



## RESEARCH ARTICLE

## Mid-Regional Proadrenomedullin as a Prognosis Biomarker of Mortality in Patients Treated with Non-Invasive Ventilation in the Emergency Room

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### Abstract

The mid-regional fragment of the peptide complex Proadrenomedullin (MR-proADM) is a ubiquitous biomarker tissue distribution in the human body with increased levels in the course of certain diseases of great importance for vital engagement and whose clinical course is often associated with dyspnoea.

Prospective observational analytical survey conducted on a group of 191 selected patients requiring urgent treatment with NIV due to acute or exacerbated chronic dyspnoea from any cause, except surgical or neuromuscular, between November 2012 and December 2013, to which they were, extracted a blood sample at the time of initiation of therapy with NIV to determine the MR-proADM.

The first aim of our study was to establish the association between plasma levels of MR-proADM and in-hospital mortality in patients undergoing NIV for acute respiratory failure regardless of source.

The median age of patients was 79-years-old and overall mortality by 22%. Mid-regional pro-adrenomedullin presented a median of 0.57 nmol/L (from 0.29 to 3.19 nmol/L), and the same amount was obtained for both survivors to deceased.

In our survey, the MR-proADM has not shown the ability to forecast for 30-day mortality of patients requiring treatment with NIV for acute respiratory failure, regardless of the precipitating pathology.

### Keywords

Proadrenomedullin, Respiratory insufficiency, Respiratory failure, Non invasive ventilation, NIV

### Background

The use of biomarkers is an essential accessory for the accuracy of diagnosis, the initiation of treatment, and the management of critical patients [1].

Kitamura published in 1993 the discovery of Adrenomedullin (ADM) [2]. ADM is a peptide which has an homology with the peptide related to the calcitonin and amylin gene, which all belong to the same family. These features are essential for its biological activity [3,4].

A reliable quantification of ADM in plasma is difficult because of its short half-life, due to the fact that it varies its values in a short period of time [5]. However, a por-

tion of the native protein, the mid-regional fragment of the peptide complex Proadrenomedullin (MR-proADM), has been identified being more stable than the active molecule itself, whose synthesis is stoichiometrically related, and is secreted in equimolar amounts to the ADM [6], which indirectly allows its quantification [7].

Hypoxia stimulates the secretion of ADM [3]. The several effects, such as neuro-hormonal compensatory channel on target organs, gives it its wide biological activity, it is suggested that ADM acts as a powerful protective factor for the organism in situations of cellular stress, using mechanism diuresis and natriuresis, or contributing with the fight against infection, among others [4,8]. The relevance of the ADM is based on plasma concentrations of MR-proADM in humans, it has been shown to be increased in the course of major life-threatening diseases (sepsis, pneumonia, chronic obstructive pulmonary disease, myocardial infarction and heart failure), combining as counter-regulatory mechanism [9], and being very useful in risk stratification as it has been able to predict mortality in patients with these critical processes [5,10-15].

Patients with secondary dyspnea towards Respiratory infections, Aggravated chronic obstructive pulmonary disease, Acute Cardiogenic Pulmonary Edema (ACPE), Shock, etc., pathologies that cause or may cause, directly or indirectly, Acute Respiratory Failure (ARF), are in many occasions treated with Non-Invasive Ventilation (NIV) [16] as supportive therapy in the emergency room due to severity of the process. In various studies published on the MR-proADM, it has been found that patients suffering from the above described symptoms have high MR-proADM having been postulated as a prognosis of mortality.

The primary aim of our survey was to establish the association between plasma concentrations of the biomarker MR-proADM and 30-day mortality of patients which require to be treated with NIV in the Emergency Room (ER), regardless of the precipitating pathology. As a secondary objective, we purposed associate any other indicators of the study with 30-day mortality of these patients.

## Methods

Prospective observational analytical survey carried out in the ER of University General Hospital Reina Sofia in Murcia (Spain) from November 2012 to December 2013 without any therapeutic implication on participants.

The survey followed the laws and regulations and was evaluated by the Clinical Research Ethics Committee C.R.E.C. The treatment, communication and transfer of personal data of the participants were in line to the Organic Act 15/1999 of December 13 on the protection of personal data.

Inclusion criteria: elderly patients who turned to ER due to acute respiratory failure of any etiology and needed urgent therapy with NIV. The inclusion of patients in the research was dynamic and consecutive.

## Exclusion criteria

Patients under 18, patients who were on dialysis, those whose admission was caused by surgical or traumatic pathology and those who could be in agony or pre-mortem at the time of the NIV set up.

## Sample collection and analysis

At the beginning of the treatment with NIV, several blood tests were taken for arterial blood gas, blood count, biochemistry and coagulation; plus a blood sample was extracted in an EDTA plasma tube that would be used to determine the MR-proADM. After extraction, the samples were processed immediately; however, the sample for MR-proADM determination was centrifuged at 3,500 rpm for 10 minutes separating the plasma fraction and distributed into aliquots which were frozen at -80 °C to be analyzed once the rest of the samples had been collected.

The quantification of MR-proADM was conducted by the ELISA technique (Enzyme-Linked Immuno Sorbent Assay); a Human mid-regional pro-adrenomedullin, MR-ProADM ELISA Kit from "SHANGHAI YEHUA Biological Technology Co., Ltd.", Shanghai, China was used; this kit uses a double antibody Biotin sandwich technology, whose intra-assay accuracy has a Coefficient Oscillation (CO) under 10% and inter-assay under 12%; measuring range is between 0.02 to 6 nmol/L and sensitivity is 0.011 nmol/L.

