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Copeptin decrease from admission to discharge has favorable prognostic value for 90-day events in patients admitted with dyspnea

Abstract

Background: With patients referred to emergency departments (EDs) for acute dyspnea, emergency physicians should consider all possible diagnoses and assess patients' risk stratification. Copeptin has been shown to have prognostic power for subsequent events, such as death and rehospitalization in patients admitted for dyspnea. The aim of this study was to investigate prognostic role of copeptin variations during hospitalization in patients admitted for dyspnea.

Methods: We conducted a prospective, multicentric, observational study in acute dyspneic patients in three ED centers in Italy. Clinical data and copeptin assessments were performed at admission, and at discharge. A 90-day follow-up was performed.

Results: A total of 336 patients were enrolled, and on the basis of final diagnosis distinguished into two groups: acute heart failure and no acute heart failure. Compared to a control group, in all studied population copeptin values at admission resulted in a significantly ($p<0.001$) higher median (maximum–minimum): 31 (0–905) versus 8 (0–13) pmol/L. Median copeptin value at admission was 42 (0–905) pmol/L in acute heart failure patients and 20 (0–887) pmol/L in no acute heart failure, respectively ($p<0.001$). In all studied patients and in each group copeptin at admission and discharge showed significant predictive value for 90-day events ($p<0.001$). Furthermore, in all patients population and in both groups Δ copeptin values from admission to discharge also showed significant predictive value for 90-day events ($p<0.001$).

Conclusions: In patients admitted for acute dyspnea, admission, discharge and Δ copeptin variations have significant prognostic value from subsequent 90-day death and rehospitalization.

Keywords: acute heart failure; copeptin; dyspnea; emergency department; prognosis; serial assessment.

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Introduction

Acute dyspnea is a common symptom for patients referred to emergency departments (EDs), accounting for 4% of all patients [1]. The multiple factors and different origins of dyspnea make the management of dyspneic patients more complicated and challenging for every physician. Usually between patients referring for shortness of breath (SOB), cardiac and pulmonary disorders, dyspnea accounts for more than 75% [2, 3]. For these patients risk assessment and prognostic evaluation in EDs are crucial to identify

candidates for aggressive therapy in order to provide a better patient outcome [4–7]. Recently, with this purpose, several studies intended to evaluate prognostic value of different biomarkers have been published [5–8].

Copeptin is one of the most important peptides involved in body fluids and electrolytes homeostasis. It has 39 amino acids, is the C-terminal part of pro-arginine vasopressin (AVP) and is released together with AVP from the hypothalamus [9]. The physiologic function of AVP is linked with peripheral vasoconstriction, as well as renal V2 receptor leading anti-diuretic effect [10–12]. Vasopressin and, consequently, copeptin is produced in response to several stressful conditions, such as acute cardiovascular diseases [acute heart failure (AHF), coronary artery disease, atrial fibrillation] [13–15], acute respiratory infections [16], stroke [17], diabetes mellitus [18], chronic obstructive pulmonary disease (COPD) [19], septic and hemorrhagic shock [20]. In these pathologic situations, copeptin seems to have prognostic value, especially in acute dyspneic patients [3].

The aim of our study was to evaluate the clinical utility for 90-day death and rehospitalization predictions of copeptin values measured at admission, at discharge and the difference from admission to discharge (Δ) in patients hospitalized for SOB from ED. The secondary endpoint was to evaluate the differences in copeptin levels between patients with cardiac dyspnea and no cardiac dyspnea.

Materials and methods

Study population

We conducted a multicenter, prospective cohort study composed by patients with acute dyspnea presenting to the ED of three teaching hospitals in Italy (Sant'Andrea Hospital, Sapienza University in Rome, as coordinating center; Padua Hospital University; Novara Hospital, Università degli Studi del Piemonte Orientale). The inclusion criterion was ED admission for acute dyspnea, with expected hospitalization. The exclusion criteria were: psychogenic dyspnea, post-traumatic dyspnea, pneumothorax, major surgery, coronary artery disease, patients younger than 18 years, and patients who were unable to give informed consent.

A total of 336 patients were enrolled from September 2011 to September 2012 and constituted the study population. At admission in ED first blood collection for copeptin was performed before starting any treatment. We also evaluated copeptin values in 20 recruited healthy volunteers used as a control group matched for age and gender. The attending ED physician made the initial symptom-based decision and proceeded to baseline data collection; he was blinded to copeptin values.

