The Amino-Terminal Fragment of Pro-Brain Natriuretic Peptide in Plasma as a Biological Marker for Predicting Mortality in Community-Acquired Pneumonia: A Cohort Study

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Abstract

Aim: Community-acquired pneumonia (CAP) is an infectious disease that causes the highest mortality rates in developed countries. The primary endpoint of this study was to evaluate the relationship between the plasma concentration of the amino-terminal fragment of pro-brain natriuretic peptide (NT-ProBNP) at the time of CAP diagnosis in a hospital emergency room (HER) and its severity, determined as mortality at 30 days.

Materials and Methods: A prospective, observational cohort study was used to determine NT-ProBNP (ng/L) in patients with CAP, with a follow-up over 30 days and analysis of the mortality rate.

Results: A total of 338 patients were assessed. Thirty patients died within the first 30 days (10.5%). The mean NT-ProBNP values in the deceased patients were 14,035 ng/L (SD: 19,271) compared to 1,711 ng/L (SD: 3,835) in survivors ($p<0.0001$). The cut-off point of 1,769 ng/L showed a negative predictive value (NPV) of 95.3%, whereas 10,808 ng/L showed a positive predictive value (PPV) of 73.3%. The diagnostic performance of NT-ProBNP reached an AUC of 0.783 (95% CI: 0.731–0.829). Entering the potential confounding variables in a logistic regression model revealed that NT-ProBNP behaved like an independent risk factor. Grouping the NT-ProBNP values by every 300, 500, 1,000, and 2,000 ng/L increased the risk of mortality at 30 days by 3%, 5.1%, 10.5%, and 22%, respectively.

Conclusion: The NT-ProBNP values at the time of CAP diagnosis are significantly higher among patients that die than those that survive the first 30 days, and it could be a good predictor of early mortality. NT-ProBNP has good overall accuracy and behaves like an independent risk factor. *(Eurasian J Emerg Med 2016; 15: 30-8)*

Keywords: Amino-terminal fragment of pro-brain natriuretic peptide (NT-ProBNP), community-acquired pneumonia, emergency room, mortality, biomarkers, severity prognostic scales

Introduction

Community-Acquired Pneumonia (CAP) is the most common cause of mortality caused by infectious disease in developed countries. Over the last few years, hospital emergency rooms (HER) have been using severity prognostic scales (predictive scales) that help determine the need for hospitalization. The two most robust, often used, and validated clinical severity scales are PSI and CURB-65 (1, 2). However, these severity indexes have limitations, as shown by the fact that up to 16% of patients admitted to the ICU for CAP belong to PSI risk groups I–III (3).

Over the last few years, Brain Natriuretic Peptide (BNP) has been investigated as a prognosis marker for CAP in emergency rooms, internal medicine, and intensive care units (4-9). Of these studies, few have compared the predictive capacity between biomarkers, and none have compared NT-ProBNP with one of the infectious markers most often used in the HER, procalcitonin (PCT). There are no studies on the capacity of NT-ProBNP to detect severe CAP when associated with other biomarkers.

As there is an established relationship between pneumonia and cardiovascular events and NT-ProBNP is a biomarker for cardiac stress, the purpose of our study was to 1) evaluate the relationship between the plasma concentration of NT-ProBNP at the time of diagnosis of CAP in the emergency room with the severity of CAP, defined as mortality at 30 days; 2) compare the prognostic capacity of NT-ProBNP with predictive scales and biomarkers normally used in

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the emergency room; 3) study the strength of association between NT-ProBNP and severity prognostic scales and biomarkers normally used in the emergency room; 4) evaluate whether the association of NT-ProBNP with predictive scales and biomarkers results in improved predictions; 5) analyze the increased risk of mortality from CAP with the grouped increase of NT-ProBNP levels; and 6) perform survival analysis.

Materials and Methods

Study design

A prospective, longitudinal cohort trial was designed with the inclusion of subjects between February 2012 and 2013 with a clinical diagnosis of pneumonia and radiographic confirmation. Consideration is given to CAP if the process takes place for a patient who has not been hospitalized during the last 14 days; in the event that the patient was already in hospital, it was diagnosed within the first 48 h of the hospital stay.

The inclusion criteria were that the patient must be over 14 years of age and comply with the definition of pneumonia and CAP. The predictor variable was considered to be the result of the determination of NT-ProBNP in blood (in ng/L); the dependent variable was mortality at 30 days.

The case report form should be completed by at least two emergency room physicians. A specialist in radiodiagnosis made a blind a posterior examination of each of the x-rays as he had no clinical knowledge of the patients. A contact interview took place at one month, either in person, by phone, or through the electronic clinical record depending on the patient's final destination, to determine the patient's progress.

This study was designed in accordance with the ethical principles of the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of our region, Cantabria (IEC/IRB act 8/2012), as well as by the training commission of Laredo Hospital, a public hospital in the north of Spain covering a population of 95,000 people.

