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Original Contribution

Thirty and ninety days mortality predictive value of admission and in-hospital procalcitonin and mid-regional pro-adrenomedullin testing in patients with dyspnea. Results from the VERyfing DYspnea trial ☆

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ABSTRACT

Introduction: Mid-regional pro-atrial natriuretic peptide (MR-proANP), procalcitonin (PCT), and mid-regional pro-adrenomedullin (MR-proADM) demonstrated usefulness for management of emergency department patients with dyspnea.
Methods: To evaluate in patients with dyspnea, the prognostic value for 30 and 90 days mortality and readmission of PCT, MR-proADM, and MR-proANP, a multicenter prospective study was performed evaluating biomarkers at admission, 24 and 72 hours after admission. Based on final diagnosis, patients were divided into acute heart failure (AHF), primary lung diseases, or both (AHF + NO AHF).
Results: Five hundred one patients were enrolled. Procalcitonin and MR-proADM values at admission and at 72 hours were significantly ($P < .001$) predictive for 30-day mortality: baseline PCT with an area under the curve (AUC) of 0.70 and PCT at 72 hours with an AUC of 0.61; baseline MR-proADM with an AUC of 0.62 and MR-proADM at 72 hours with an AUC of 0.68. As for 90-day mortality, both PCT and MR-proADM baseline and 72 hours values showed a significant ($P < .0001$) predictive ability: baseline PCT with an AUC of 0.73 and 72 hours PCT with an AUC of 0.64; baseline MR-proADM with an AUC of 0.66 and 72 hours MR-proADM with an AUC of 0.71. In AHF, group biomarkers predicted rehospitalization and mortality at 90 days, whereas in AHF + NO AHF group, they predict mortality at 30 and 90 days.

☆ Competing 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.

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Conclusions: In patients admitted for dyspnea, assessment of PCT plus MR-proADM improves risk stratification and management. Combined use of biomarkers is able to predict in the total cohort both rehospitalization and death at 30 and 90 days.

1. Introduction

Patients referring to emergency department (ED) for dyspnea may have both cardiovascular or lung diseases as an underlying etiology, thus creating a challenge for a prompt differential diagnosis [1]. Unfortunately, neither patient history nor physical examination, although of great importance [2] results in providing adequate information to immediately and accurately differentiate shortness of breath due to heart failure or pneumonia or exacerbation of chronic obstructive pulmonary disease (COPD) or asthma. In this setting, natriuretic peptides have been demonstrated to be useful for rule out or rule in for acute heart failure (AHF) [2,3].

Furthermore, once the diagnosis is confirmed, there are often equivocal agreement in determining final disposition as a consequence of the treatment decision based on disease severity. In other words, which of these patients should be adequately discharged, admitted to an ordinary ward, or to the intensive care unit (ICU) still represent an overt dilemma. In this latter attempt, biomarkers seem to be a helpful tool to immediately predict, from the moment of ED admission, short-term patient mortality and hospital readmission [3,4]. In a recent study, our group demonstrated the utility of procalcitonin (PCT) and mid-regional pro-adrenomedullin (MR-proADM) in the risk stratification of critically ill patients presenting for fever in the ED [4]. Moreover, in undifferentiated ED patients with acute dyspnea, MR-proADM has been demonstrated to be useful in guiding initial disposition and might therefore be helpful to improve resource use and patient care [5]. Moreover, The Biomarkers in Acute Heart Failure (BACH) trial demonstrated the diagnostic role of mid-regional pro-atrial natriuretic peptide (MR-proANP) to identify patients with AHF and the prognostic role of MR-proADM in the same cohort of patients [6,7].

However, so far, there are no reliable data on the prognostic utility of serial assessment of PCT, MR-proANP, and MR-proADM used together from ED admission and during hospitalization in patients referring for dyspnea.

The objective of this study was to assess the prognostic usefulness for 30 and 90 days mortality and rehospitalization, of serial assessments of a multimarker panel consisting of PCT, MR-proADM, and MR-proANP in adult patients hospitalized from ED with dyspnea of different etiology.

The secondary end point was to confirm in the whole study population the diagnostic accuracy of MR-proANP for AHF and PCT for infectious diseases.

2. Material and methods

2.1. Study population

From December 2010 to December 2011, we conducted a multicenter, prospective cohort study of patients presenting to the EDs in 9 teaching and nonteaching hospitals in Italy (Sant'Andrea Hospital, University of Rome Sapienza, coordinating center; San Martino–IST University Hospital in Genoa; Vittorio Emanuele–Teaching Hospital in Catania; SS Giovanni e Paolo Hospital in Venice, University of Padua; San Matteo Teaching Hospital, Pavia; Parma Teaching Hospital, Parma; Maggiore Teaching Hospital, Milan; Città della Scienza e della Salute Hospital, Turin; and S. Orsola–Malpighi Teaching Hospital, Bologna). The VERyfing DYspnea trial inclusion criteria were ED admission for acute dyspnea, with an expected hospital stay of at least 72 hours. First blood collection for the biomarkers had to be done before beginning any treatment. Exclusion criteria were psychogenic dyspnea (diagnosed based on negative clinical and instrumental evaluation during the first assessment for disease), posttraumatic dyspnea, pneumothorax, major surgery (abdominal cardiothoracic or orthopedic surgery), ST elevation, myocardial infarction, burns, patients younger than the age of 18 years, patients who were unable to give informed consent, life expectancy less than 72 hours.