## Data collect

The general diagnose and analytical data were obtained from the clinical record, which had been transferred after having been determined; finally, the relating survival data was obtained from the files once they were reflected or directly from their families by telephone survey when we could not get the information any other way.

The variable "30-day Mortality" was the only dependent in the survey which took the values "YES" and "NO" including the positive value for all the patients deceased within 30 days of their admission to the ER, consigning the date of death for further statistical treatment.

The variable "Diagnose" corresponds to the consigned on the hospital discharge clinical report from the ER, the diagnostic "Respiratory Failure (RF)" refers to the one with pulmonary origin, mainly aggravated COPD; likewise, the diagnostic "Congestive Heart Failure (CHF)" which corresponds mainly to the ACPE.

## Statistical analysis

For statistic calculations the program "IBM SPSS Statistics" v-19 was used.

The categorical variables were described by their absolute values and percentages; and the continuous by their mean, typical deviations and confidence intervals of 95% (CI 95%) and/or median followed by the interquartile range and its CI 95% in case the variable did not follow a normal distribution. Each one of the categorical variables were analyzed for the survivor and non-survivor group; checking the type of quantitative variable distribution by the Kolmogorov-Smirnov test.

The differences between the categorical variables were established on the “ji-square” or the Fisher’s *F*-test; and for the quantitative the Student’s *t*-test or the Mann-Whitney’s *U*-test; what is more the relative risks were calculated with its CI 95%. To find out if there was an association between the quantitative variables and the different groups (quartiles of the MR-proADM) the ANOVA or Kruskal-Wallis test was used.

