ORIGINAL ARTICLE

Prognostic value of pro-adrenomedullin and NT-proBNP in patients referred from the emergency department with influenza syndrome

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Objectives. To assess the prognostic value of procalcitonin (PTC), C-reactive protein (CRP), N-terminal prohormone of brain natriuretic peptide (NT-proBNP), and mid-regional pro-adrenomedullin (MR-proADM) in patients with influenza syndrome.

Methods. Prospective study in patients admitted from the emergency department with influenza syndrome. Biomarker concentrations were measured in the first 24 h after admission and a test for influenza. The results were analyzed for ability to predict a hospital stay longer than 7 days, intensive care unit admission, or in-hospital death.

Results. Ninety-eight patients were included; the prognosis of 44 (44.9%) was classified as poor. The areas under the receiving operator characteristic curve were 0.68 (95% CI, 0.56-0.80) for NT-proBNP, 0.73 (95% CI, 0.62-0.84) for MR-proADM, and nonsignificant for PCT and CRP. The following variables were independently associated with a poor prognosis: pneumonia (OR, 7.46 [95% CI, 2.08-26.73]; *P*=.002), heart failure (OR, 5.16 [95% CI, 1.35-19.74]; *P*=.016), and NT-proBNP > 580 pg/mL (OR, 4.68 [95% CI, 1.53-14.26]; *P*=.006). In the 53 patients with confirmed A(H1N1) influenza, only NT-proBNP was an independent predictor of prognosis (adjusted OR, 5.75 [95% CI, 1.46-22.61]; *P*=.012).

Conclusions. NT-proBNP and MR-proADM were the only biomarkers with prognostic value. Only NT-proBNP was a useful predictor in patients with confirmed influenza.

Keywords: Biological markers. Prognosis. Pandemics, influenza. Influenza virus A(H1N1)pmd09. NT-proBNP. Pro-adrenomedullin. Procalcitonin. C-reactive protein.

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Valor pronóstico de la proadrenomedulina y el NT-proBNP en los pacientes procedentes de urgencias con síndrome gripal

Objetivos. Analizar el valor pronóstico de la procalcitonina (PCT), la proteína C reactiva (PCR), el NT-proBNP y la región medial de la proadrenomedulina (MR-proADM) en pacientes hospitalizados con síndrome gripal.

Método. Estudio prospectivo realizado en pacientes hospitalizados desde urgencias por síndrome gripal. Se analizaron las concentraciones de biomarcadores en las primeras 24 h de ingreso y el test de gripe y se analizó su capacidad predictiva de mal pronóstico: estancia superior a 7 días, ingreso en unidad de cuidados intensivos o fallecimiento intrahospitalario.

Resultados. Se incluyeron 98 pacientes, 44 (44,9%) de ellos con mal pronóstico. Las áreas bajo la curva COR para mal pronóstico fueron de 0,68 (IC 95% 0,56-0,80) para NT-proBNP y de 0,73 (IC 95% 0,62-0,84) para la MR-proADM, y no significativas para PCT y PCR. Las variables asociadas independientemente con mal pronóstico fueron: neumonía (OR 7,46 [IC 95% 2,08-26,73]; p = 0,002), insuficiencia cardiaca (OR 5,16 [IC 95% 1,35-19,74]; p = 0,016) y NT-proBNP > 580 pg/ml (OR 4,68 [IC 95% 1,53-14,26]; p = 0,006). En los 53 pacientes con gripe A(H1N1) confirmada, solo el NT-proBNP tuvo un valor pronóstico independiente (OR ajustado 5,75 [IC 95% 1,46-22,61]; p = 0,012).

Conclusiones. En pacientes con síndrome gripal, el NT-proBNP y la MR-proADM fueron los únicos biomarcadores con valor pronóstico, y solo el primero de ellos mantuvo esta asociación en pacientes con gripe confirmada.

Palabras clave: Biomarcadores. Pronóstico. Gripe pandémica. Virus de la gripe A(H1N1)pmd09. NT-proBNP. Proadrenomedulina. Procalcitonina. Proteína C reactiva.