Patients transferred to another hospital within 72 hours after ED admission were withdrawn from the study after transfer.

The research protocol was reviewed by the Ethics Committee from Sant'Andrea Hospital in Rome, and all participating sites approved the study.

Five hundred one patients were enrolled and constituted the study population. Attending physicians made the initial symptom-based decision and proceeded to baseline data collection; they were blinded to MR-proADM, MR-proANP, and PCT values. Informed written consent was obtained from all patients before enrollment. The study protocol conforms to the ethical guidelines of Declaration of Helsinki.

2.2. Clinical evaluation and follow-up

Trained investigators collected data on blood samples taken at T0 (ED admission), T24 (24 hours), T72 (72 hours) that coincided with blood sampling for biomarkers (MR-proADM, MR-proANP, and PCT) measurement. Data collected included clinical history and vital signs at the time of each blood sample. To determine the criterion standard diagnosis, 1 cardiologist and 1 pulmonologist independently reviewed all medical records of the patients and independently classified the diagnosis as dyspnea due to heart failure or due to another cause. Specialists were blinded to the other's assessments, investigational markers, and the ED physician's diagnosis. They had access to the ED case report forms, which included medical history plus data on blood analysis (creatininemia, azotemia, glycemia, blood sodium level, blood potassium level, transaminase, arterial blood gas analysis, complete blood count), chest x-ray, echocardiography, and cardiac catheterization as available as well as the hospital course for patients who were admitted. Current guidelines were used to confirm final diagnosis of AHF [8]. In cases of COPD and pneumonia, the diagnosis was defined by the criteria of Global Initiative for Chronic Obstructive Lung Disease guidelines and pneumonia guidelines of British Thoracic Society, respectively [9,10]. Thirty and 90 days after discharge, follow-up documenting subsequent readmission and mortality were obtained by telephone interview with patients, their relative, or patient's family practitioner. We considered adverse event medical outcome as any event (hospital readmission, death).

According to the final diagnosis, patients were divided into 3 groups:

(1) "AHF" group (final adjudicated diagnosis of AHF);
(2) "NO AHF" group (final adjudicated diagnosis of asthma, acute exacerbation of chronic obstructive pulmonary disease (AECOPD), pneumonia (NO AHF); and
(3) "AHF + NO AHF" group (final adjudicated diagnosis including the presence of AHF plus the contemporary presence of 1 or more pulmonary diseases.

2.3. Laboratory measurement

Study personnel collected patient samples in tubes containing ethylenediaminetetraacetic acid and separated plasma by centrifugation within 1 hour of collection. Plasma samples were frozen immediately and stored at −40°C until the study completion. Mid-regional pro-adrenomedullin, MR-proANP, and PCT were measured using an automated sandwich chemiluminescence immunoassay on the KRYPTOR system (Thermo Fisher Scientific Inc, Hennigsdorf/Berlin, Germany) [11,12]. The laboratory measurement process complied with standard quality for a medical laboratory.

2.4. Statistical analysis

The results are expressed as mean ± standard deviation (SD) or median and interquartile range (IQR) in parentheses [13]. Statistical analysis was performed using GraphPad Prism 5.0 (GraphPad Software Inc, San Diego, CA) and MedCalc Version 12 (MedCalc Software, Mariakerke, Belgium). The normality of data distribution was checked with D'Agostino and Pearson normality test [14].

Comparisons of sex, age, systolic blood pressure, diastolic blood pressure, saturation, heart rate, respiratory rate, medical history, length of stay, and diagnosis at discharge between AHF, NO AHF, and AHF+NO AHF groups were performed using the χ^2 test for categorical variables and one-way analysis of variance for continuous variables. Comparisons of MR-proADM, MR-proANP, and PCT between AHF, NO AHF, and AHF + NO AHF groups were performed using Kruskal-Wallis test. A value of $P < .05$ was considered significant.

A receiver-operating characteristic (ROC) curve was used to determine the ability of MR-proADM, MR-proANP, and PCT to predict rehospitalization and death at 30 and 90 days from discharge in AHF, NO AHF, and AHF + NO AHF groups patients. The area under the curve (AUC) indicated the predictive value of MR-proADM, MR-proANP, and PCT at baseline (ED admittance value) and at 72 hours. For the AUC, a value of $P < .05$ was considered significant.

Moreover, an ROC curve was used to determine the ability of MR-proANP and PCT to identify patients with AHF and infections, respectively.