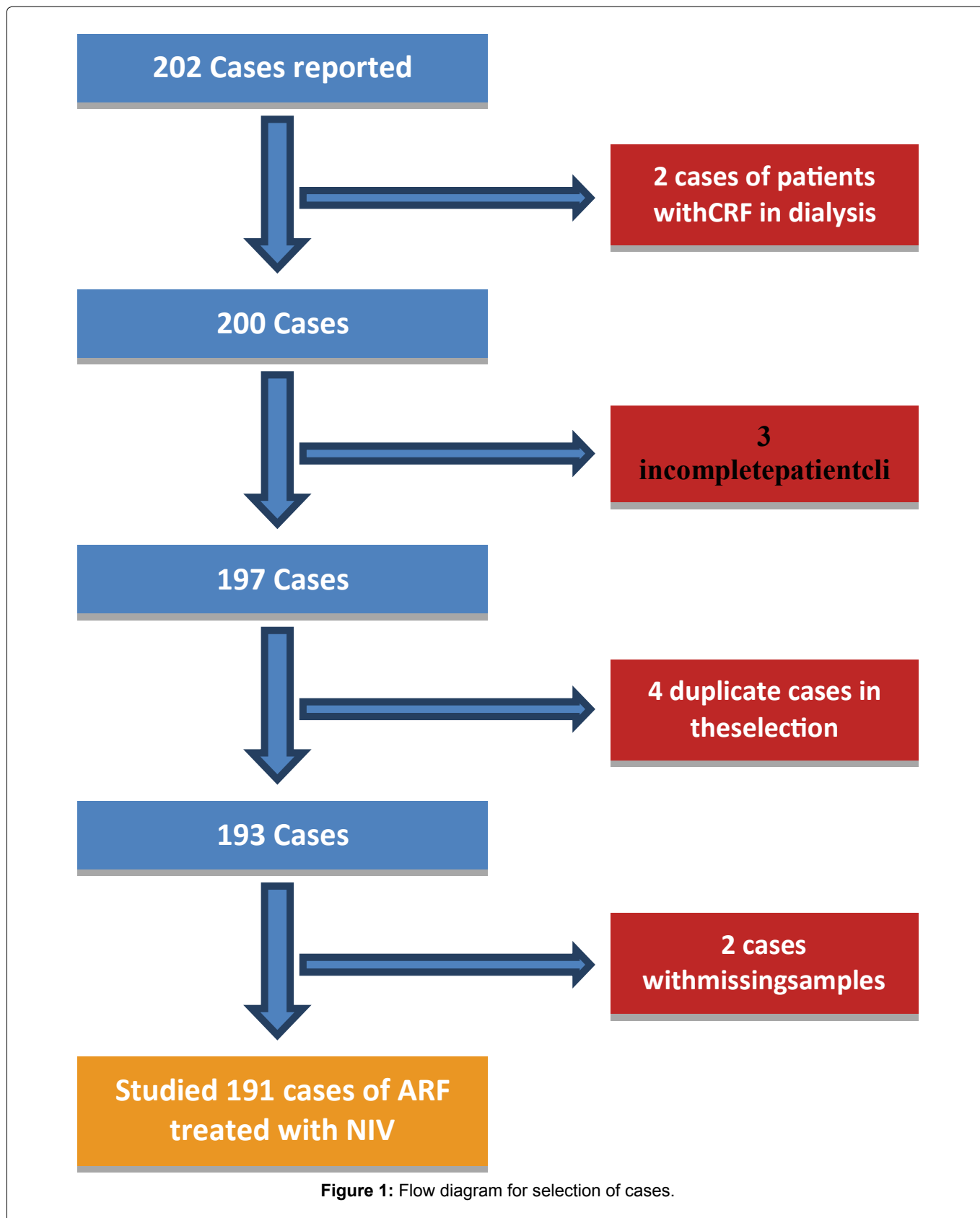
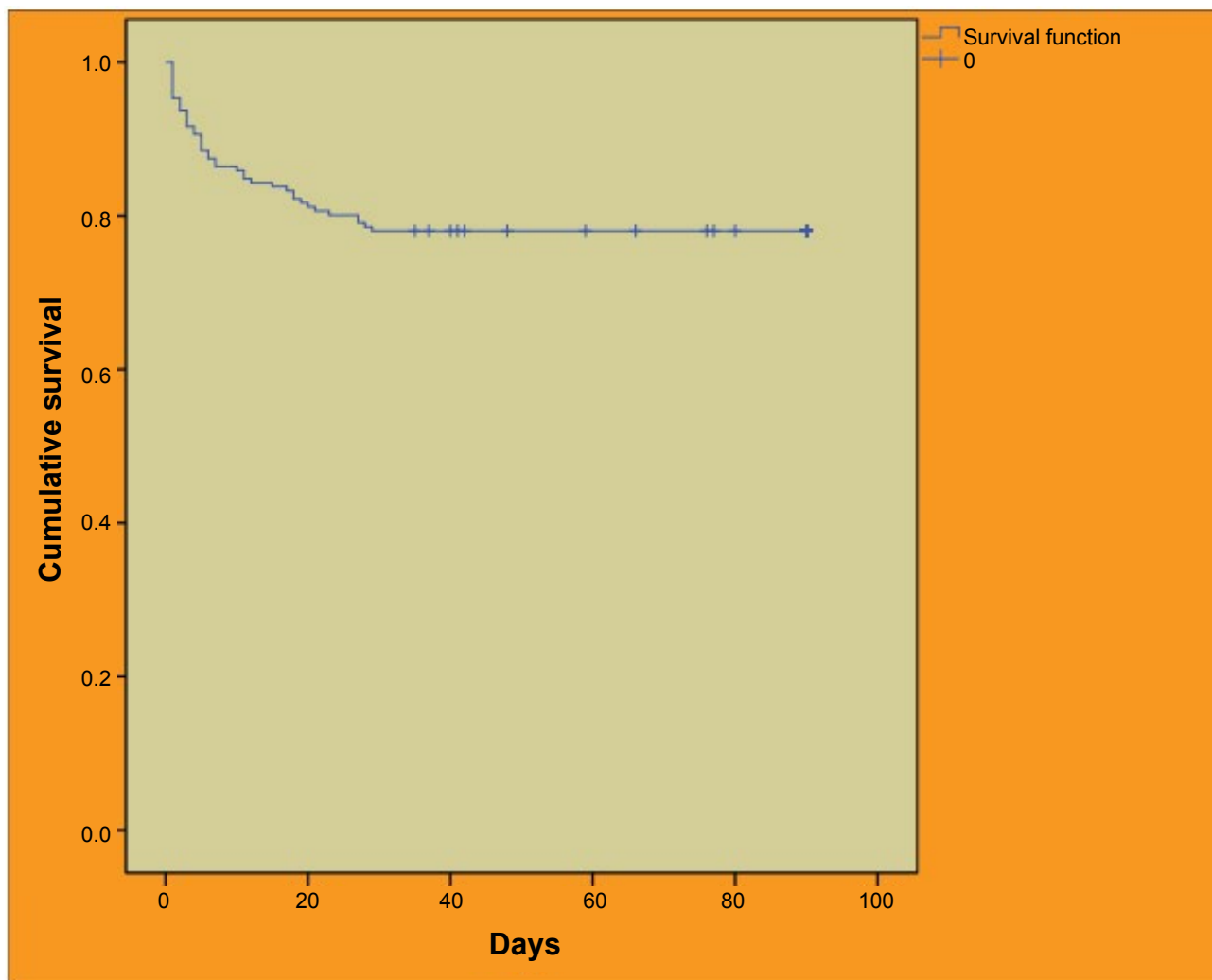


Figure 1: Flow diagram for selection of cases.



**Figure 2:** Survival Kaplan-Meier curve.

To discriminate the potential confusion of the variables in which association was found, a Cox regression was made in which it was introduced, and further including to the model the main variable of the survey, the MR-proADM.

ROC curves were used to search the discriminative power of the target biomarker for 30-day mortality, calculating the area under the curve.

The level of signification accepted was of  $p < 0.05$ .

### Sample size calculation

We considered an 80% potency, a type I error of 0.05 and a cut-off point of 1.5 nmol/L for the MR-proADM, as well as a rate of adverse events in the control group of 13% and 30% in the case group; to this 15% of estimation of losses was added, resulting a sample size of 202 cases.

### Results

202 patients were valued being included 191 cases. The losses (5.44%) were due to inappropriate inclusion (2 cases), incomplete patient clinical record (3 cases), duplicated (4 cases) and sample loss (2 cases) (Figure 1).

The age was between 24 and 96-years-old, average of 79-years-old, 51.3% were males (76 for men and 81

for women); 61.78% exceeded 75-years-old (57.6% women). The deceased within 30 days since their admittance were 42 (22%) (Figure 2), 21 men (21.4%) and 21 women (22.6%) ( $p > 0.05$ ).