Data collection

The following baseline data was obtained from the patients: demographic (age and sex), comorbidity, personal history (alcohol and tobacco use and body mass index), physical examination (heart and respiratory rate, pulsoximetry, and systolic and diastolic blood pressure), laboratory tests (leukocytes, neutrophils, hematocrit, haemoglobin, platelets, glucose, urea, creatinine, sodium, bilirubin, prothrombin time, activated partial thromboplastin time, arterial oxygen and carbon dioxide partial pressure, arterial pH), chest X-ray, and biomarkers (C-reactive protein (CRP), procalcitonin (PCT), lactate, D-dimer (D-D), high-sensitivity troponin T, and NT-ProBNP). The severity of the CAP was assessed using severity prognostic scales (PSI, CURB-65, and ATS/IDSA).

Blood samples

Blood samples were obtained on arrival of the patient in the emergency room. The physicians responsible for the patient requested NT-ProBNP and all determinations considered necessary for correct care of the patient.

Determinations of NT-ProBNP and other biomarkers

The NT-ProBNP sample was collected in a biochemistry tube and analyzed using the proBNP II-Elecsys 2010 kit (Roche Diagnostics GMBH, SandhoferStrasse 116, D-68305 Mannheim, Germany). The analytical technique used was an electrochemiluminescence immunoassay (ECLIA) using the sandwich principle. The measurement range of the assay was between 5 and 35,000 ng/L; however, measurements of up to 70,000 ng/L could be performed using appropriate dilutions.

Statistical analysis

For statistical analysis, categorical variables were described as absolute value and percentage, and continuous variables were described by their means, standard deviations, and 95% confidence intervals (95% CI) and/or medians and interquartile ranges. The analyses were performed using the SPSS Statistics Package for Windows (version 20.0) and MedCalc (version 11.7).

A comparison was made for each variable between the surviving and non-surviving groups. The assessment of differences between the NT-ProBNP concentrations of patients with CAP, survivors, and non-survivors with different biomarkers and SPS as quantitative variables was performed by bivariate analysis using Student's t-test if they followed a normal distribution or the Mann–Whitney non-parametric U test if not. The type of distribution for quantitative variables was first checked using the Kolmogorov–Smirnov Z test. The differences between groups for qualitative variables were evaluated using the Chi-square or Fisher's test.

NT-ProBNP was analysed as a predictor of mortality by calculating the ideal cutoff point optimised by multiplying sensitivity by specificity using mortality at 30 days as a reference and plotting the receiver operating characteristic (ROC) curve. The strength of the relationship between numerical variables was evaluated using Spearman's non-parametric coefficient of correlation test.

Survival was analysed using the Kaplan–Meier method, comparing curves by the Log-Rank test. Logistic regression analysis and the Enter method were then applied to estimate whether the variable of interest, NT-ProBNP, provided any additional predictive improvement to consolidated predictive scales. The personal history of ischaemic cardiopathy, heart and kidney failure, and age were included as categorical confusion variables. Multivariate analysis using NT-ProBNP as a dichotomous variable according to the cutoff point was used to calculate the raw risk after including the confounders in the model. The prediction models were compared using the Hosmer–Lemeshow test.

Results

General characteristics of the patients with pneumonia in cluded to the study

A total of 338 patients were assessed, 287 being included in the study (84.9%). In total, 2% of the rejected patients had nasocomial pneumonias, 8% were pediatric patients, 20% had no request for NT-ProBNP, 22% had a final diagnosis other than CAP, and 48% were rejected by the radiologist as they had no clear radiological condensation.

Overall, 42.2% of patients included in the study were women. The mean age was 66±21 years (min. 14, max. 104). The main demographic characteristics, comorbidity, clinical and radiological variables, prognostic scales, and biomarkers for each group are shown in Tables 1 and 2.

Table 1. General characteristics of the sample. Comparison between survivors and deaths in the first 30 days