3. Results

We enrolled 501 patients hospitalized from ED for shortness of breath. Fig. 1 shows a flow chart that describes the study. Statistical analysis was performed in 441 patients (23 withdrew consent, 16 had incomplete data, 21 withdrew from the study: 15 patients because they were transferred to other hospital within 72 hours after ED admittance, 6 patients because the cardiologist and pulmonologist did not agree on the final diagnosis). Patients' characteristics are shown in Table 1. Patients were equally distributed within the different centers: 209 (47.4%) were males. Median (IQR) age was 80 (72-85) years. The

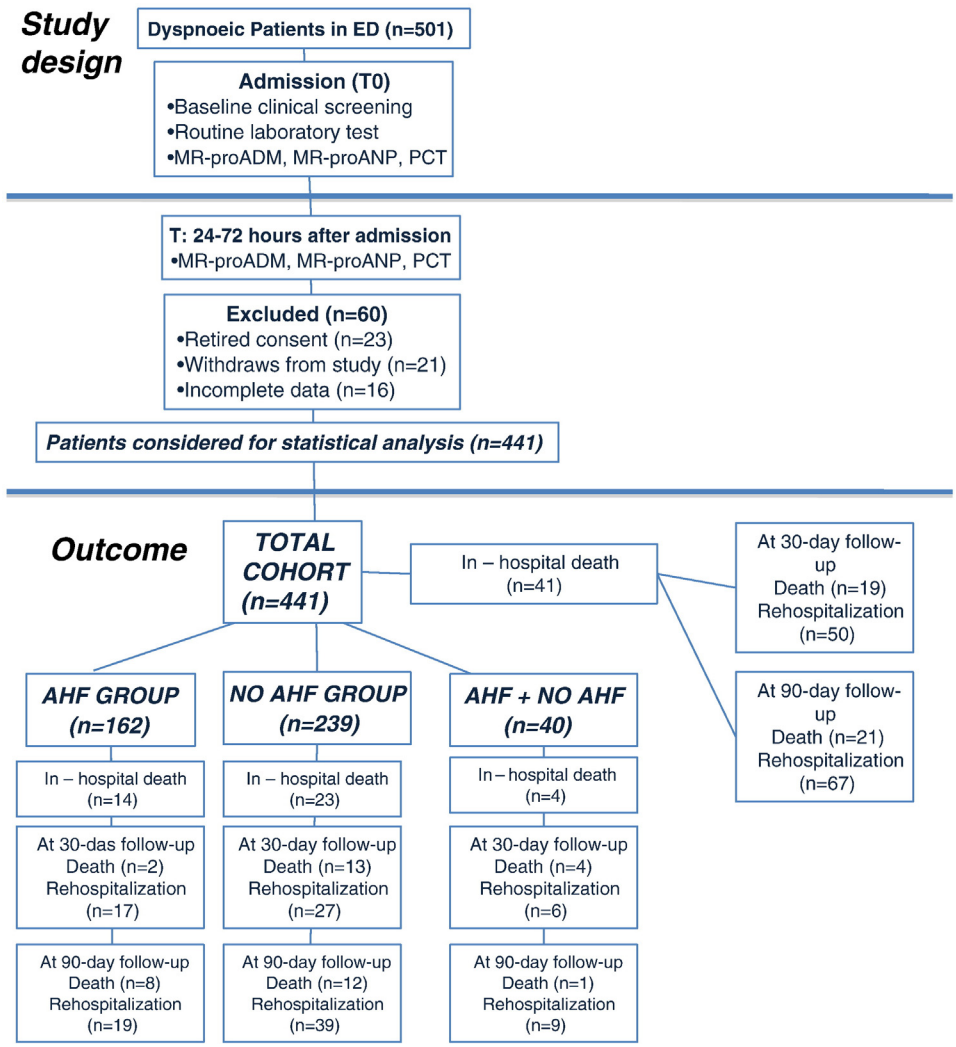


Fig. 1. Design of the study and patients' outcome.