The values of MR-proADM were between 0.29 and 3.19 nmol/L, mean of  $0.67 \pm 0.37$  nmol/L; they were not normally distributed with a median for the global population of 0.57 nmol/L (IQR = 0.22) and did not show significant statistical differences ( $p > 0.05$ ) between the two groups of global population, survivors and deceased, therefore it was not possible to obtain an optimal cut-off point; the figures in the survivors group were 0.57 nmol/L (IQR = 0.26) and also 0.57 nmol/L (IQR = 0.14) in the deceased. No significant statistical differences were shown in the MR-proADM between survivors and deceased at sample stratification by gender with an AUC = 0.451 (CI 95%: 0.312-0.590,  $p = 0.499$ ) for females and AUC = 0.512 (CI 95%: 0.381-0.664,  $p = 0.863$ ) for males, nor by discharge diagnose from the ER with AUC = 0.345 (CI 95%: 0.213-0.477,  $p = 0.643$ ) for CHF and with AUC = 0.526 (CI 95%: 0.372-0.679,  $p = 0.526$ ) for RF from pulmonary origin.

The general characteristics of the patients can be

**Table 1:** General characteristics of the patients. Comparison between survivors and deceased within 30 days from emergency room admission. Qualitative variables.

Variables	All cases n (%)	Survivors n (%)	Deceased n (%)	P value	RR	C.I. 95%
<b>Personal characteristics</b>						
Age > 75 a.	118/191 (61.8)	82/149 (55)	36/42 (85.7)	< 0.0001	3.712	1.645-8.373
Gender = female	93/191 (48.7)	72/149 (48.3)	21/42 (50)	ns	1.054	0.618-1.798
BMI > 30	82/173 (47.4)	68/139 (48.9)	14/34 (41.2)	ns	0.777	0.420-1.436
Smoking	97/187 (50.8)	81/146 (55.5)	16/41 (39)	ns	0.594	0.340-1.038
<b>Personal history</b>						
HBP	166/191 (86.9)	127/149 (85.2)	39/42 (92.9)	ns	1.958	0.654-5.861
DM	93/191 (48.7)	77/149 (51.7)	16/42 (38.1)	ns	0.648	0.373-1.129
COPD	76/191 (39.8)	60/149 (40.3)	16/42 (38.1)	ns	0.931	0.537-1.616
FEV1 < 50%	45/79 (23.6)	37/65 (56.9)	8/14 (57.1)	ns	1.007	0.386-2.632
Hypov. Syndr.	41/190 (21.5)	33/148 (22.3)	8/42 (19)	ns	0.855	0.430-1.702
Heart diseases	125/190 (65.4)	98/149 (65.8)	27/41 (65.9)	ns	1.003	0.566-1.776
Arrhythmias	88/190 (46.1)	65/148 (43.9)	23/42 (54.8)	ns	1.403	0.820-2.399
LTOT	64/191 (33.5)	47/149 (31.5)	17/42 (40.5)	ns	1.349	0.788-2.311
Domiciliary NIV	47/191 (24.6)	41/149 (27.5)	6/42 (14.3)	ns	0.511	0.230-1.135
<b>Laboratory variables</b>						
Hb < 12	78/191 (40.8)	62/149 (41.6)	16/42 (38.1)	ns	0.82	0.513-1.548
Creat > 1.5	81/191 (42.4)	62/149 (41.6)	19/42 (45.2)	ns	1.122	0.657-1.917
Bicarb < 22	56/191 (29.3)	40/149 (26.8)	16/42 (38.1)	ns	1.484	0.865-2.544
Lact > 2	76/182 (39.8)	54/143 (37.8)	22/39 (56.4)	0.036	1.805	1.031-3.160
<b>ER discharge diagnoses</b>						
CHF	88/191 (46.1)	70/149 (47)	18/42 (42.9)	ns	0.878	0.511-1.508
RF	82/191 (42.9)	67/149 (45)	15/42 (35.7)	ns	0.738	0.421-1.296
Sepsis	6/191 (3.1)	1/149 (0.7)	5/42 (11.9)	< 0.001	4.167	2.632-6.597
Pneumonia	7/191 (3.7)	6/149 (4)	1/42 (2.4)	ns	0.641	0.807-1.507
Others	8/191 (4.2)	5/149 (3.4)	3/42 (7.1)	ns	1.17	0.689-4.491
<b>ER discharge destination</b>						
Hospitaliz	159/191 (83.2)	131/149 (87.9)	28/42 (66.7)	0.001	0.403	0.240-0.675
ICU	17/191 (8.9)	12/149 (8.1)	5/42 (11.9)	ns	1.383	0.628-3.048
Deceased	7/191 (3.7)	0/149 (0)	7/42 (16.7)	< 0.001	5.257	3.902-7.083
Home	6/191 (3.1)	5/149 (3.4)	1/42 (2.4)	ns	0.752	0.123-4.593

**Abbreviations:** RR: relative risk; C.I.: confidence interval; BMI: body-mass index; HBP: high blood pressure; DM: diabetes mellitus; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in one second; Hypov. syndr.: hypoventilation syndromes; LTOT: long-term oxygen therapy; Smoking: personal history of smoking; Hb: hemoglobin (gr/L); Creat: creatinine (mg/dL); Bicarb: bicarbonate (mmol/L); Lact: lactic acid (mmol/L); ER: emergency room; CHF: congestive heart failure; RF: respiratory failure due to pulmonary origin; Hospitaliz.: hospitalization ground; ICU: intensive care unit; ns: not significant.

**Table 2:** General characteristics of the patients. Comparison between survivors and deceased within 30 days from emergency room admission. Quantitative variables.