	Survivors n=257				Death n=30				
Personal characteristics	**Mean**	**SD**	**Med**	**IQR**	**Mean**	**SD**	**Med**	**IQR**	**p**
Age	64.1	21.3	67.0	37.0	82.9	14.2	86.0	11.0	<0.001
BMI	25.9	5.5	25.0	7.0	22.9	3.9	23.0	5.0	0.163
Alcohol C. g/week	21.9	62.6	0	0	36.8	130.7	0	0	0.450
Smoker cigarette/day	4.6	9.7	0	2.0	0	0	0	0	0.014
Vital Signs									
HR, bpm	97.5	19.4	97	27.8	97.2	21.9	95	24.0	0.957
RR, rr	20.2	6.0	20.0	8.0	31.1	7.8	30.0	13.3	<0.001
SBP, mm Hg	132.3	24.5	132.0	32.8	119.2	26.1	115.0	34.0	0.004
DBP, mmHg	72.1	12.7	72.0	17.0	60.8	13.0	61.0	20.0	<0.001
Body temperature, ºC	37.7	1.1	37.8	1.7	37.3	1.2	37.2	1.5	0.046
Blood oxygen level, %	93.7	4.4	95.0	6.0	86.1	9.1	88.0	14.3	<0.001
Laboratory values									
Leukocytes per, mm^3	12027	5586	11100	6800	14703	9065	13050	12300	0.158
Neutrophils per, mm^3	9876	5398	8900	6350	12713	8082	10950	11375	0.072
Haematocrit, %	39.5	5.1	40.0	6.0	36.0	7.9	36.5	10.3	0.008
Haemoglobin, g/dL	13.2	2.5	13.1	2.1	11.7	2.5	11.5	3.5	<0.001
Platelets per, $1000/mm^3$	231	89	220	103	277	159	240	171	0.209
Glucose, mg/dL	146	78	124	52	175	70	159	103	0.005
Urea, mg/dL	45.6	30.8	39.0	24.5	106.5	85.6	78.5	54.3	<00001
Creatinine, mg/dL	1.0	0.5	0.9	0.4	2.0	2.6	1.3	0.9	0.005
Sodium, mEq/L	136	5.8	136	5.0	138	9.7	136	9.5	0.483
Bilirubin, mg/dL	0.53	0.29	0.50	0.30	0.64	0.54	0.50	0.30	0.253
Prothrombin time, %	74.9	23.1	81.0	23.3	70.3	17.0	69.0	20.5	0.021
APTT sec.	35.8	3.9	35.5	7.8	33.4	3.3	32.8	6.3	0.480
PO_2 mmHg	63.3	14.7	61.0	15.0	51.5	14.2	50.0	23.0	<0.001
pCO_2 mmHg	37.4	6.6	37.0	8.0	41.1	18.1	34.5	18.3	0.518
Arterial, pH	7.47	0.06	7.46	0.06	7.40	0.13	7.45	0.19	0.047
GFR est. mL/min/1.73 m^2	86.2	34.4	85.4	41.8	73.2	61.3	47.7	55.9	0.049
Biomarkers									
CRP, mg/dL	13.6	13.7	8.9	17.1	16.1	16.4	11.6	17.2	0.333
PCT, ng/mL	1.6	5.6	0.2	0.5	4.8	100	0.4	2.8	0.007
Lactate, mg/dL	14.3	8.4	13.0	10.0	30.6	11.4	36.0	23.8	0.058
D-Dimer, mcg/mL	2.3	2.0	1.9	2.2	4.3	2.2	5.1	4.2	0.082
Troponin T high sensitive, ng/L	58.1	198	11.0	27.0	214.4	321.6	95.0	248	<0.001
NT-ProBNP, ng/L	1711	3835	411	13400	14035	19271	5192	1968	<0.001
Prognostic scales									
PSI	77.4	36.5	78.0	57.5	137.2	38.1	137.2	50.0	<0.001
CURB-65	1.06	1.07	1.0	2.0	3.0	1.2	3.0	2.0	<0.001
ATS/IDSA major criteria	0	0.06	0.0	0.0	0.17	0.46	0	0	<0.001
ATS/IDSA minor criteria	0.77	1.05	0.0	1.0	2.97	1.27	3.0	2.0	<0.001
Progress									
Length of stay	8.7	5.2	7.0	5.0	------	-----	-------	------	------
Days to death	------	------	------	------	7.5	6.4	5.5	6.7	------

Med: median; IQR: inter-quartile range; Alcohol C: alcohol use consumption; Smoker: tobacco use HR: heart rate; RR: respiratory rate; BMI: body mass index; bpm: beats per minute; rr: respiratory rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; ºC: degrees centigrade; GFR: glomerular filtration rate; APTT: activated partial thromboplastin time; CRP: C-reactive protein; PCT: procalcitonin; ATS/IDSA: American Thoracic Society/Infectious Diseases Society of America; PSI: pneumonia severity index; CURB-65: acronym for Confusion; BUN: Blood Urea Nitrogen, Respiratory rate, Blood pressure, age over 65 years

Table 2. General characteristics of the sample. Comparison between survivors and deaths in the first 30 days

	Survivors		Death		
	No	%	No	%	p
Total	257	89.5	30	10.4	
Sex					
Female	106	41.2	15	50	0.358
Male	151	58.8	15	50	
Comorbidity					
Heart failure	20	7.8	3	10	0.719
Ischemic cardiopathy	19	7.4	5	16.7	0.089
Chronic kidney failure	13	5.1	3	10	0.227
Chronic respiratory disease	52	20.2	1	3.3	0.024
Essential HBP	101	39.3	19	6.3	0.012
DM-1	0	0	1	3.3	0.105
DM-2	47	18.3	8	26.7	0.270
Chronic hepatopathy	7	2.7	1	3.3	0.519
Cerebral vascular disease	12	4.7	6	20	0.006
Severe psychiatric disorder	5	1.9	0	0	1.000
Dementia	20	7.8	13	43.3	<0.001
Malignancy	19	7.4	4	13.3	0.279
Immunosuppression	2	0.8	0	0	1.000
Disorder preventing oral treatment	1	0.4	0	0	0.732
Construction work at home or workplace	6	2.3	0	0	0.398
Cohabitation with animals	33	12.8	4	13.3	0.939
Risk Groups					
ATS/IDSA	19	7.4	21	70	<0.001
PSI	257		30		<0.001
I	73	28.4	0	0	
II	40	15.6	0	0	
III	58	22.6	4	13.3	
IV	66	25.7	10	33.3	
V	20	7.8	16	53.3	
CURB-65	257		30		<0.001
1	180	70	3	10	
2	52	20.2	8	26.7	
3	25	9.7	19	63.3	

HER: hospital emergency room; HBP: high blood pressure; DM-1: diabetes mellitus type 1; DM-2: diabetes mellitus type 2; ATS/IDSA: American Thoracic Society/Infectious Diseases Society of America; PSI: pneumonia severity index; CURB-65: acronym for Confusion, BUN: Blood Urea Nitrogen, Respiratory rate, Blood pressure, age over 65 years

Description of the outcome predictor variable

The results interval found was between 8 and 70,000 ng/L, with an arithmetic mean of 3,000 ng/L (SD 8,068 ng/L) and a median of 492 ng/L (IQR: 138–2.003). The values for survivors and death are shown in Figure 1.