Table 1
Patient characteristics

	Total cohort N = 441 (%)	AHF n = 162 (%)	NO AHF n = 239 (%)	AHF + NO AHF n = 40 (%)	*P*
Total	441	162	239	40	
Men	209 (47.4%)	72 (44.4%)	114 (47.7%)	23(57.5%)	.33
Women	232 (52.6%)	90 (55.6%)	125 (52.3%)	17(42.5%)	
Mean age median, IQR	80 [72-85]	82 [75-86]	78 [71-83]	79[72-87]	.04
Mean systolic blood pressure ± SD mm Hg	144 ± 28	147 ± 29	143 ± 26	144 ± 35	.36
Mean diastolic blood pressure ±SD mm Hg	82 ± 15	84 ± 15	80 ± 14	81 ± 19	.02
Saturation median, IQR	92 [88-96]	94 [89-97]	92 [89-96]	89 [87-92]	.03
Heart rate median, IQR	93 [80-110]	94 [80-110]	90 [80-108]	99 [80-106]	.04
Respiratory rate median, IQR	25 [20-30]	24 [22-30]	24 [20-30]	28 [24-36]	.05
Medical history					
Chronic heart failure	120 (27%)	58 (36%)	48 (20%)	14 (35%)	.0006
COPD	185 (42%)	42 (26%)	121 (51%)	22 (55%)	<.0001
Hypertension	151 (34%)	55 (34%)	80 (33%)	16 (40%)	.29
Length of stay					
<3 days	34 (8%)	6 (4%)	27 (11%)	1 (2%)	.008
3-10 days	185 (42%)	70 (43%)	105 (44%)	10 (25%)	.07
>10 days	222 (50%)	86 (53%)	107 (45%)	29 (72%)	.003
Diagnosis at discharge					
Sepsis	15/441 (3%)	0	15/239 (6%)	0	
Pneumonia	92/441 (21%)	0	92/239 (39%)	0	
Asthma	3/441 (0.7%)	0	3/239 (1%)	0	
Exacerbation COPD	129/441 (29%)	0	129/239 (54%)	0	
AHF	162/441 (37%)	162/162 (100%)	0	0	
Cancer	3/441 (0.7%)	0	0	3/40 (8%)	
Sepsis + AHF	2/441 (0.5%)	0	0	2/40 (5%)	
Pneumonia + AHF	19/441 (4%)	0	0	19/40 (47%)	
Asthma + AHF	1/441 (0.2%)	0	0	1/40 (2%)	
Exacerbation COPD + AHF	15/441 (3%)	0	0	15/40 (38%)	

patients were divided into 3 different groups based on the different etiology of dyspnea: AHF dyspnea, NO AHF dyspnea, and AHF + NO AHF dyspnea (Fig. 1). The different diagnoses were adjudicated by an independent cardiologist and a pulmonologist according to current guidelines [8-10]. Fig. 2 shows the different values (median [IQR]) of biomarkers at the different times for each group. Mid-regional pro-atrial natriuretic peptide at ED admission had a diagnostic value for diagnosis of AHF with AUC of 0.66 ($P < .001$) with a cutoff of 327.7 pg/mL, whereas PCT at ED admission had a diagnostic power for detecting with the presence of infectious diseases with an AUC of 0.65 ($P < .0001$) with a cutoff of 0.09 ng/mL. All events (rehospitalization and death), in all different groups, are shown in Fig. 1. The analysis for whole population's events showed that none of the biomarkers, collected at admission was able to predict rehospitalization at both 30- and 90-day follow-up. On the other hand, admission PCT and MR-proADM had a strong predictive value for mortality during the follow-up period. For 30-day mortality prediction, both PCT and MR-proADM baseline and 72 hours values were statistically significant: baseline PCT had an AUC of 0.70 ($P < .0001$), and PCT at 72 hours had an AUC of 0.61 ($P < .005$); baseline MR-proADM had an AUC of 0.62 ($P < .05$), and MR-proADM at 72 hours had an AUC of 0.68 ($P < .0001$). In addition, for 90-day mortality both PCT and MR-proADM baseline and 72 hours values were statistically significant: baseline PCT had an AUC of 0.73 ($P < .0001$), and PCT at 72 hours had an AUC of 0.64 ($P < .001$); baseline MR-proADM had an AUC of 0.66 ($P < .001$), and MR-proADM at 72 hours had an AUC of 0.71 ($P < .0001$) (Table 2). Furthermore, Table 2 shows the predictive value for mortality of each biomarker separately in each of the 3 studied groups. Multimarker values of the AUC of the ROC curve are shown in Table 3.

Furthermore, we also evaluated the variations (δ changes) of each biomarker over the time of hospitalization in the whole population for the prognostic strength, divided into 2 groups: patients with and without events (Fig. 3).

Compared with the single values of each of the 3 biomarkers considered at admission and 72 hours for the different groups, trends of biomarkers variations values during hospitalization seemed to be nonsignificant for predicting events during 30 and 90 days follow-up.