The research protocol was reviewed by the Human Research Committee from Sant'Andrea Hospital in Rome as the 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 Declaration of Helsinki.

Clinical evaluation and follow-up

Trained investigators collected data collection and blood samples for copeptin evaluation, in each patient, at admission in ED (T0) and before discharge (Td). Data collection included: clinical history, vital signs parameters at each time, blood analysis values (creatinine, azotemia, glycemia, blood sodium level, blood potassium level, transaminase, arterial blood gas analysis, complete blood count), electrocardiogram (ECG), chest X-ray, biomarkers, echocardiography, and cardiac catheterization as available, as well as the hospital course for patients who were admitted. In order to assess the final diagnosis, two cardiologists independently reviewed all medical records pertaining to the patient and independently classified the diagnosis as dyspnea due to AHF or due to no-AHF on the basis of current guidelines [21]. If there was not a common final diagnosis, a third cardiologist was asked to give its conclusion.

Follow-up was recorded at the end of 90 days from discharge by telephone interview with patients, or a relative, or the family practitioner. We considered adverse event medical outcome as any event (readmission after hospitalization and death within 90 days). We underlined the global prognostic value of copeptin because, as emergency physicians, we need only distinguish patients with events or not. These data could be useful, at our opinion, to start an adequate treatment at the moment of presenting in ED and to decide the specific disposition for each patient.

Finally, on the basis of median copeptin value of our control group, we divided all studied population into three groups according with copeptin level at T0:

- Group 1: ≤8 pmol/L;
- Group 2: 8.1–99.9 pmol/L;
- Group 3: ≥100 pmol/L.

Copeptin measurement

Study research personnel collected patient samples in tube containing ethylenediaminetetraacetic acid (EDTA) and separated plasma by centrifugation within 1 h of collection. Plasma samples were immediately frozen and stored at −40 °C until the study procedures were completed. Copeptin was measured using an automated sandwich chemiluminescence immunoassay on the KRYPTOR system (Thermo Fischer Scientific Inc., Hennigsdorf/Berlin, Germany). The laboratory measurement process complied with standard quality for a medical laboratory and was performed for all the determinations of copeptin in a central laboratory.

Statistical analysis

Statistical analysis was performed by using the Statistical Package for Social Science (SPSS), release 15.0. All data were first analyzed for normality of distribution using the Kolmogorov-Smirnov test of normality. Continuous variables were expressed as mean±SD, 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 were variables displayed as frequencies and compared using the χ^2-test. A multivariate logistic backward regression analysis was built to evaluate the relationship between the occurrence of combined events and clinical/laboratory findings introducing in the model covariates associated with the presence of events at the univariate analysis. The coefficients obtained from the logistic regression were expressed in terms of odds ratio with 95% confidence intervals [OR (95% CI)]. Delta copeptin value (ΔT) is the difference between Td and T0 absolute copeptin concentration value. All of the tests were two-sided and statistical significance was set at $p<0.05$.

Results

Patients' characteristics are shown in Table 1. The most frequent leading causes of dyspnea in non-cardiac dyspneic patients were: COPD exacerbation, pneumonia, asthma, and pulmonary embolism. Patients with AHF showed significant lower estimated glomerular filtration rate (eGFR), significant more clinical and radiological signs of congestion and higher brain natriuretic peptide (BNP) values. Included and excluded patients, patients' group and follow-up are shown in Figure 1. The copeptin median (minimum–maximum) levels in the control group was 8 (0–13) pmol/L. Copeptin median values in all patients were 31 (0–905) pmol/L at T0 and 19 (0–1093) pmol/L at Td, respectively, and significantly higher at both determinations compared to the control group ($p<0.001$). At T0 median copeptin value was 42 (0–905) pmol/L in AHF patients and 20 (0–887) pmol/L in no-AHF, respectively, with a significant difference between two groups ($p<0.001$). Furthermore, at Td median copeptin value was 25 (0–1039) pmol/L in AHF group and 13 (0–1054) pmol/L in no-AHF, respectively, resulting statistically significant ($p<0.001$).

We evaluated the prognostic value of copeptin on our studied population, 113 had events within 90 days of which 39 patients died due to cardiovascular diseases.

The prognostic value of T0, Td and Δ copeptin was as follows:

- T0 copeptin (median value) 23 (0–745) pmol/L in patients without events and 48 (3–905) pmol/L in patients with events ($p<0.05$).
- Td copeptin (median value) 12 (0–405) pmol/L and 27 (1–1093) pmol/L in patients without and with events, respectively ($p<0.05$).