Variable	All cases		Survivors		Deceased		P value
	n (191)	Value	n (149)	Value	n (42)	Value	
<b>Main objective biomarker</b>							
MR-proADM (median)	191	0.57 (0.22)	149	0.57 (0.26)	42	0.57 (0.14)	ns
<b>Personal characteristics</b>							
Age (median)	191	79 (15)	149	77 (17)	42	83 (10)	0.001
BMI (mean)	173	30.508 ± 7.343	139	30.53 ± 6.975	34	30.4 ± 8.811	ns
<b>Vital status variables</b>							
Glasgow (median)	184	15 (1)	144	15 (1)	40	15 (3)	0.006
MAP (median)	181	92 (22)	147	93 (23)	42	88 (22)	ns
H.R. (mean)	181	90 ± 21.462	147	89 ± 21.598	42	95 ± 21.198	ns
Temp. (median)	181	36.5 (0.8)	142	36.4 (0.8)	39	36.6 (0.8)	ns
<b>Laboratory variables</b>							
pH (mean)	190	7.28 ± 0.099	148	7.28 ± 0.101	42	7.27 ± 0.093	ns
PaCO <sub>2</sub> (median)	191	60.3 (24.34)	149	60.3 (24.08)	42	50.5 (25.18)	ns
HCO <sub>3</sub> <sup>-</sup> (media)	191	25.44 ± 5.954	149	25.84 ± 5.957	42	24 ± 5.785	ns
PaO <sub>2</sub> /FiO <sub>2</sub> (mean)	77	213.39 ± 117.59	65	214.31 ± 122.19	12	208.42 ± 93.03	ns
Lact. (median)	182	1.7 (1.7)	143	1.6 (1.3)	39	2.3 (2)	ns
Hb. (mean)	191	12.57 ± 2.137	149	12.51 ± 2.160	42	12.78 ± 2.064	ns



Leuk. (mean)	191	11.7 ± 5.391	149	11.3 ± 4.414	42	13.1 ± 7.867	ns
Plat. (median)	191	244 (104)	149	244 (117)	42	258 (87)	ns
Urea (median)	191	55 (40)	149	54 (41)	42	65 (45)	ns
Creat. (median)	191	1.3 (0.8)	149	1.3 (0.7)	42	1.5 (1.43)	ns
Na <sup>+</sup> (median)	191	139 (7)	149	139 (7)	43	139 (11)	ns
K <sup>+</sup> (median)	177	4.6 (1)	143	4.6 (0.8)	34	4.75 (1.3)	ns
INR (median)	191	1.09 (0.64)	149	1.09 (0.77)	42	1.23 (0.45)	ns

**Abbreviations and measurement units:** BMI: body-mass index; MAP: mean arterial pressure (mmHg); H.R.: heart rate (beats per minute); Temp: temperature (degrees Celsius); PaCO<sub>2</sub>: arterial carbon dioxide tension (mmHg); HCO<sub>3</sub><sup>-</sup>: bicarbonate in arterial blood (mmol/L); PaO<sub>2</sub>/FiO<sub>2</sub>: arterial oxygen tension/fraction of inspired oxygen; Lact.: lactic acid in arterial blood (mmol/L); Hb.: hemoglobin (gr/L); Leuk.: leukocytes (x1000); Plat.: platelets (x1000); Serum urea (mg/dL); Creat.: serum creatinine (mg/dL); Na<sup>+</sup>: sodium ion (mmol/L); K<sup>+</sup>: potassium ion (mmol/L); INR: international normalized ratio; MR-proADM: mid-regional proadrenomedullin (nmol/L); ns: not significant.

**Note:** The means are expressed followed by standard deviation and refer to variables with normal distribution while the medians are expressed followed (in parentheses) of the interquartile range and refer to non-parametric variables.

**Table 3:** General characteristics of the patients according to the concentrations of MR-proADM stratified by quartiles. Qualitative variables.

Variable	I Quartil (n = 56) < 0.5 nmol/L	II Quartil (n = 44) 0.51-0.57 nmol/L	III Quartil (n = 44) 0.571-0.718 nmol/L	IV Quartil (n = 47) > 0.718 nmol/L	P value*
<b>Personal characteristics</b>					
Age > 75 años	32 (27)	33 (28)	25 (21.2)	28 (23.7)	ns
Gender = male	31 (29.3)	22 (23)	26 (23)	19 (19.4)	ns
BMI > 30	29 (35.4)	18 (22)	16 (29.5)	19 (23.2)	ns
Smoking	33 (34)	18 (18.6)	24 (24.7)	22 (22.7)	ns
<b>Personal history</b>					
HBP	49 (29.5)	41 (24.7)	38 (22.9)	38 (22.9)	ns
DM	26 (28)	23 (24.7)	23 (24.7)	21 (22.6)	ns
COPD	25 (32.9)	14 (18.4)	19 (25)	18 (23.7)	ns
FEV1 < 50%	10 (22.2)	8 (17.8)	13 (28.9)	14 (31.1)	ns
Hypov. Syndr.	13 (31.7)	12 (29.3)	8 (19.5)	8 (19.5)	ns
Heart diseases	37 (29.6)	28 (22.4)	31 (24.8)	29 (23.2)	ns
Arrhythmias	23 (26.1)	20 (22.7)	20 (22.7)	25 (28.4)	ns
LTOT	21 (32.8)	8 (12.5)	16 (25)	19 (29.7)	ns
Domiciliary NIV	16 (34)	11 (23.4)	10 (21.3)	10 (21.3)	ns
<b>Laboratory variables</b>					
Hemoglobin < 12 gr/L	23 (29.5)	18 (23.1)	18 (23.1)	19 (24.4)	ns
Creatinine > 1.5 mg/dL	19 (23.5)	22 (27.2)	16 (19.8)	24 (29.6)	ns
Bicarbonate < 22 mmol/L	9 (16.1)	14 (25)	16 (28.6)	17 (30.4)	ns
Lactic acid > 2 mmol/L	22 (28.9)	17 (22.4)	18 (23.7)	19 (25)	ns
<b>ER discharge diagnoses</b>					
CHF	23 (25.8)	26 (29.2)	22 (24.7)	18 (20.2)	ns
RF	28 (34.6)	12 (14.8)	16 (19.8)	25 (30.9)	ns
Sepsis	0 (0)	2 (33.3)	2 (33.3)	2 (33.3)	ns
Pneumonía	2 (28.6)	2 (28.6)	2 (28.6)	1 (14.3)	ns
Others	3 (37.5)	2 (25)	2 (25)	1 (12.5)	ns
<b>ER discharge destination</b>					
Hospitalization ground	50 (31.1)	40 (24.8)	35 (21.7)	36 (22.4)	ns
ICU	2 (11.8)	3 (17.6)	5 (29.4)	7 (41.2)	ns
Deceased	1 (14.3)	0 (0)	4 (57.1)	2 (28.6)	ns
Home	3 (50)	1 (16.7)	0 (0)	2 (33.3)	ns