Introduction

Over the last few years there has been an increasing interest in the use of biomarkers as tools for predicting prognosis, in such a way that they help the clinician with a more precise risk stratification and serve as an aid in decision-making in the emergency department (ED)[1]. In the specific case of a new pandemic strain of influenza A(H1N1)pdm09 this help could be especially relevant, in view of the broad spectrum of clinical severity and the high morbidity and mortality that it shows in young patients[2]. This fact has led to studies that have demonstrated the prognostic value of C-reactive protein (CRP) and procalcitonin (PTC) in this infec-

tion[3,4]. A novel marker, the medial region of proadrenomeduline (MR-proADM), has also been associated with increased mortality and the need for admission to the intensive care unit (ICU) in patients with pneumonia caused by influenza A(H1N1)pdm09[5], as well as pneumonia contracted in the community, regardless of its etiology[6]. In this sense, a high correlation has been observed between the figures of this biomarker and different scales of severity[7], although its role in patients with uncomplicated influenza is still little known. NT-proBNP has previously been related to the prognosis of patients with sepsis[8,9], exacerbation of chronic obstructive pulmonary disease (COPD)[10] or pneumonia[11]. However, its role in patients with influenza has not been specifically studied through prospective studies. This study aims to analyze the prognostic value of CRP, PTC, MR-proADM and NT-proBNP in ED patients who needed to be hospitalized for influenza during an outbreak of influenza A(H1N1)pdm09.

Method

Prospective, observational cohort study, which consecutively included all patients with clinical influenza criteria from the ED who required hospital admission during an influenza A(H1N1)pdm09 (Feb-March 2014) epidemic outbreak in a 330-bed, second-level hospital. The inclusion criteria were clinical and defined as: fever associated with respiratory clinic of any type, arthromyalgia and chills. Admission criteria were established from the ED by physicians different from those of the research team, following clinical practice guidelines. We excluded patients who, at the time of admission or during the course of admission, had an alternative diagnosis (confirmed infection other than influenza) and also had a negative influenza test.

Oropharyngeal samples were collected from all patients in the ED for antigenic (rapid immunofluorescent test) and viral RNA (by means of polymerase chain reactionretrotranscriptase) determination of influenza A(H1N1). In addition, urinary antigens of Legionella and pneumococcus were requested in patients with radiological infiltration, as well as sputum cultures in cases with productive cough. Sociodemographic data, vaccination status, personal history, radiological findings and data on acute or respiratory heart failure at the time of arrival in the ED were also collected. The Sepsis-Related Organ Failure Assessment (SOFA) index was calculated based on clinical and analytical criteria (creatinine, bilirubin and platelets).

Plasma MR-proADM was measured in an external laboratory using a "sandwich" immunoassay (Kryptor Compact Plus® immunoassay) and the results of this biomarker were hidden from the clinicians in charge of care. PTC, CRP and NT-proBNP were measured in the laboratory of the hospital and the results were visible to the physicians in charge during admission. All biomarkers were obtained within 24 hours of arrival at the ED.

Those with prolonged hospital stay, need for ICU admission or death during admission were classified as poor prognosis. A prolonged stay was considered when this was greater than 7 days, according to the average stay of patients with respiratory infections (influenza, bronchiolitis, bronchitis and pneumonia) of the Minimum Basic Data Set of hospital discharges in Spain of the previous 4 years[12].

The software SPSS® 19.0 (IBM, Armonk, NY, USA) was used. Quantitative variables were expressed as mean and standard deviation (SD) or as median and interquartile range, and qualitative variables were described by absolute frequencies with 95% confidence interval (95% CI). The Student t or Mann-Whitney U test was used to compare means of quantitative variables between 2 groups, depending on whether the variables had a normal distribution or not. Chi-square or Fisher's exact test was used for comparison of qualitative variables, as appropriate. Prognostic performance was evaluated with the area under the curve (AUC) of the receiver operating characteristic (ROC) and to establish possible cut-off points to discriminate poor prognosis. In addition to the comparison of means and the establishment of cut-off points, the presence of linear correlation between biomarker figures and days of hospital stay was investigated. A multivariate analysis (binary logistic regression) was performed to calculate the independent effect of each variable on the "bad prognosis" variable. The value of $p < 0.05$ was considered significant.

The patients selected gave written consent to participate in the study and this was approved by the Ethics Committee of the Reina Sofia University General Hospital, Murcia. All patient data were handled with complete confidentiality by the research team, following the recommendations of the Helsinki Conference on biomedical research.