Table 1 Patients characteristics in all studied population and in two subgroups.

	Total population	AHF	No AHF	p-Value
n	336	221	115	
Gender	F 183 (55%)	F 129 (58%)	F 54 (47%)	
	M 153 (45%)	M 92 (41%)	M 61 (53%)	
Age[a]	78±10	79±8	76±12	p<0.001
SBP[a]	139±26	140±27	138±25	p=0.5
DBP[a]	75±15	77.4±16	76±14	p=0.5
HR[a]	88±21	87±22	92±18	p<0.05
Medical history				
History of HF	167 (49.7%)	150 (68%)	17 (14.7%)	p<0.001
MI	67 (20%)	55 (25%)	12 (10%)	p<0.01
CAD	108 (32%)	90 (41%)	18 (15%)	p<0.001
Physical exam				
Cardiac asthma	20 (6%)	17 (8%)	3 (2.6%)	p=0.12
Jugular distension	151 (45%)	130 (59%)	21 (18%)	p<0.001
Edema	227 (67%)	177 (80%)	50 (43%)	p<0.001
Orthopnea	113 (33%)	93 (42%)	20 (17%)	p<0.001
Thorax	233 (69%)	179 (81%)	54 (47%)	p<0.001
Radiology				
Chest X-ray	224 (66%)	178 (80.5%)	46 (40%)	p<0.001
Laboratory				
BNP[a]	658±896	859±985	229±433	p<0.001
eGFR[a]	58.7±28	54.8±26	67±29	p<0.001
Na[a]	137.6±4.9	137.5±5	137.8±4	p=1

[a]Values express as mean±standard deviation. BNP, brain natriuretic peptide; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; eGFR estimated glomerular filtration rate; HR, heart rate; MI, myocardial infarction; SBP, systolic blood pressure.

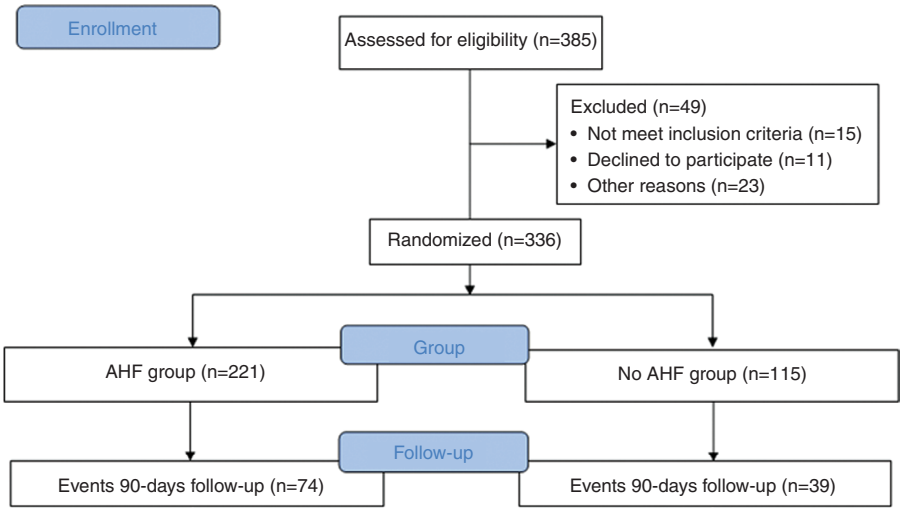

Figure 1 Studied population, included and excluded patients and 90-day follow-up.

We also described the correlation between copeptin value and events in AHF and in no-AHF group at T0 (Figure 2A) and Td (Figure 2B), resulting in patients with events at 90 days had higher copeptin values independently from their dyspnea origin (p<0.001).

Furthermore, we calculated copeptin variation during hospitalization in all dyspneic patients and the median Δ copeptin from admission to discharge (ΔT). Figure 3 shows patients with smallest reduction of copeptin had more events [ΔT=30 (–892 to 683) pmol/L] compared to patients with higher decrease [ΔT=–6.0 (–491 to 62) pmol/L]. Therefore, the difference between copeptin values at Td and at T0 in ED showed significant predictive value for 90-day events in all studied patients (p<0.001). The ΔT copeptin in AHF patients was –9 pmol/L (–491 to 61) in those without events and 43 pmol/L (–892 to 683) in those with events, while in no-AHF patients it was –5 pmol/L (–279 to 25) in no events and 18 pmol/L (–384 to 467) in events. In both groups, patients with high variability in copeptin values have a better outcome at 90 days than patients with less variation.