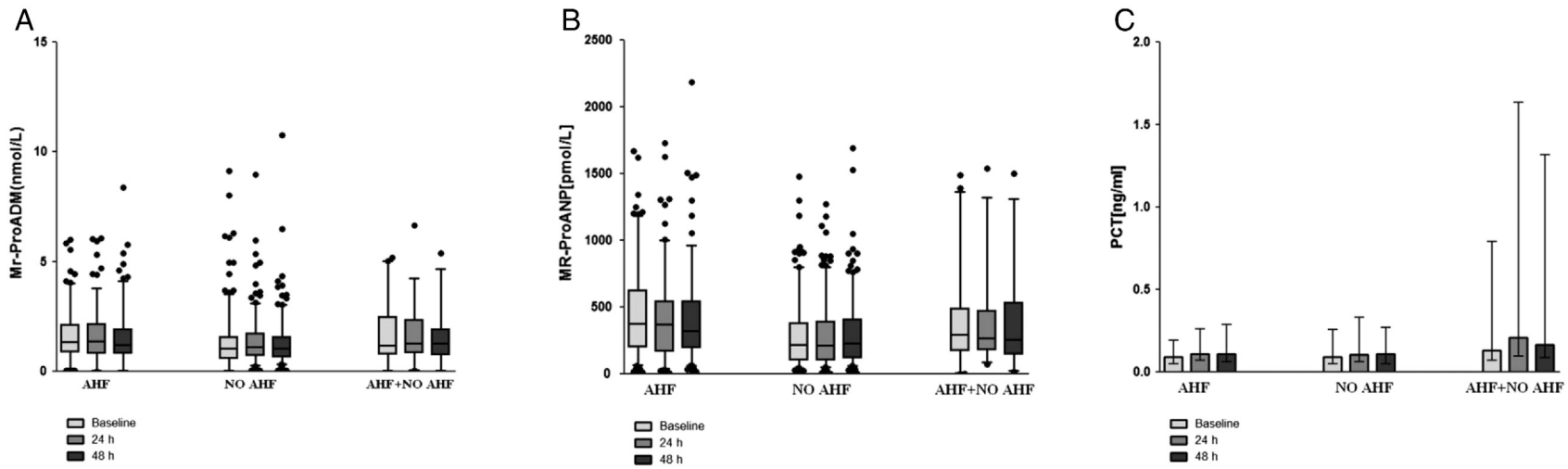
4. Discussion

In managing patients with acute dyspnea in the ED, it is mandatory to establish an early and certain cause of the origin of the shortness of breath to start an appropriate treatment (2-5). On the other hand, immediately defining patient severity at the moment of presentation and ascertainment of risk stratification may be very useful for treatment and therapeutic decisions. To be helpful in clinical routine practice, a biomarker should provide additional actionable information not already available by standard method that accomplishes at least 1 or more of the following: (*a*) assisting in establishing a rapid and reliable diagnosis, (*b*) providing an indication of prognosis, (*c*) selecting those patients most likely to benefit from a specific intervention, (*d*) reflecting the efficacy of specific interventions, and (*e*) warning in advance of disease progression.

Our study supports the concept that a multimarker panel consisting of MR-proANP, MR-proADM, and PCT may be helpful for ED physicians in the early risk stratification for patients presenting with acute dyspnea. The use of this panel may improve the accuracy of standard clinical judgment of ED physicians.

Maisel et al [6] in the BACH trial demonstrated that MR-proANP levels may provide additional diagnostic information for the diagnosis of AHF in addition to B-type natriuretic peptide (BNP) or N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) levels in subgroups for which a correct diagnosis is considered difficult but clinically highly desirable, and in addition to this, they determined that MR-proADM was superior to BNP and NT-proBNP for predicting 90-day mortality in patients with dyspnea due to AHF. In that study, only 1 determination of biomarkers at the moment of patient presentation with acute shortness of breath in ED was performed [6].

Similarly to the BACH trial [6,7], we also confirmed the diagnostic capacity of MR-proANP in identifying dyspnea due to AHF. Dyspneic patients who present to the ED could have different underlying causes of dyspnea. Our results underline that, in patients with AHF, the use of MR-proANP had a diagnostic value with an AUC of 0.66 ($P < .001$) with a cutoff of 327.7 pg/mL. The AUC value in our study is lower than the



	TOTAL COHORT N 441	AHF (Acute Heart Failure) Median [IQR] (N 162)	NO AHF (No Acute Heart Failure) Median [IQR] (N 239)	AHF + NO AHF Median [IQR] (N 40)	p value
MR-pro ADM (T0)	1.19 [0.74 –1.89]	1.34 [0.89 – 2.12]	1.04 [0.60 – 1.58]	1.19 [0.79 – 2.46]	**0.0008**
MR-pro ADM(T24)	1.21 [0.75 –1. 89]	1.37 [0.82 – 2.14]	1.12 [0.71 – 1.72]	1.26 [0.87 – 2.33]	0.05
MR-pro ADM(T72)	1.13 [0.74 –1.76]	1.22 [0.83 – 1.92]	1.04 [0.65 – 1.56]	1.28 [0.82 – 1.91]	0.07
MR-pro ANP (T0)	277 [141.8 – 485.28]	374.6 [205.3 – 621.7]	220.1 [104 – 380.6]	295.1 [175.5 – 486.1]	**<0.0001**
MR-pro ANP(T24)	259.7[133.2 – 482.2]	372.6 [172.6 – 542.3]	211.2 [104.6 – 387.3]	268.5 [188.5 – 467.3]	**<0.0001**
MR-proANP(T72)	260[143.18 – 467.9]	321.2 [196 – 541.6]	228.3 [122.4 – 405.4]	256.3 [157.8 – 532.2]	**0.001**
PCT (T0)	0.09 [0.06 – 0.22]	0.09 [0.05 – 0.19]	0.09 [0.05 – 0.26]	0.13 [0.075 – 0.62]	0.05
PCT (T24)	0.12 [0.07 – 0.34]	0.11 [0.07 – 0.26]	0.11 [0.06 – 0.33]	0.21 [0.10 – 1.59]	**0.01**
PCT (T72)	0.11 [0.06 – 0.31]	0.11 [0.06 – 0.29]	0.11 [0.05 – 0.27]	0.17 [0.10 – 1.09]	**0.02**
eGFR	**59 [38 - 82]**	**55 [35.25 - 69]**	**62 [43.5 – 86.5]**	**57.55 [40.73 – 73.75]**	

Fig. 2. Different values of the 3 biomarkers at the different times for each group, expressed as median (IQR). Abbreviation: *eGFR*, estimated glomerular filtration rate.