Results

Ninety-eight patients with a mean age of 64.1 years (SD 19.8) were included. Fourteen (14.3%) had no chronic disease or comorbidity and the most frequent were: diabetes mellitus (37; 37.8%), structural heart disease (37; 37.8%) and chronic obstructive pulmonary disease (COPD, 35; 35.7%). At admission, 60 (61.2%) had pneumonia, 28 (28.6%) heart failure criteria and 15 (15.3%) had respiratory failure. Fifty-three patients (54.1%) were positive in the flu test, and these were younger (57 [SD 19.4] vs 72.5 [SD 16.8] years; $p < 0.001$) and with a lower frequency of heart disease (26.4 vs 51.1%);$p = 0.012$), cognitive impairment (9.4 vs 24.4%; $p = 0.045$), history of neoplasia (1.9 vs 17.8%; $p = 0.017$), and with heart failure on admission (15.1 vs 44.4%; $p = 0.001$). The median stay was 7 days (ICR 4-10) and 4 patients (4.1%) required admission to the ICU. Overall in-hospital mortality was 4.1%. The SOFA index was equal to or greater than 2 in 27 patients (27.6%), and in all cases it was less than 6 points.

Forty-four patients (44.9%) were classified as "poor prognosis". Factors associated with poor prognosis were age, structural heart disease, dementia, history of neoplasia and pneumonia on admission, acute heart failure data or higher baseline levels of MRproADM and NT-proBNP (Table 1).

The baseline figures for NT-proBNP and MR-proADM presented, unlike CRP and PTC, a statistically significant positive linear correlation with days of hospital stay (Figure 1) and AUC-ROC of 0.68 (95% CI 0.56-0.80) and 0.73 (95% CI 0.62-0.84), respectively, to predict poor prognosis. The cut-off points with the greatest specificity and sensitivity are shown in Table 2.

For multivariate analysis, the variables "age over 70", "MR-proADM greater than 1 nmol/l", "NT-proBNP greater than 580 pg/ml", "pneumonia" and "heart failure" were included in a binary logistic regression analysis. These variables were chosen after performing several models of less statistical significance. The variables independently associated with poor prognosis were pneumonia (OR 7.46 (95% CI 2.08-26.73), P = 0.002), NTproBNP greater than 580 pg/ml (OR 4.68 (95% CI 1.53-14.26), P = 0.006) and heart failure (OR 5.16 (95% CI 1.35-19.74), P = 0.016). The regression model was statistically significant with a Nagelkerke R2 of 40.7%. Subgroup analysis showed that in patients with a negative influenza test, MR-pro-MDM greater than 1 nmol/L (adjusted OR 16.37 (95% CI 2.36-113.37) was independently associated with a poor prognosis; p = 0.005) and the presence of pneumonia (adjusted OR 14.41 (95% CI 2.27-91.40); p = 0.005), while in the subgroup of patients with a positive influenza test, NT-proBNP was the only independent variable (adjusted OR 5.75 (95% CI 1.46-22.61); p = 0.012).

Discussion

In this study the concentrations of MR-proADM and NT-proBNP are shown for the first time as independent prognostic factors in emergency patients hospitalized for Influenza. The relationship of NT-proBNP with prognosis is also maintained in patients with a positive influenza test (which did not occur with MR-proADM), and is the best prognostic marker, regardless of the presence of pneumonia, structural heart disease and cardiac insufficiency. Song et al.[13] already observed that cardiovascular clinical events in patients with influenza A were associated with a worse evolution and higher numbers of NT-proBNP, but did not analyze the prog-

Table 1. Sociodemographic, clinical, evolutionary characteristics and biomarker values of the sample and univariate analysis concerning prognosis