Figure 4 shows the areas under the receiver operating characteristic curve (AUC) to predict 90-day mortality in all dyspneic-studied populations were 0.67 (95% CI 0.61–0.73) for copeptin T0 (p<0.001), 0.83 (95% CI 0.79–0.88) for copeptin Td (p<0.001) and 0.85 (95% 0.88–0.91) for ΔT copeptin (p<0.001).

Groups 1, 2 and 3 were 60, 210 and 66 patients, respectively. Furthermore, we analyzed the number of patients

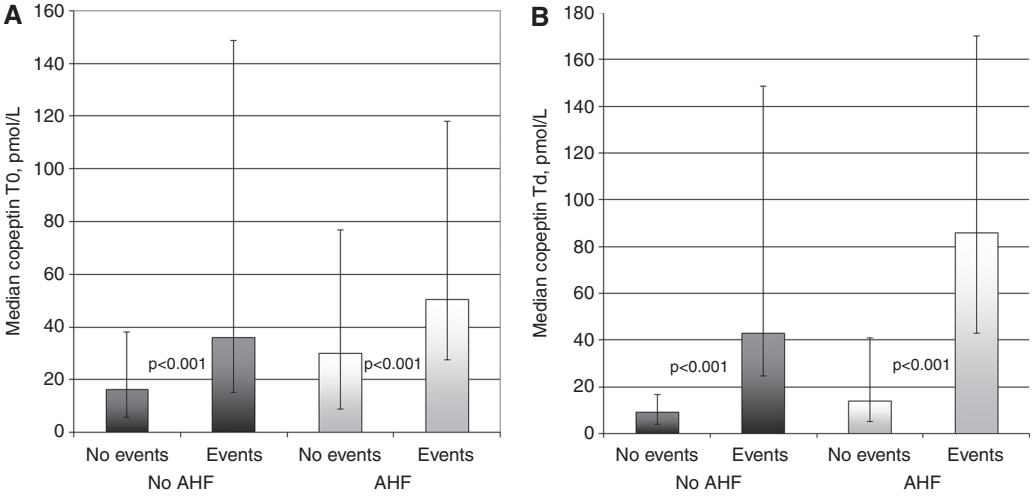

Figure 2 Median values [IQR] copeptin values in two groups (AHF and no-AHF) in patients with 90-day events and without events at admission (A) and discharge (B).

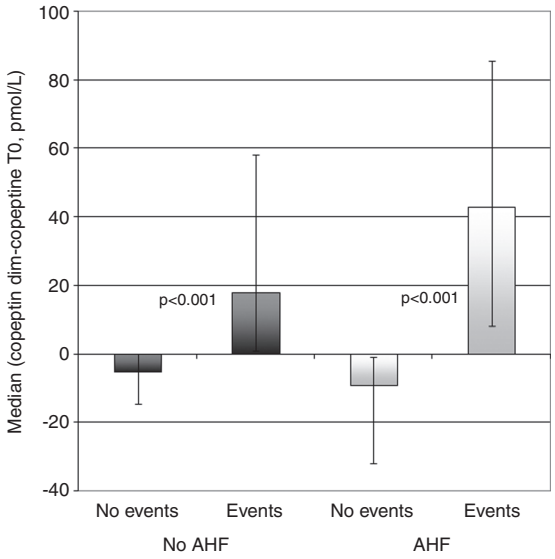

Figure 3 Delta median [IQR] copeptin values at admission in both groups (AHF and no-AHF) in patients with 90-day events and without events.

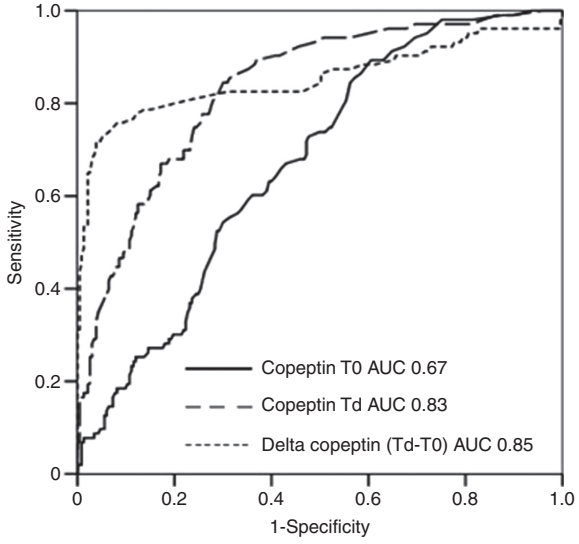

Figure 4 ROC analysis for 90-day events (death and rehospitalization).