There were statistically significant differences between the surviving and deceased patients at 30 days (median 5,192 ng/L; IQR 19,685 vs. median 411; IQR 1,340 ng/L, p<0.001).

Prognostic capacity of NT-ProBNP in CAP

The cutoff points were calculated depending on the mortality at 30 days. The cutoff point was 1,769 ng/L to optimize sensitivity (66.7%; 95% CI: 47.2–82.7), specificity (78.2%; 95% CI: 72.7–83.1), positive predictive value (PPV, 26.3%), and negative predictive value (NPV, 95.3%). For a cutoff point of 232 ng/L, the sensitivity was 93.3% (95% CI: 77.9–99.2), specificity was 39.3% (95% CI: 33.3–45.6), PPV was 15.2%, and NPV was 98.1%. For a cutoff point of 10,808 ng/L, the sensitivity was 36.7% (95% CI: 19.9–56.1), specificity was 98.4% (95% CI: 96.1–99.6), PPV was 73.3%, and NPV was 93% (Figure 2).

When proposing mixed models with demographic variables (age), predictive scales (PSI, CURB-65 and ATS/IDSA 2007), and biomarkers (CRP, PCT, and NT-ProBNP), the most advantageous model combines ATS/IDSA with PCT and NT-ProBNP with an AUC of 0.94.

The diagnostic performance of NT-ProBNP, some other markers such as procalcitonin, and diverse scoring systems used for pneumonia are depicted in Table 3.

Correlation between NT-ProBNP and predictive scales

A study was made of the correlation between NT-ProBNP and the PSI, CURB-65 predictive scales, and minor ATS/IDSA criteria. There was a good association between NT-ProBNP and the PSI scales (Rho 0.71 p=0.0001) and CURB-65 (Rho 0.65 p=0.0001) and a slight association with the ATS/IDSA minor criteria (Rho 0.48 p=0.0001).

Logistic regression model

a. NT-ProBNP as an independent risk factor for early mortality

Initially, a univariate analysis was performed depending on mortality for the following variables as dichotomous variables: age, background of heart failure, ischaemic cardiomyopathy and chronic kidney failure, serum creatinine, NT-ProBNP, PSI score, CURB-65 score, minor ATS/IDSA criteria score, and ATS/IDSA scale. The variables with p<0.25 (age, ischaemic cardiomyopathy, creatinine, NT-ProBNP, PSI, CURB-65, minor ATS/IDSA criteria, and ATS/IDSA as dichotomous variables) were entered into a logistic regression model. Furthermore, forced multivariate analysis was performed on the personal history of heart failure and chronic kidney failure, as these variables have an established relationship with NT-ProBNP levels and therefore could be confusion factors. After adjustment for all these variables, the only ones that maintained statistical significance were age (p=0.002), ATS/IDSA 2007 (p=0.001), and NT-ProBNP (p=0.001).

b. Assess improved outcome prediction by associating NT-ProBNP and other biomarkers

A univariate analysis of NT-ProBNP and the CRP and PCT biomarkers revealed that only PCT (p=0.043) and NT-ProBNP (p<0.0001) showed significant differences between patients that died and survived at 30 days.