AUC of the BACH trial (AUC 0.90, $P < .0001$). This could be due to the fact that the characteristics of our patient population were probably different from those of the BACH trial. Our patients tended to be older, with increased comorbidities and mirrored the real life of the ED situation in Italy, whereas the BACH study included primarily selected AHF patients.

Furthermore, our results underline that, in dyspneic patients, which refer to ED, PCT can identify patients with a respiratory infection with accuracy and specificity, with an AUC of 0.65 ($P < .0001$) with a cutoff of 0.09 ng/mL. Prognostic value of biomarkers in ED can have a major impact from a decision-making prospective [5,15]. For the ED physician, it is very important to know the priority of treatment to optimize the patient's care: this should allow a good management and a better outcome. For this reason, the use of biomarkers with prognostic value is very helpful for ED physicians and should ameliorate the patient's clinical assessment. Published studies have already demonstrated that MR-proADM, MR-proANP, and PCT have a prognostic value in critically ill patients [16], but in addition, our study used a serial assessment approach with these biomarkers, to evaluate the risk stratification in dyspneic patients. The analysis for all patients' events showed that none of the biomarkers was able to predict rehospitalization at 30- or 90-day follow-up.

On the other hand, PCT and MR-proADM had a strong predictive value for mortality (30 and 90 days) both at baseline value and at 72 hours follow-up. Previous studies have shown that MR-proADM could be useful for predicting outcomes in patients with community-acquired pneumonia [17], sepsis [18,19], acute myocardial infarction [20,21], and in patients with acute decompensated heart failure. Mid-regional pro-adrenomedullin release in acute dyspneic patients is due to many mechanisms: volume overload, bacterial endotoxins, proinflammatory cytokines, and impaired removal of circulating biomarker during lung injury and kidney dysfunction [22].

In our study, MR-proADM, particularly the value at 72 hours, seems to assume a stronger predictive role. Therefore, serial measurements of this biomarkers seem to give important additional prognostic information in better identifying patients after the start of treatment still prone to a higher risk of death in the next few months.

Procalcitonin concentration appears to be correlated with the severity of infection [23-27]. The usefulness of PCT as a diagnostic and prognostic marker has been reviewed in some meta-analyses, but the results are still somewhat controversial [28,29]. Although some data have been published on the use of PCT in detecting infectious diseases in ED [30-35], there are relatively nondefinitive information regarding the diagnosis and prognosis of sepsis in patients presenting to the ED and of serial PCT measurements to follow the course of infection [36-39].

To date, a lot of studies in the literature showed the prognostic value of PCT in infectious patients, and also, our group demonstrated in a previous study the correlation of PCT and MR-proADM with Acute Physiology and Chronic Health Evaluation II score, as a known prognostic score in critically ill patients [4,40,41]. Our results for the AHF group showed that MR-proADM at T0 and T72 for 90-day mortality had an AUC of 0.76 ($P < .005$) and an AUC of 0.77 ($P < .05$), respectively. The same results were illustrated in the BACH trial, where MR-proADM had superior accuracy for predicting 90-day mortality compared with BNP (AUC: 0.674 vs 0.606, respectively; $P < 0.001$) in AHF [7].

In our NO AHF group (NO AHF—asthma, AECOPD, pneumonia), MR-proADM at T72 had an AUC of 0.71 ($P < .01$) for 30-day mortality. For 90-day mortality, PCT at T0 had a prognostic value with an AUC of 0.74 ($P < .001$) and MR-proADM at T72 with an AUC of 0.71 ($P < .001$). Stolz et al [42] demonstrated that MR-proADM had a statistically significant correlation with the length of stay, with patients who required ICU admission and in long-term nonsurvivors. Moreover, Christ-Crain et al [43] underlined the capacity of MR-proADM to predict severity and outcome in community-acquired pneumonia.