who underwent 90-day events in each group. Figure 5 shows the proportional number expressed in percentage of dyspneic patients with events at 90-day follow-up. In group 1 patients with events at 90 days were 3.3%, in group 2 were 34.8% and in group 3 were 42.4%. Groups 2 and 3 have a higher frequency of patients with events compared to group 1 with a statistically significant difference ($p<0.001$).

Table 2 shows the multivariate logistic analysis for the prognostic value of copeptin was performed with the

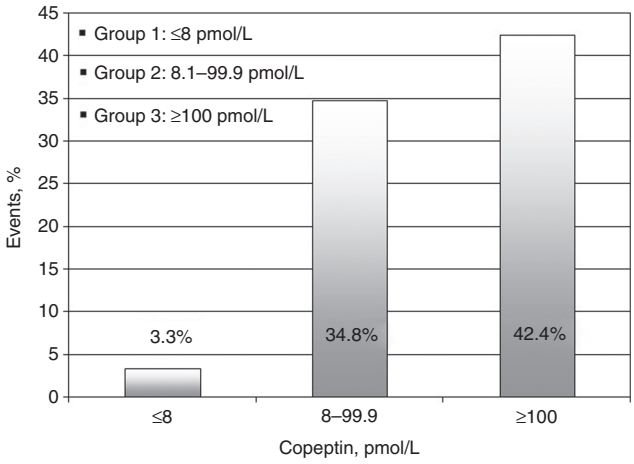

Figure 5 Percentage of 90-day events (death and rehospitalization) in each copeptin class at admission.

Table 2 Multivariate logistic analysis.

Covariate	B	S.E.	Sig.	Exp(B)
Gender	0.516	0.261	0.048	1.675
GFR	−0.018	0.005	0.000	0.982
Group 2	2.579	0.740	0.000	13.184
Group 3	2.787	0.769	0.000	16.228

variables that significantly correlated at the univariate: gender, age, sodium, BNP, systolic blood pressure (SBP), diastolic blood pressure (DBP), eGFR (calculated with Modification of Diet in Renal Disease, MDRD), group 1, group 2 and group 3.

Discussion

Acute dyspnea is a common cause of admission to ED. In clinical practice, the identification and management of dyspnea patients at risk of a worse prognosis is difficult, since dyspnea is usually associated with various origins, such as cardiac, pulmonary, metabolic and others. In this context we evaluated the prognostic role of copeptin assessed at admission, discharge and its Δ for identifying patients with poor prognosis also differentiating between patients with cardiac and non-cardiac dyspnea. First, looking at the plasma level of copeptin assessed in our study of healthy volunteers we found a medial value of 8 pmol/L. This result is slightly higher compared to the one obtained from Bhandari et al. [22] who conducted a large study on 706 healthy individuals and found a copeptin median value of 4.3 (0.4–44.3) pmol/L in males, and

3.2 (1.0–14.8) pmol/L in females. Our results in the control group were significantly lower compared to that obtained in dyspneic patients in each considered time.

Patients with AHF had higher copeptin levels than patients with non-cardiac dyspnea. Our data confirm the results obtained in acute dyspneic patients by Potocki et al. [3] who observed that copeptin levels at T0 were significantly elevated. Moreover, we demonstrated when comparing patients with AHF and no-AHF, the copeptin values in the AHF group were significantly higher at admission and discharge confirming data of other studies [3, 13]. From our results we can speculate, also in agreement with literature data, that copeptin, although it is not a specific marker for disease etiology, is able to accurately identify patients with dyspnea of cardiac origin [9, 14].