	Good prognosis N = 54 n (%)	Bad prognosis N = 44 n (%)	p	OR (IC 95%)
Age				
Under 35	8 (14.81)	2 (4.5)	NS	0.27 (0.06-1.32)
35-50 years	16 (29.6)	6 (13.6)	NS	0.40 (0.14-1.12)
51-70 years	13 (24.1)	8 (18.2)	NS	0.73 (0.28-1.93)
Over 70 years	17 (31.5)	28 (63.6)	**0.002**	**3.51 (1.55-8.01)**
Male	31 (57.4)	22 (50.0)	NS	1.35 (0.6- 3.02)
Comorbidity				
DM	16 (29.6)	21 (47.7)	NS	2.17 (0.94-4.98)
Tobacco	16 (29.6)	7 (15.9)	NS	0.45 (0.17-1.22)
Heart disease	15 (27.8)	22 (50.0)	**0.024**	**2.60 (1.12-6)**
Dementia	5 (9.3)	11 (25.0)	**0.036**	**3.27 (1.04-10.27)**
CLD	17 (31.5)	18 (40.9)	NS	1.52 (0.66-3.46)
CKD	4 (7.4)	7 (15.9)	NS	2.36 (0.64-8.68)
Hepatopathy	3 (5.6)	3 (6.8)	NS	1.24 (0.24-6.49)
Neoplasia	1 (1.9)	8 (18.2)	**0.005**	**11.78 (1.41-98.27)**
Immunosuppression	4 (7.4)	3 (6.8)	NS	0.91 (0.19-4.32)
Obesity	6 (11.1)	10 (22.7)	NS	2.35 (0.78-7.1)
Influenza test positive	35 (64.8)	18 (40.9)	NS	0.49 (0.22-1.10)
Complications				
Pneumonia	27 (50.0)	33 (75.0)	**0.012**	**3 (1.26-7.13)**
Heart failure	9 (16.7)	19 (43.2)	**0.004**	**3.81 (1.50-9.65)**
Respiratory failure	8 (14.8)	7 (15.9)	NS	1.09 (0.36-3.28)
SOFA ≥ 2	12 (22.2)	15 (34.1)	NS	2.07 (0.87-4.9)
Biomarkers [medium (IQR)]				
MR-proADM (nmol/l)	0.87 (0.59-1.21)	1.39 (0.92-1.80)	< **0.001**	**3.02 (1.47-6.22)**
NT-proBNP (pg/ml)	310 (55-1.177)	1.244 (297-3.694)	**0.006**	**1.09 (0.99-1.20)**
PTC (ng/ml)	0.05 (0.05-0.13)	0.065 (0.05-0.82)	0.086	1.11 (0.92-1.33)
CRP (mg/dl)	3.15 (0.90-9.75)	4.54 (0.86-13.14)	0.386	1.02 (0.97-1.08)

DM: diabetes mellitus; CLD: chronic lung disease; CKD: chronic kidney disease; MR-proADM: medial region of proadrenomedulin; NS: not significant; OR: odds ratio; NT-proBNP: N-terminal fragment of the cerebral natriuretic peptide; CRP: C-reactive protein; PTC: procalcitonin. IQR: interquartile range. Significant variables are marked in bold.

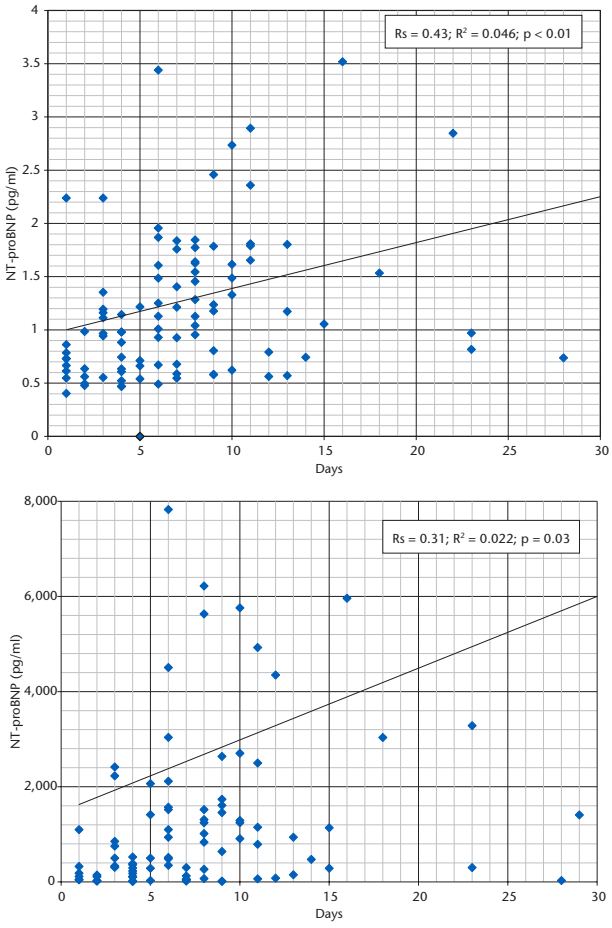

Figure 1. Dispersion diagram. Positive linear correlation of biomarkers with days of hospital stay. Linear correlation between baseline figures for the medial region of proadrenomeduline (MR-proADM) (top) and NTproBNP (bottom) and days of hospital stay.

