in AHF therapy is the reduction of volume overload by diuretics and vasodilators. However, determination of a patient's total body fluid assessment is still a challenge, since peripheral congestion without pitting oedema is difficult to establish. Indeed, oedema is not usually detectable until the interstitial fluid volume has risen to 30% above normal.<sup>15</sup> Fluid balance during hospitalization is helpful in monitoring diuretic therapy efficacy but it has no prognostic relevance; in fact, as showed by Kociol et al., a net fluid and weight loss at 72 h have no prognostic value for 60 day events.<sup>7</sup>

In our cohort of dyspnoeic AHF patients, BIVA at arrival in the ED was able to detect and quantify peripheral congestion, which was not remarkable in the no AHF group. In a study conducted on dyspnoeic patients, Piccoli<sup>15</sup> demonstrated that BIVA is useful in differentiating between cardiac and non cardiac dyspnoea. In particular, in the AHF group, impedance vector was shorter, suggesting an increased fluid volume, and these findings were in agreement with those of lung ultrasound and N-terminal pro-BNP. Similar results were showed by Parriniello<sup>16</sup> in a study conducted in patients coming to the ED for shortness of breath, in which 172 patients received a final diagnosis of AHF. Also from our study, in AHF patients impedance vector was mostly localized in the left lower part of the 75% and 95% tolerance ellipse (corresponding to a median Hydration Index of  $82.8 \pm 6$ ).

In the AHF group BIVA parameters from arrival to discharge showed a statistically significant improvement, while no relevant changes were described in the no AHF



**Figure 6.** (a) Compared ROCs for death at 90 days: clinical signs evaluated at t0 and tdis presented higher probability in predicting events at 90 days. (b) Clinical signs combined with BIVA variables for the prediction of events: the ROC curve showed an higher predictive power with an AUC 0.97,  $p < 0.0001$ .

ROC: Receiver Operating Characteristics; AUC: area under the curve; CI: confidence interval; BIVA: Bioelectrical Impedance Vector Analysis; Hydra\_0: Hydration Index; R\_0: Resistance; Xc\_0: Reactance; Jugul\_Dist: Jugular Distention; Thorax: rales.

patients. This is due to the presence of congestion in AHF patients, which decreased during hospitalization as a consequence of medical therapy. This is also confirmed by the vector analysis since we observed a significant increase of R and Xc during hospitalization, with a resulting migration of the vector toward normovolaemia. These results have great clinical relevance, demonstrating BIVA utility in monitoring body fluid and diuretic prescriptions in order to achieve haemodynamic stability. Indeed, despite diuretic therapy remaining the cornerstone of AHF treatment,<sup>23</sup> it is very often empirical. This can mean that an inadequate fluid removal is determined at discharge because many patients may experience a significant improvement in clinical congestion during hospitalization, but have persistent evidence of subclinical congestion.<sup>1</sup> On the other hand, excess in diuretic doses may cause risk of development of acute kidney injury or hypotension, or determine diuretics tolerance or resistance. Also, current guidelines do not give

strict directions about dosage of diuretics in AHF, suggesting to use them in patients with evidence of volume overload according to renal function and history of chronic oral diuretic dose.<sup>17</sup> This is due to the complexity of the syndrome and the great individual variability in the response to therapy, and it is the reason why diuretic therapy should be precisely individualized. In a previous study conducted by our group,<sup>12</sup> we showed how the combined use of BIVA and BNP could improve the management of AHF patients in order to assess a more accurate diagnosis and to guide diuretic therapy. Also we demonstrated that patients with more death and rehospitalization probabilities are those with more peripheral congestion as determined by BIVA and a significant correlation with events at three months was observed in patients with hydration values  $> 80\%$ .<sup>9</sup> The same results were presented by Valle et al. in a study conducted on 300 AHF patients:<sup>8</sup> a BIVA-BNP guided management during hospitalization is associated with lower



events after discharge, independently of other prognostic variables.

In this complex scenario it is very important to underline that our results give physicians a practical direction. On the basis of our results it seems to be necessary to achieve an increase of at least  $11 \Omega/\text{m}$  of  $\text{dR}/\text{H}$  to improve survival at 90 days from discharge. Importantly, our results show also that if AHF patients are discharged with still the presence of at least one sign of congestion, their survival expectation is lower. Nevertheless the persistence of rales and lower limb pitting oedema at discharge still represents a very powerful prognostic indicator for prediction of death in these patients, confirming the relevance of clinical signs. Moreover when compared with BIVA, AUC for clinical signs showed greater significance than BIVA variables (Hydration Index, R and Xc). But when the BIVA variables were combined with clinical signs the AUC for total events was higher (AUC 0.97) than for clinical signs considered alone. This means that, although BIVA per se represents a good predictive tool in heart failure patients, when used together with clinical signs it could provide the best results in the prediction of risk to develop cardiovascular events at 90 days. Therefore, in evaluating hydration status, alongside classical tools able to evaluate the different fluids compartments of the body (physical examination, laboratory exams, chest X-ray, inferior vena cava), BIVA can be considered a new resource in the management of AHF patients. Recently, the European Society of Cardiology – Acute Cardiovascular Care Association published a position paper on AHF management, proposing a multidisciplinary algorithm for AHF diagnosis and care.<sup>24</sup> One of the fundamental steps is intravascular volume status assessment, which is considered to be not easy to determine but nevertheless very important because it may lead to incorrect treatment decisions. In this context, BIVA could give physicians important complementary information about interstitial fluids. Indeed, while the evaluation of intravascular fluids is essential during the first line ED treatment in order to assess an appropriate therapy based on the use of vasodilators and diuretics, BIVA could play a role during the following hours, considering that diuretic therapy only marginally affects intravascular volume status, causing mainly a fluid loss from the interstitial space.<sup>25</sup> Currently, EDs have a central role in the management of the majority of AHF patients<sup>26</sup> and bioimpedance could help in the optimal management of these patients.

## Conclusions

An accurate physical examination remains the cornerstone in the management of fluid overload in patients with acute heart failure. However, besides the clinical judgment, the use of BIVA could represent a valid tool for congestion evaluation in these subjects. BIVA assessment at the moment of hospitalization has a confirmatory diagnostic

value, quantifying the presence of fluid overload. Serial evaluations of BIVA from hospital admission to discharge seem to be useful in monitoring congestive status variations; in particular, an increase in  $\text{dR}/\text{H} > 11 \Omega/\text{m}$  is recommended having prognostic additive value at 90 days. In patients with AHF, when used together with clinical signs of congestion, BIVA assessment could provide good results in detecting the presence of fluid overload and in predicting the risk to develop cardiovascular events.

## Conflict of interest

The authors declare that there is no conflict of interest.

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