Table 2
Area under the curve for mortality prediction of PCT and MR-proADM for all patients and separately in each group

Biomarkers	30-Day mortality		90-Day mortality	
	AUC	*P*	AUC	*P*
In all patients				
PCT				
T0	0.70	<.0001	0.73	<.0001
T72	0.61	<.05	0.64	<.001
MR-proADM				
T0	0.62	<.05	0.66	<.001
T72	0.68	<.001	0.71	<.0001
AHF group				
PCT				
T0	0.56	NS	0.64	NS
T72	0.50	NS	0.50	NS
MR-proADM				
T0	0.78	NS	0.76	<.001
T72	0.78	NS	0.77	<.001
NO AHF group				
PCT				
T0	0.70	<.0001	0.74	<.0001
T72	0.65	<.05	0.70	<.001
MR-proADM				
T0	0.62	NS	0.63	<.05
T72	0.71	<.01	0.71	<.001
AHF + NO AHF group				
PCT				
T0	0.66	NS	0.75	<.02
T72	0.63	NS	0.63	NS
MR-proADM				
T0	0.60	NS	0.69	NS
T72	0.55	NS	0.64	NS

Our results showed that serial measurements provide additional information on top of the first measurement, in particular for MR-proADM, and at which time a reevaluation could be clinically useful, Fig. 3B showed how this biomarker is statistically different in patients with events. We demonstrated that the use of combined biomarkers is really useful as a prognostic factor (Table 3). In particular, the use of combined biomarkers at baseline is able to predict in total cohort of patients all events, such as rehospitalization and death at 30 and 90 days. For other groups, we underlined the use of combined biomarkers to predict rehospitalization and mortality at 90 days in the AHF group. In the AHF + NO AHF group, Table 3 showed the usefulness of combined biomarkers to predict mortality at 30 and 90 days. We demonstrated that MR-proADM, PCT, and MR-proANP could work as outcome monitoring markers in patients with dyspnea presenting to the ED and subsequently admitted to hospital.

In addition to the prognostic value of the biomarkers at the admission and at 72 hours, we analyzed the prognostic value of the 3 biomarkers also at 24 hours from ED admission. We tested it for both mortality and rehospitalization without finding any clinical relevance regarding prognostic significance both at 30 and 90 days.

Results from our study indicate that the use of a combination of these biomarkers predicts outcome in patients admitted for acute dyspnea: the clinical relevance depends on the ability to promptly identify patients at higher risk who need to be treated more carefully. Furthermore, high values of biomarkers at admission suggest to perform more tests during hospitalization that follows ED admission because serial assessment seems to be useful for more accurate risk stratification. In particular, in our study population considered globally, a cutoff value more than 1.80 nmol/L for MR-proADM and a cutoff value more than 0.88 ng/mL for PCT at admission, added to a cutoff value more than 1.38 nmol/L for MR-proADM and more than 0.75 ng/mL for PCT 72 hours after admission significantly predict risk of death, either at 30 or 90 days after hospital discharge. However, further studies need to be done to

Table 3
Area under the curve values of the biomarkers in predicting mortality and rehospitalization in all patients and in the different groups

Biomarkers	Event	Time	AUC	*P*
All patients				
MR-proADM + PCT + MR-proANP	Rehospedalization 30-day	Baseline	0.597	.031
MR-proADM + PCT + MR-proANP	Rehospedalization 30-day	72 h	0.583	.086
MR-proADM + PCT + MR-proANP	Rehospedalization 90-day	Baseline	0.598	.008
MR-proADM + PCT + MR-proANP	Rehospedalization 90-day	72 h	0.534	.386
MR-proADM + PCT + MR-proANP	Mortality 30-day	Baseline	0.666	.032
MR-proADM + PCT + MR-proANP	Mortality 30-day	72 h	0.633	.045
MR-proADM + PCT + MR-proANP	Mortality 90-day	Baseline	0.691	.0002
MR-proADM + PCT + MR-proANP	Mortality 90-day	72 h	0.727	<.0001
AHF group				
MR-proADM + PCT + MR-proANP	Rehospedalization 30-day	Baseline	0.686	.006
MR-proADM + PCT + MR-proANP	Rehospedalization 30-day	72 h	0.531	.756
MR-proADM + PCT + MR-proANP	Rehospedalization 90-day	Baseline	0.703	.0001
MR-proADM + PCT + MR-proANP	Rehospedalization 90-day	72 h	0.582	.209
MR-proADM + PCT + MR-proANP	Mortality 30-day	Baseline	0.731	.393
MR-proADM + PCT + MR-proANP	Mortality 30-day	72 h	0.614	.767
MR-proADM + PCT + MR-proANP	Mortality 90-day	Baseline	0.748	.006
MR-proADM + PCT + MR-proANP	Mortality 90-day	72 h	0.721	.024
NO AHF group				
MR-proADM + PCT + MR-proANP	Rehospedalization 30-day	Baseline	0.575	.230
MR-proADM + PCT + MR-proANP	Rehospedalization 30-day	72 h	0.602	.121
MR-proADM + PCT + MR-proANP	Rehospedalization 90-day	Baseline	0.577	.119
MR-proADM + PCT + MR-proANP	Rehospedalization 90 day	72 h	0.593	.069
MR-proADM + PCT + MR-proANP	Mortality 30-day	Baseline	0.652	.063
MR-proADM + PCT + MR-proANP	Mortality 30-day	72 h	0.658	.128
MR-proADM + PCT + MR-proANP	Mortality 90-day	Baseline	0.638	.048
MR-proADM + PCT + MR-proANP	Mortality 90-day	72 h	0.647	.039
AHF + NO AHF group				
MR-proADM + PCT + MR-proANP	Rehospedalization 30-day	Baseline	0.520	.900
MR-proADM + PCT + MR-proANP	Rehospedalization 30-day	72 h	0.674	.241
MR-proADM + PCT + MR-proANP	Rehospedalization 90-day	Baseline	0.587	.512
MR-proADM + PCT + MR-proANP	Rehospedalization 90-day	72 h	0.591	.470
MR-proADM + PCT + MR-proANP	Mortality 30-day	Baseline	0.946	<.0001
MR-proADM + PCT + MR-proANP	Mortality 30-day	72 h	0.770	.141
MR-proADM + PCT + MR-proANP	Mortality 90-day	Baseline	0.908	<.0001
MR-proADM + PCT + MR-proANP	Mortality 90-day	72 h	0.696	.240