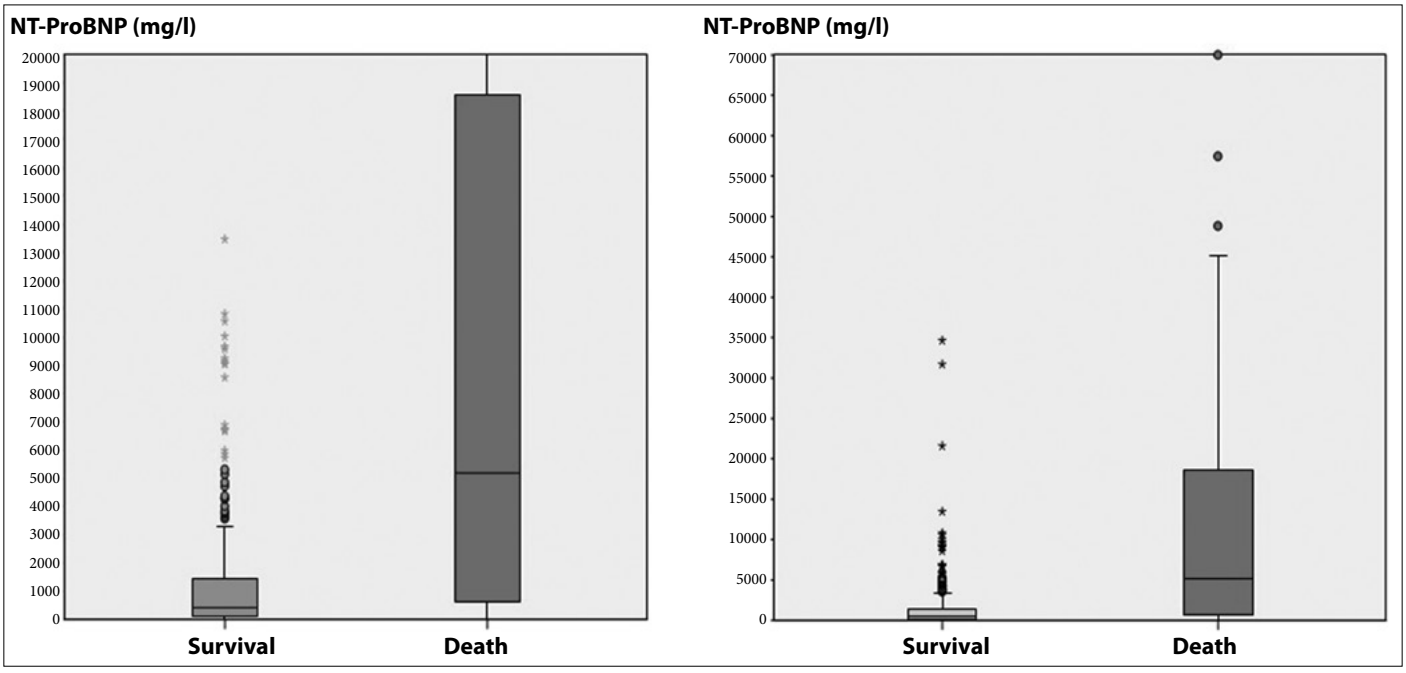

Figure 1. NT-ProBNP values on a scale of 0–20,000 ng/L (left) and on a scale of 0–70,000 ng/L (right)

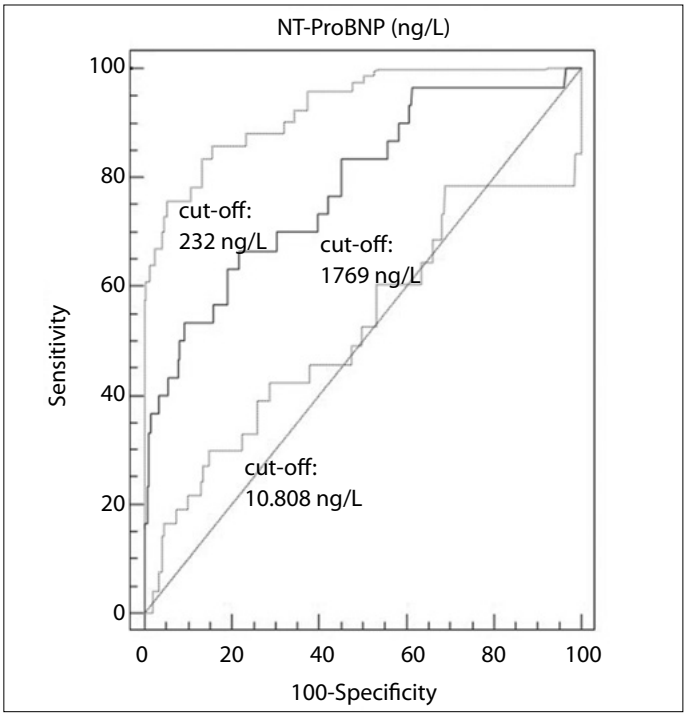

Figure 2. NT-ProBNP ROC curves. AUC 0.783; CI 95%: 0.731–0.829; p<0.001

Survival analysis

It was observed that 20% of patients died within the first 48 hrs and 50% within the first 5 days. Comparison of the survival curves depending on the cutoff point showed significant differences between the patients that died for values over 1,769 ng/L [(hazard ratio 6.2 (CI 2.9-13.2, p=0.0001)], as can be seen in Figure 3.

The survival curves were also compared depending on sex, background of heart failure, ischaemic cardiomyopathy and chronic kidney failure, and creatinine serum levels above and below 1.2 mg/dL.

Table 3. Comparison of diagnosis performance curves

Models	ROC Curves
CRP	0.56
PCT	0.66
NT-ProBNP	0.78
CRP + NT-ProBNP	0.79
PCT + NT-ProBNP	0.85
CRP + PCT + NT-ProBNP	0.82
PSI + NT-ProBNP	0.90
CURB65 + NT-ProBNP	0.91
ATS/IDSA + NT-ProBNP	0.93
PCT + ATS/IDSA + NT-ProBNP	0.94
Age + PCT + NT-ProBNP	0.86
Age + PCT + ATS/IDSA + NT-ProBNP	0.95

ROC: receiver operating characteristic; PCT: procalcitonin; CRP: C-reactive protein; ATS/IDSA: American Thorax Society/Infectious Diseases Society of America; CURB-65: acronym for Confusion, BUN: Blood Urea Nitrogen, Respiratory rate, Blood pressure, age over 65 years

The only significant differences were found for the latter variable (p<0.001).

Discussion

The World Health Organisation estimates that infections of the lower airways are the most common cause of death by infectious disease in the world, with close to 3.5 million deaths a year (10). Early assessment of the severity of pneumonia is crucial to the correct management of these patients. Over the last few years, a multitude

of clinical tools have been designed and developed to predict mortality and help decide the care site, with PSI and CURB-65 being the most reliable and most often used in the HER (1-2). However, these scales are quite often not applied, either because they are simply not used or because objective data such as low blood oxygen level or subjective data such as poor family support recommend admission of the patient (11).