\*Based on the statistical "ji-square" test.

**Abbreviations:** BMI: body-mass index; HBP: high blood pressure; DM: diabetes mellitus; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in one second; Hypov. syndr.: hypoventilation syndromes; LTOT: long-term oxygen therapy; NIV: non-invasive ventilation; ER: emergency room; CHF: chronic heart failure; RF: respiratory failure due to pulmonary origin; ICU: intensive care unit; ns: not significant.

**Note:** The values in the table correspond to the "n" represented in each group followed by the corresponding percentage.

found in (Table 1) and (Table 2), in which the possible relation between the factors and the dependant variable is also shown "30-day mortality", finding an association (p < 0.05) with the variables "Age > 75-years-old",

"Lactic Acid > 2 mmol/L" and Sepsis diagnose.

A statistical analysis was carried out distributing the variable MR-proADM in quartiles, generating 4 groups and the patients main characteristics were studied

again in order to find out if there were any differences between them (Table 3) and (Table 4), but no differences were found.

In the multivariate analysis only the statistically significant were associated "Age > 75-years-old", and Sepsis diagnose (Table 5, Figure 3), while the "Lactic Acid" and "MR-proADM were not included in the model.

## Discussion

Remember that the medians found from MR-proADM were 0.57 nmol/L for the survivors and for the deceased, and that there were no significant statistical differences in median MR-proADM for both groups when stratifying the sample.

The ARF, regardless of its cause, has been associated with a very poor prognosis and has been identified as a significant risk factor for mortality which includes

from cardiac causes to any other cause in patients with dyspnea [17]. In our survey we have included patients with various diseases which were the source of severe acute dyspnea, such major diseases range from cardiac causes like CHF, Coronary ischemia or ACPE; causes of respiratory origin as exacerbation of COPD or asthma; causes of infectious origin like sepsis or pneumonia; and any other development that could be within the range of the adjunctive spectrum of ARF. The fact that many of these etiologies have demonstrated their expression in the MR-proADM and its reflection on predicting mortality marked our research process; however, in view of the results, we are able to say that we did not find statistically significant differences between the figures for MR-proADM obtained during admission of survivors and deceased patients, neither as a whole nor after stratifying our results according to gender, age or diagnosis group.

**Table 4:** General characteristics of patients depending on the concentrations of MR-proADM stratified into quartiles. Quantitative variables.

Variable	n	I Quartil (n = 56) < 0.5 nmol/L	II Quartil (n = 44) 0.51-0.57 nmol/L	III Quartil (n = 44) 0.571-0.718 nmol/L	IV Quartil (n = 47) > 0.718 nmol/L	P value*
<b>Personal characteristics</b>						
Age (median)	191	79 (20)	80 (12)	77 (15)	77 (11)	ns
BMI (mean)	173	30.74 ± 9.01	31.28 ± 7.14	29.85 ± 5.73	30.51 ± 6.66	ns
<b>Vital status variables</b>						
Glasgow (median)	184	15 (3)	15 (0)	15 (1)	15 (2t)	ns
MAP (median)	181	94 (24)	92 (22)	92 (19)	91 (27)	ns
H.R. (media)	181	91 ± 18	90 ± 25	89 ± 22	91 ± 23	ns
Temp. (median)	181	36.4 (0.8)	36.6 (0.9)	36.5 (1)	36.4 (0.7)	ns
<b>Laboratory variables</b>						
pH (mean)	190	7.29 ± 0.1	7.28 ± 0.09	7.28 ± 0.1	7.27 ± 0.11	ns
PaCO <sub>2</sub> (median)	191	66.07 (40.03)	57.36 (26.4)	54.36 (23.56)	62.82 (18.5)	ns
HCO <sub>3</sub> <sup>-</sup> (mean)	191	27.7 ± 6.4	24.5 ± 4.7	23.9 ± 5.6	25.1 ± 6.1	ns
PaO <sub>2</sub> /FiO <sub>2</sub> (mean)	77	210 ± 102	208 ± 97	211 ± 118	231 ± 172	ns
Lact. (median)	182	1.5 (1.5)	1.8 (1.7)	1.8 (1.7)	1.9 (2.1)	ns
Hb. (mean)	191	12.4 ± 2.03	12.4 ± 2.02	12.9 ± 2.4	12.5 ± 2.2	ns
Leuk. (mean)	191	10.8 ± 4.5	11.7 ± 4.3	11.8 ± 4.4	12.7 ± 7.7	ns
Plat. (median)	191	251 (98)	226 (96)	232 (99)	262 (128)	ns
Urea (median)	191	49 (32)	56 (47)	58 (45)	61 (53)	ns
Creat. (median)	191	1.1 (0.6)	1.5 (0.6)	1.3 (0.8)	1.5 (0.8)	ns
Na <sup>+</sup> (median)	191	139 (8)	139 (7)	138 (9)	140 (8)	ns
K <sup>+</sup> (median)	177	4.6 (1.1)	4.6 (0.8)	4.6 (1.1)	4.5 (1.3)	ns
INR (median)	191	1.1 (0.5)	1.1 (0.5)	1.1 (0.4)	1.2 (1)	ns