nostic value of the biomarker independently. Other authors highlight the high frequency of subclinical cardiomyopathy in patients with influenza and the usefulness of troponins in its detection[14]. This could justify the predictive effect of NT-proBNP in the present work and place it as a potentially useful tool in the management of patients with asymptomatic influenza from the cardiological point of view. Recently, Kwong et al.[15] observed a higher incidence of acute myocardial infarction during the first 7 days after the diagnosis of influenza (compared to a control period), suggesting that viral infection may behave as a trigger of acute coronary syndrome in patients at risk. However, some authors highlight as possible causes of this association the treatment with anti-inflammatories[16] or the coexistence of bacterial pneumonia[17]. Hospital stay was the main prognostic criterion, a factor less consistent and used than mortality, but which, adjusted for the rest of the variables, may be of high practical clinical utility and has been used in other studies on the prognostic value of NT-proBNP in related pathologies[9,10].

MR-proADM was associated with prolonged hospital stay and worse prognosis in the total of patients, but not in the subgroup of patients with confirmed influenza. However, it is worth noting that this group was small and with a low number of events, which would limit the statistical power of this subanalysis. Lacoma et al.[7] observed that the numbers of this biomarker had a high prognostic value in patients with pneumonia, while patients with non-condensing respiratory infections (acute bronchitis or acute chronic bronchitis) had significantly lower concentrations of MRproADM, so the role of this biomarker would be uncertain in these entities. In patients with COPD a good predictor of stable phase mortality has been described, but not in patients hospitalized for exacerbations[18]. In our study we found a predictive effect of a longer hospital stay in the total number of patients and, especially, in those with a negative flu test, independently of the presence of pneumonia, which may contribute to defining the role that this biomarker may have in non-condensing respiratory infections and without sepsis criteria, although more studies are needed in this field.

Among the limitations of this study we must highlight its small sample size, the non-specificity of the selection criteria (clinical picture compatible with influenza syndrome) and that would only be applicable to hospitalized patients. However, and given the limited accessibility of microbiological confirmation tests in some media, the sample becomes representative of a heterogeneous clinical spectrum of patients with respiratory infection who show a high suspicion of influenza during outbreaks, being accepted in these situations a clinical diagnosis. The absence of determination of other respiratory viruses could be highlighted among the weak points.

Despite its limitations, we can conclude that in patients with influenza symptoms, a single determination of NT-proBNP would help the emergency physician to detect those patients at higher risk of poor prognosis regardless of the result on the influenza test, as well as

Table 2. Prognostic performance of biomarkers (MR-proADM and NT-proBNP) according to influenza test

		S (%)	Sp (%)	PPV (%)	NPV (%)	OR (IC 95%)	p
Total patients	MR-proADM > 1 nmol/l	70.0	64.0	60.8	72.7	4.15 (1.7-10.1)	0.001
	NT-proBNP > 580 pg/ml	71.4	680.	65.2	73.9	5.32 (2.17-13.02)	< 0.001
Negative flu test	MR-proADM > 1 nmol/l	91.2	61.1	81.6	78.6	11.01 (2.36-51.14)	0.001
	NT-proBNP > 580 pg/ml	76	61.1	73.1	64.7	4.98 (1.33-18.61)	0.014
Positive flu test	MR-proADM > 1 nmol/l	43.8	65.6	38.9	70	1.48 (0.43-5.07)	NS
	NT-proBNP > 580 pg/ml	64.7	71.9	55.0	79.3	4.68 (1.33-16.49)	0.013

Sp: specificity; MR-proADM: medial region of proadrenomeduline; NS: not significant; NT-proBNP: N-terminal fragment of the cerebral natriuretic peptide; OR: odds ratio; S: sensitivity; NPV: negative predictive value; PPV: positive predictive value.

other variables. MR-proADM would be useful in patients with a negative flu test, and would be a better predictor of poor prognosis than any other clinical variable, including the CRP and PTC biomarkers.

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