Biological markers and their role in the inflammatory response and relationship to the severity of pneumonia are undering study. Biomarkers may be an alternative to assess the seriousness of pneumonia and predict mortality. These biomarkers include natriuretic peptides (NP) (12-14). The first team to assess NT-ProBNP as a predictor of early mortality at 30 days were Jeong et al. (4), who in 2011 conducted a retrospective study of hospitalized patients, obtaining promising results in their series of 167 patients. According to our information, this NP was recently studied as a prognosis marker for CAP in different scenarios: emergency room (5, 9), hospitalized patients (6), and intensive care units (7, 8).

Description of the outcome predictor variable

We found large differences between NT-proBNP values in survivors and deaths within the first 30 days; there were statistically significant differences between both groups, as in other studies conducted to date.

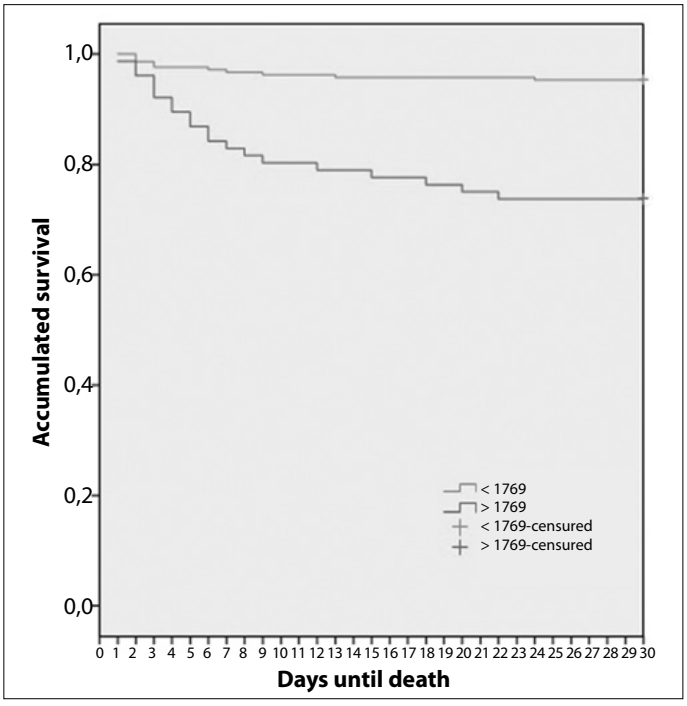

Figure 3. Comparison of the survival curves

Prognostic capacity of NT-ProBNP in CAP

The ideal cutoff point balancing sensitivity and specificity found in our study was 1,769 ng/L. This result is in line with that of studies by Jeong (1,795.5 pg/mL), Nowak (1,935 ng/L), and Chang (1,860 ng/L) in patients diagnosed in the Emergency Room and admitted to a conventional hospital ward (4-6). Our cutoff point differs from that of the cohort by Lin et al. (7) (2,177.5 ng/L). Their patients had more severe CAP, with 83% of patients meeting ATS/IDSA criteria compared to 14% in our series. They also evaluated other types of pneumonia, including hospital-acquired (25%) and that associated with social and health care (40%). We also found differences with the cutoff point established by Xiao et al. (8), almost certainly because this group reduced the cutoff point to obtain a sensitivity of 98.7%.

As severe CAP is a dangerous, but treatable, disease whose severity should be assessed as soon as possible, lowering the cutoff point to 232 ng/L would provide a sensitivity of 93.3% (95% CI: 0.78–0.99), higher than 90% (95% CI: 0.87–0.92), in reference to the Fine's score in the above meta-analysis. This could therefore be useful in the HER to identify patients with non-severe pneumonia and low risk of death who could be safely discharged. Our sensitivity is very close to those of the studies by Jeong and Nowak when they dropped their cutoff points to 235.6 ng/L and 628 ng/L, respectively (4, 5).

A higher cutoff point (10,808 ng/L) would indicate patients requiring a more aggressive initial treatment.

Assessment of the diagnostic performance of NT-ProBNP

After studying the general accuracy of the diagnostic test using ROC curves, NT-ProBNP has good capacity as a diagnostic test to predict mortality at 30 days, with an AUC of 78%. The studies performed to date found an AUC of between 71% and 88% (Table 4).

Comparison of the prognostic capacity of NT-ProBNP compared to a scale to predict severity

The accuracy of these two prediction scales has been compared in various reviews and meta-analyses, resulting in a high NPV in populations with a low prevalence of death, a PSI sensitivity of about 90%, a CURB-65 specificity of close to 80%, and suitable diagnostic capacity with an AUC of around 80% (15-17). However, in spite of the value of these tools, approximately 30%–60% of low risk CAP patients are hospitalized, there being considerable disagreement between the recommendations of the scales and the final destination of the patient (18).