In our opinion the most interesting results from our data are those that correlated with the prognostic role of copeptin. We showed that dyspneic patients with high levels of copeptin at both T0 and Td had significantly higher risk of developing events (death or rehospitalization) at 90 days. Similar results have been found by Potocki et al. [3], who demonstrated that copeptin was the strongest independent predictor for 30-day mortality in all patients with acute dyspnea, especially in patients with AHF, and by Stoiser et al, in a prospectively study, who showed that copeptin is an excellent predictor of outcome in AHF [23]. Also in the BACH trial [24] it was demonstrated that elevated copeptin concentrations were associated with increased 90-day mortality, heart failure related admission, and heart failure related ED visits. Also Alehagen et al. showed an association between copeptin high level and increased risk of all-cause mortality in AHF patients [25]. In our study we confirmed the prognostic value of admission copeptin in dyspneic patients both from cardiac and non-cardiac origin but we added also the importance of assessing copeptin at discharge. In fact, a measurement of plasma copeptin at Td seems to be able to predict 90-day events in all dyspneic patients with an AUC greater than at T0 (0.83 vs. 0.67) (Figure 4).

No data are available on copeptin variations during hospitalization and its prognostic significance. Therefore, we monitored copeptin variation from admission to discharge. Our results showed the usefulness of serial copeptin assessment and demonstrated that there is a better 90-day prognosis in dyspneic patients with a higher decrease of copeptin from admission to discharge compared to patients who showed a lower decrease of copeptin. Considering the difference between AHF and no-AHF patients, it seems that in both groups of patients a great reduction of copeptin from admission to discharge is desirable and is linked to a better outcome. This result could underline that copeptin release is not only related to cardiac stress but it is also caused by different physiopathology mechanisms. Indeed the reason of copeptin variations during hospitalization depends on multiple factors (diseases, therapies, comorbidities, etc). The variation of copeptin level could be linked with loop diuretic doses as analyzed by Balling et al. [26], or reflect sodium and water abnormalities [27, 28], very common in heart failure patients. Otherwise a great reduction of copeptin was obtained in patients treated with more adequate or intensive therapy or it depends on patient response. Miller et al. performed serial measurements of copeptin in patients with heart failure, and this biomarker showed a good predictive value in detecting and managing the highest risk outpatients with heart failure [29]. The ΔT is able to significantly predict events better than a single measurement of copeptin (Figure 4). The copeptin reduction during hospitalization and correlation with the prognosis could lead to an innovative use of this biomarker. If we hypothesize that a greater copeptin reduction is due to clinical improvement as consequence of medical therapies and of patient's response to therapy, the physician could monitor copeptin variations together with other variables to make more appropriate risk stratification, such as our group demonstrated for BNP in AHF [30].

On the basis of copeptin level at T0 and the median value in our control group, we divided the dyspneic population into three groups. We assumed group 1 as low risk of events (<8 pmol/L, as our control group), group 2 as intermediate risk and group 3 as high risk. From our results only 3.3% of patients in group 1 had events at 90 days while 34.8% in group 2 and 42.4% in group 3. Furthermore, groups 2 and 3 showed high OR (13.1 and 16.2, respectively) for the risk of events. These findings could give a great support in clinical practice and decision making for determining patient's risk stratification and outcome. Physicians could decide on a more aggressive treatment and tight monitoring in patients with admission copeptin level >8 pmol/L in ED and for patient with low in hospital copeptin variation.

Limitations

Our study was limited by the modest size of patients and short follow-up period, resulting in a relatively small number of 90-day events. We assessed the copeptin only at admission and discharge, but a more accurate serial assessment probably needs more in-hospital measurements. Actually, the prognostic value of Td copeptin and ΔT copeptin are very similar (AUC 0.83 and 0.85, respectively),

but they express different aspects of copeptin value. Td copeptin is only a single discharge value while ΔT copeptin expresses a mirror of all the entire period of hospitalization for each patient. We used a cut-off of 8 pmol/L as suggested by the literature and from our control group, but this value could be too low. Indeed, only 60 patients on 336 have these low copeptin levels. It means that more than 80% of all the patients need an aggressive treatment. Finally, we did not evaluate other biomarkers and their variations in addition to copeptin. Further studies should evaluate the potential role of copeptin, alone or with other biomarkers, in driving in- and out-hospital therapy.

Conclusions

This study confirms the prognostic role of single measurement of copeptin at admission and discharge in patients admitted with acute dyspnea, from cardiac or non-cardiac origin, Serial assessment of copeptin during hospitalization seems to provide additional value in identifying patients at higher risk for death and rehospitalization at 90 days. A high biomarker decrease during hospitalization, from admission to discharge, seems to be linked with a better outcome and could help the physicians in therapy, risk stratification and follow-up.

Conflict of interest statement

Authors' conflict of interest disclosure: The authors stated that there are no conflicts of interest regarding the publication of this article.
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