confirm these values and before the multimarker prognostic strategy can be routinely used in clinical practice.

In addition, the variations (δ change) of each biomarker over the time in the whole population did not seem to be statistically significant for prognosis (Fig. 3).

This could be explained with the assumption that the δ change after 72 hours was too premature in reflecting treatment significant changes of biomarkers. If the δ change was measured relative to the last value before discharge, the prognostic strength would have been significant. Nevertheless, the δ change over the hospitalization time was not 1 of principal aims of our study because we simply focused on the prognostic value of the measurements of biomarkers at different times in the different groups during hospitalization.

5. Conclusions

In patients referring to the ED for dyspnea, a multimarker approach including PCT, MR-proADM, and MR-proANP could aid physicians in promptly identifying the origin and the severity of the underlying disease. As a consequence, the use of a panel with these 3 biomarkers could improve the treatment of adult patients admitted to the ED for acute dyspnea. Additional measurements of MR-proADM and PCT

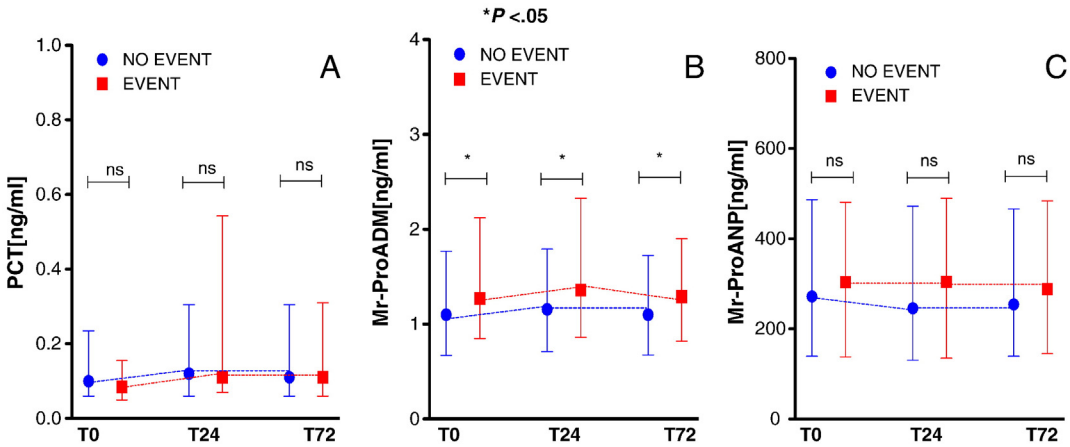


Fig. 3. Correlation between PCT (A), MR-proADM (B), MR-proANP (C) variation during the hospitalization and mortality at 30 and 90 days in all patients.

during the subsequent hospitalization could provide additional information in predicting mortality for these patients compared with a single admittance value. Our results outlined the importance of a serial multimarker panel assessment in the management of patients admitted from ED for dyspnea to predict mortality at 30 days and 90 days.

Therefore, MR-proADM and PCT have a prognostic value, both at ED admission and 72 hours after hospitalization, identifying patients at higher risk for future adverse events, suggesting the need for more attention and accuracy in the management of such patients, both in the treatment and in the final disposition.

6. Limitations

Our study has several limitations, such as the lack of a further value of the biomarkers at the exact discharge time from the hospital. In addition, we do not have data about the causes of rehospitalization or the causes of death during the follow-up.

Key message

- The use of a panel with 3 biomarkers can ameliorate the diagnosis (MR-proANP) and can improve the risk stratification (PCT, MR-proADM) and the treatment of the adult patients admitted to the ED for acute dyspnea.
- Importance of a biomarkers' panel and the serial assessment of the biomarkers in dyspnea management.
- Biomarkers can permit a shorter decision making by emergency physicians to prevent ED overcrowding and can ameliorate patients' clinical outcome.

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