Table 4. Assessment of the predictive capacity of NT-ProBNP and SPS for mortality at 30 days

Studies	NT-ProBNP		PSI		CURB-65		ATS/IDSA	
	AUC	95% CI	AUC	95% CI	AUC	95% CI	AUC	95% CI
Jeong et al. (4)	0.71	0.61–0.81	0.80	0.74–0.85	0.76	0.70–0.83	-	-
Nowak et al. (5)	0.73	0.67–0.77	0.76	0.71–0.81	0.65	0.61–0.70	-	-
Chang et al. (6)	0.88	0.82–0.94	0.87	0.83–0.91	-	-	-	-
Lin et al. (7)	0.72	0.65–0.78	-	-	-	-	0.65	0.58–0.63
Xiao et al. (8)	0.77	0.71–0.84	0.87	0.82–0.92	0.81	0.75–0.87		
Tazón Varela et al. (9)	0.78	0.73–0.83	0.88	0.83–0.91	0.87	0.83–0.91	0.89	0.85–0.92

SPS: Severity Prognostic Scale

In our sample, the two scales to predict severity showed better diagnostic performance than the biomarker. Nevertheless, the AUC obtained in our study for the predictive scales was at the same height of the upper range of the AUC found in systematic reviews and meta-analyses (16, 17). We therefore understand that the diagnostic capacity of NT-ProBNP could be useful in the same terms as the use of PSI and CURB-65 scales.

Comparison of the prognostic capacity of NT-ProBNP compared to other biomarkers

Over the last few years, medical literature has accepted the usefulness of PCT to differentiate acute systemic bacterial infections in CAP to assess the response to treatment or predict hospitalization (19, 20). However, there is still controversy regarding its capacity to predict early mortality. Some studies, such as those by Krüger et al. (21), Horie et al. (22), or Park et al. (23), attribute good capacity to PCT. However, in a systematic review of 30 publications, the ability of PCT to predict early mortality was found to be very similar to our results (24). In our sample, the association of NT-ProBNP with PCT, a combination not used to date, provided high specificity (98%) to detect severe CAP. This combination of infectious and cardiovascular stress biological markers could be useful in the HER or ICU to detect potentially severe patients.

Among the studies that analyze NT-ProBNP and its relationship to CAP, there are very few that study and compare other biomarkers. Only Jeong et al. (4) and Nowak et al. (5) assessed infectious-inflammatory biological markers (leukocytes and CRP); they obtained results very similar to ours, attributing a low predictive capacity to both variables (Table 5).

Correlation between NT-ProBNP and predictive scales

A study was made of the association between NT-ProBNP and predictive scales such as quantitative variables. There was positive and significant interdependence between the severity of pneumonia and the PSI and CURB-65 scales and minor ATS/IDSA 2007 criteria, the strongest association being with Fine's score (Rho 0.71 p<0.0001). These findings are in agreement with Nowak et al. (5), who also found a significant interrelationship between early mortality and the PSI scale (Rho 0.53 p<0.001).

Correlation between NT-ProBNP and other biomarkers

A study was made of the strength of the association between NT-ProBNP and the analyzed biomarkers. Except for troponin T, the correlation was weak with the other inflammatory markers normally used in an emergency room, such as leukocytes (Rho 0.14 p=0.02), CRP (Rho 0.18 p=0.003), and PCT (Rho 0.33 p=0.001). Of special note is the low interrelationship between NT-ProBNP and CRP. Nowak et al. (5) also did not find any correlation between NT-ProBNP, leukocytes, and CRP.

Logistic regression model

a. NT-ProBNP as an independent risk factor for early mortality

A logistic regression analysis was performed, adjusting for possible confusing factors. Only age, the ATS/IDSA scale, and NT-ProBNP maintained statistical significance. However, NT-ProBNP was the only factor maintaining statistical significance in all models. Therefore, age, meeting ATS/IDSA 2007 criteria, and high NT-ProBNP levels are independent predictors of early mortality. These results are consistent with the literature, where NT-ProBNP is also highlighted as an independent risk factor (4-6).

From the evolutionary point of view, an increase of 1 ng/L is not relevant for the clinician; therefore, we grouped the increases of NT-ProBNP as 300, 500, 1,000 and 2,000 ng/L, noting that the risk of death with the first 30 days increased from 3% to 22%. Future studies will be required to determine the solidity of these results and whether this biomarker could be a useful tool in HER and observation units to determine the progress of patients with CAP.

Table 5. Assessment of the predictive capacity of NT-ProBNP and biomarkers for mortality at 30 days

Study	NT-ProBNP		Leukocytes		Neutrophils		D-Dimer	
	AUC	95% CI	AUC	95% CI	AUC	95% CI	AUC	95% CI
Jeong et al. (4)	0.71	0.61–0.81	-	-	-	-	-	-
Nowak et al. (5)	0.73	0.67–0.77	0.52	0.42–0.61	-	-	-	-
Chang et al. (6)	0.88	0.82–0.94	-	-	-	-	-	-
Lin et al. (7)	0.72	0.65–0.78	-	-	-	-	-	-
Xiao et al. (8)	0.77	0.71–0.84	-	-	-	-	-	-
Tazón Varela et al. (9)	0.78	0.73–0.83	0.58	0.51–0.64	0.60	0.54–0.66	0.75	0.56–0.88
Study	**CRP**		**PCT**		**Lactate**		**Troponin T**	
	AUC	95% CI	AUC	95% CI	AUC	95% CI	AUC	95% CI
Jeong et al. (4)	-	-	-	-	-	-	-	-
Nowak et al. (5)	0.55	0.46–0.64	-	-	-	-	-	-
Chang et al. (6)	-	-	-	-	-	-	0.79	0.71–0.87
Lin et al. (7)	-	-	-	-	-	-	-	-
Xiao et al. (8)	-	-	-	-	-	-	-	-
Tazón-Varela et al. (9)	0.56	0.49–0.62	0.66	0.60–0.72	0.80	0.60–0.93	0.85	0.72–0.93