**Abbreviations and measurement units:** BMI: body-mass index; MAP: mean arterial pressure (mmHg); H.R.: heart rate (beats per minute); Temp: temperature (degrees Celsius); PaCO<sub>2</sub>: arterial carbon dioxide tension (mmHg); HCO<sub>3</sub><sup>-</sup>: bicarbonate in arterial blood (mmol/L); PaO<sub>2</sub>/FiO<sub>2</sub>: arterial oxygen tension/fraction of inspired oxygen; Lact.: lactic acid in arterial blood (mmol/L); Hb.: hemoglobin (gr/L); Leuk.: leukocytes (x1000); Plat.: platelets (x1000); Serum urea (mg/dL); Creat.: serum creatinine (mg/dL); Na<sup>+</sup>: sodium ion (mmol/L); K<sup>+</sup>: potassium ion (mmol/L); INR: international normalized ratio; MR-proADM: mid-regional proadrenomedullin (nmol/L); ns: not significant.

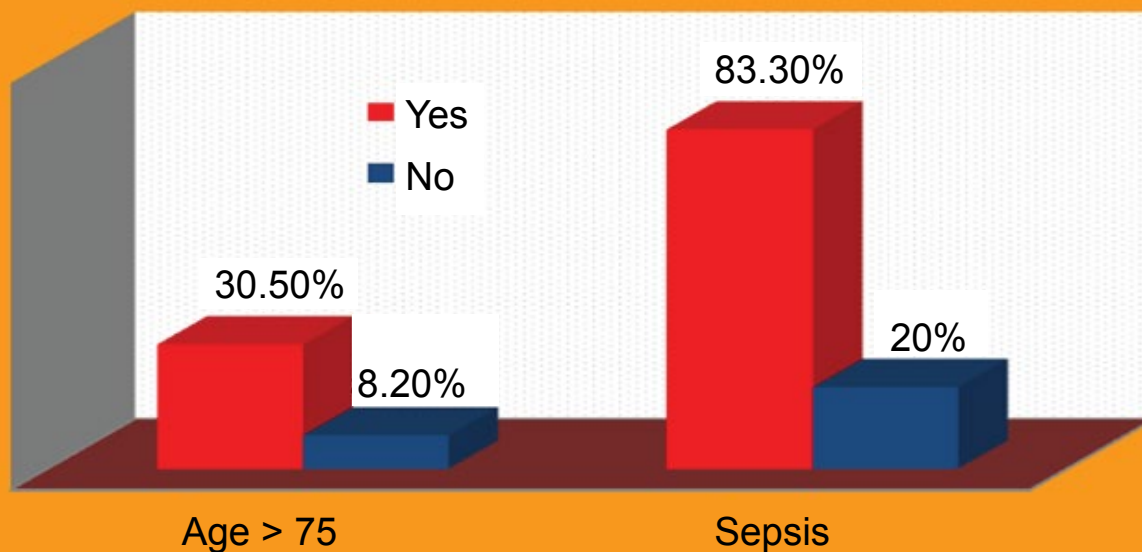
**Note:** The means are expressed with standard deviation and they make reference to variables with normal distribution while the medians are expressed followed (in parentheses) of the interquartile range and refer to non-parametric variables.

\*Comparisons between groups were performed by the ANOVA test for normally distributed variables and Kruskal-Wallis for non-parametric.

**Table 5:** Multivariate analysis. Variables in the equation as risk prognosis after the analysis by Cox regression.

	B	P value	Hazard ratio	C.I. 95%
<b>Step 2</b>				
Age > 75 años	1.493	0.002	4.449	1.722-11.497
Outcome = Sepsis	1.911	< 0.001	6.76	2.550-17.921

## 30-Day Mortality



**Figure 3:** Distribution of the “30-day mortality” for the two variables which remained after Cox regression.

**YES** = complies with the condition imposed by the variable. **NO** = does not comply with the condition imposed by the variable.