AUC: area under the curve; CI: confidence interval; CRP: C reactive protein; PCT: Procal citonin

b. Assess improved prediction of outcome by associating NT-ProBNP and predictive scales

Some studies are headed in the direction of adding a biomarker to predictive scales to improve the predictive capacity for mortality and the absence of severe complications (25, 26). Several biochemical markers improve the prediction of mortality at 30 days for predictive scales in hospitalized patients, including vitamin D status with PSI (27), CRP with PSI, CURB-65 and CRB-65 (28), CRP and PCT with CURB-65 (29), cortisol with CRB-65 (30), or albumin with PSI and CURB-65 (31).

In our sample, NT-ProBNP improves the prognostic capacity of all three scales. It improves PSI by 3% and CURB-65 by 4%. It is important to note the predictive improvement of the ATS/IDSA scale improved by 11% when associated with NT-ProBNP, reaching an AUC of 93% with a correct classification of 91%. The results in this regard are dissimilar in different studies. When Jeong et al. associated NT-ProBNP with PSI and CURB-65, they found no statistically significant improvement; nor did Lin et al. find an improvement in critical patients when associating NT-ProBNP with the ATS/IDSA scale, although there was an improvement when NT-ProBNP was associated with the APACHE II scale (4, 7). Therefore, this subject is still open to debate.

c. Assess improved outcome prediction by associating NT-ProBNP and other biomarkers

To our knowledge, there is no study using the assessment of diagnostic tests to improve the predictive of a prognosis of mortality by combining NT-ProBNP with another biomarker.

In our study, NT-ProBNP improves the diagnostic performance of classic inflammatory-infectious biomarkers by 24% for CRP and 19% for PCT. It is worthy of note that the PCT model together with NT-ProBNP reaches an AUC of 85%, greater than the AUC provided for PSI (15, 16). Furthermore, in this sample, these two biomarkers had a specificity of 98% in detecting mortality at 30 days, an extremely valuable combination for detecting high risk patients.

d. Assess improved prediction of outcome by associating NT-ProBNP with predictive scales and biomarkers

A study of predictive improvement by associating predictive scales with NT-ProBNP has already been analyzed, with inconsistent results. Jeong et al. did not find that NT-ProBNP improved PSI, CURB-65, or APACHE II (4). Lin et al. (7) did not find that association of NT-ProBNP with minor ATS/IDSA 2007 criteria improved these predictions, although it did do so with APACHE II.

Nowak et al. (5) considered that associating NT-ProBNP with the categorical value of PSI provided additional information. They observed that NT-ProBNP helps detect high or intermediate risk patients when PSI alone marked them as high risk.

In our sample, of all the logistic regression models proposed that included age together with biomarkers and predictive scales, the simplest and most profitable variant would be to use the ATS/IDSA scale and NT-ProBNP, which would give a sensitivity of 80%, a specificity of 92%, good classification of 91% of patients, and an AUC of 93%. That is, in our study, NT-ProBNP combined with the ATS/IDSA 2007 scale is the best combination between biomarkers and predictive scales for detecting severe CAP.

Survival analysis

In the case of CAP, mortality is concentrated within the first few days, with 20% of patients dying in the first 48 h and 50% within the first week. Corrales-Medina et al. (32) detected the majority of cardiovascular complications in the first week. As these complications have a very early onset, the patient may be in the emergency room, observation area, or short stay ward, thus reasserting the importance of early diagnosis and treatment in the HER but also the need for tools that help predict mortality. In our study, survival analysis also revealed that 20% of patients die within the first 48 h and 50% within the first 5 days. Apart from the patients that died, those with NT-ProBNP values above the 1.769 ng/L cutoff point showed statistically significant differences in survival time compared to those that died with values below the cutoff point (Figure 3).

Study limitations

The limitations are basically those derived from a single-center followup study. This study did not include patients with suspected CAP treated in primary healthcare without being referred to the hospital for assessment.

No analytical controls of NT-ProBNP or any other biomarker were performed during the month of followup, thus limiting our conclusions to assess the evolutionary prognostic capacity. Although we analyzed eight biomarkers, the sample numbers were low for lactate, high-sensitivity troponin T, and D-dimer.

Conclusion

In our sample, elevation of NT-ProBNP at the time of diagnosis in the emergency room was associated with increased short term mortality. This biomarker could be an independent risk factor to predict this mortality. These findings are in agreement with current literature; NT-ProBNP is a prognosis tool that has begun to appear in review articles as an emerging biomarker (33). Until its individual prognostic value is confirmed, this marker could be useful in the initial assessment of CAP patients and be included as a tool in addition to predictive scales; also, it could perhaps be used in the future to design individual treatment strategies.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Cantabria University.

Informed Consent: All the patients who entered in the study fulfilled an informed consent

Peer-review: Externally peer-reviewed.

Conflict of Interest: No conflict of interest was declared by the authors.

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