The BACH (Biomarkers in Acute Heart Failure) assay included 1,641 patients treated at the emergency room with dyspnea and distributed in 15 hospital facilities, 6 in two European countries and 8 in the US, generating after confirmation, two groups of patients diagnosed with acute dyspnea: those suffering from AHF (34.6%) and those without it (65.4%). Among the biomarkers studied, MR-proADM played a key role; in fact, Maisel, et al. published in 2010 in the Journal of the American College of Cardiology [18] the results obtained of the BACH, in it he warns that the MR-proADM income obtained a range between 0.1 and 12.6 nmol/L, with the median of 0.88 nmol/L (IQR 0.57 to 1.44 nmol/L); This is the first major difference with our findings whose median was 0.57 nmol/L (IQR = 0.22) covering the range from 0.29 upto 3.19 nmol/L. Another big difference is found in overall mortality, in his results, the survivors at 30 days had 0.739 nmol/L median against 0.57 nmol/L for ours. Continuing with inter assay differences, there were also differences within cardiovascular mortality at 30 days with a median of 0.790 nmol/L for them and 0.54 nmol/L for us.

As a matter of fact, we have not found similarities between our MR-proADM results and those from other consulted surveys, for instance, Herrero Puente, et al. in a pilot survey on the usefulness of MR-proADM in the assessment of dyspnea from respiratory origin in the ER [19] obtained an average figure of 1 nmol/L (range between 0.23 and 2.69) while our average was 0.67 nmol/L (range between 0.29 and 3.19). Dieplinger, et

al. [20] published his results on patients with dyspnea in the ER and finds that the survivors have a median of MR-proADM 0.69 nmol/L compared to 1.14 for those who deceased, also showing its discrepancies with our data. Another survey published by Courtais, et al., on community-acquired pneumonia [21], shows median MR-proADM of 1.035 nmol/L for survivors, admitted for this reason, at 30 days versus 3.017 nmol/L for the ones deceased ( $p = 0.003$ ); our results in this condition and for the same monitoring time show 0.53 nmol/L for survivors and 0.62 nmol/L for the deceased ( $p = 0.614$ ). Finally, with respects to the diagnosis of “sepsis” we did not find matches with other authors; our results in this subgroup reflect a median of 0.66 nmol/L with a range between 0.53 and 3.19 for the deceased, which we will recall that amounted to 83.3%; however Christ-Crain, et al. [22] found that his patients with severe sepsis who did not survive on admission were 8.5 nmol/L median (range 0.8 to 21) compared to 1.7 nmol/L of which overcame the crisis; or Suberviola, et al. [23] who obtained figures of 5.0 nmol/L for patients deceased during hospitalization vs. 1.7 nmol/L for survivors.

It is clear therefore, that in our survey no evidence is related between the concentrations of MR-proADM and mortality, as it was objectified in the other described surveys. The first striking difference between our survey and the rest is the type of patients; ours had severe ARF, while in others there was a greater amalgam of them, and therefore, less severe than ours; thus, it is possible that the MR-proADM is more effective diffe-



rentiating patients between degrees of severities. The second difference could be due to the fact that we have included a wide range of precipitating causes of acute dyspnea with diagnostic groups which comprehend entities, that even though having common peculiarities, indeed with no consistent physiopathology and perhaps too small to stratify in the analysis.

One of the major limitations of the survey was due to the heterogeneity of the target population in terms of clinical diagnoses (various causes of dyspnea), which surely prevents that there is a correlation between the concentrations of biomarkers and mortality; in addition, cut-off points can vary depending on the target population (emergencies, critical patient, post-surgery) and depending on the clinical diagnosis, as well as in accordance of clinical diagnosis; also the single survey nature of the survey has limited the “n” analyzed both as global and as groups, which we believe has been very important to find significant differences in the stratification, but not to respond to the main objective which referred to patients treated with NIV globally. With respect to plasma sample’s freezing, the recommendations from the International Agency for Research on Cancer of the World Health Organization were followed, by what we believe that this process could not have interfered with the results, nor the chosen analysis technique (ELISA), which has demonstrated its high sensitivity for the determination of proteins and hormones and is internationally guaranteed for these procedures. Either way, we believe that wider new surveys with selected patient groups would be required.

Among the prognosis of failure for NIV, guides do not include age [24,25], however, it seems logical that age can be a factor that worsens the prognosis of patients undergoing NIV. In our survey, when we group 75-years-old patients and compare their 30-day mortality with the below that age, we found statistically significant differences in HR = 4.449. Other authors like Echave-Sustaeta have also found this association [26]; therefore it is important to consider this variable were not due to being obvious must not it be forgotten.

3.1% of the cases included in our survey were diagnosed with sepsis. Of these, we had a fairly high percentage of deaths, 83.3% especially if compared to other hospital-based surveys; a multicenter survey in Spain reported 40% [27]; Another survey in the Madrid Region (Spain) found 33% mortality [28], and other countries like France and Australia published figures between 35% and 47% [29,30]. This can be explained, however, due to the fact that they conducted the survey on the global sepsis mortality, while we have focused only on those patients who were treated with NIV during admission, regardless of whatever the etiology of sepsis was, which should explain the significant differences found. It is important to point out that all deaths from sepsis occurred during hospitalization and within the first 30 days from admission.

## Conclusions

MR-proADM in our survey, and taking into account the constraints already referred, not predict the 30-day mortality since admission to the ER for the patients who require treatment with NIV, regardless of the precipitant pathology.

Other indicators such as age > 75-years-old and the diagnosis of sepsis should be taken into account to establish the risk.

## Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

The submitting author takes responsibility for the paper and is responsible for all the other coauthors which ensure that the paper has not been published elsewhere and is not currently under consideration by another journal published by Hindawi or any other publisher; moreover, the article’s publication has been approved by all them, and they allow editing of the paper for readability. Finally, the authors declare that there is no conflict of interest regarding the publication of this paper.

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