Prognostic power of proadrenomedullin in community-acquired pneumonia is independent of aetiology

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ABSTRACT: Biomarkers are useful in community-acquired pneumonia (CAP). Recently, midregional (MR) proadrenomedullin (proADM) has been shown to be of potential prognostic use. We sought to determine whether this prognostic role depends on the cause of CAP.

We conducted a prospective cohort study of immunocompetent patients with CAP. Pneumonia Severity Index (PSI) and CURB-65 score (confusion (abbreviated mental test score of $\leqslant 8$), urea $\geqslant 7$ mol·L^{-1}, respiratory rate $\geqslant 30$ breaths·min^{-1}, blood pressure <90 mmHg systolic or <60 mmHg diastolic, and age $\geqslant 65$ yrs), blood C-reactive protein, procalcitonin, MR-proADM, and microbiological studies were systematically performed. Patients were grouped as bacterial, viral/atypical and mixed CAP, and were followed up at 30, 90 and 180 days, and 1 yr.

We recruited 228 CAP patients. Identification of at least one pathogen was achieved in 155 (68%) patients. MR-proADM levels closely correlated with increasing severity scores, and showed an important predictive power for complications and short- and long-term mortality (1 yr). Its addition to PSI and CURB-65 significantly improved their prognostic accuracy. A MR-proADM cut-off of 0.646 nmol·L^{-1} identified 92% of patients scored as PSI classes IV and V as high risk. MR-proADM outcome prediction power was not affected by different aetiologies.

MR-proADM has high short- and long-term prognostic accuracy, and increases the accuracy of clinical scores. The prognostic value of MR-proADM is not modified by different possible CAP aetiologies.

KEYWORDS: Aetiology, biomarkers, community-acquired pneumonia, midregional proadrenomedullin, outcome

ommunity-acquired pneumonia (CAP) is a disease with a very wide range of possible outcomes. Clinical severity scores, mainly the Pneumonia Severity Index (PSI) [1] and CURB-65 score (confusion (abbreviated mental test score of $\leqslant 8$), urea $\geqslant 7$ mol·L^{-1}, respiratory rate $\geqslant 30$ breaths·min^{-1}, blood pressure <90 mmHg systolic or <60 mmHg diastolic, and age $\geqslant 65$ yrs) [2], are useful tools for evaluating CAP-associated risk of mortality and, therefore, for making decisions about the most appropriate allocation of healthcare resources [2–5]. However, none of these tools is exempt from false-positive and -negative results. Biomarkers may improve the diagnostic accuracy of both PSI and CURB-65.

In recent years, many studies involving biomarkers for CAP have been performed [6]. C-reactive

protein (CRP) and procalcitonin (PCT) have shown their usefulness for diagnosis [6], suspicion of typical bacteria as the causal agent [7], guiding antibiotic therapy [8], and assessing severity, mortality risk and the potential for complications [9, 10]. Other new biomarkers have been proposed to provide information on severity and prognosis, including midregional (MR) proadrenomedullin (proADM).

MR-proADM is a fragment of proADM, the precursor of adrenomedullin (ADM), that is more stable than full-length proADM. MR-proADM is easy to measure and directly reflects levels of ADM. ADM is a member of the calcitonin peptide family that is widely expressed and intensively synthesised during severe infections, which has multiple effects, including immune

modulation, vasodilatation, antimicrobial activity and electrolyte balance [11, 12].

Four large, multicentre reports involving this biomarker in CAP outcomes have been published. They found a strong discriminatory power of MR-proADM for predicting serious complications [13], short-term [12, 14], mid-term [12] and long-term [15] mortality, and improved risk stratification of clinical scores [12–14]. These four multicentre studies included a very large number of patients, but some cohorts [13, 14] had been recruited for previous studies with heterogeneous objectives.

So far, no studies have been published that test whether the outcome prediction power of MR-proADM depends on the aetiology of CAP. Increased levels of PCT (and of CRP) have been found in *Streptococcus pneumoniae* CAP when compared with atypical bacterial or viral pneumonias [7, 16], but a possible aetiological discrimination capacity of MR-proADM is not yet known.

One objective of this study was to determine whether biomarkers, especially MR-proADM, alone or in association with the PSI and CURB-65 severity scores, are accurate in their assessment of outcome in hospitalised patients, independently of CAP aetiology. We also studied the potential role of biomarkers in predicting complications and short- and long-term mortality.

MATERIAL AND METHODS
Selection of patients
Consecutive adult (>18 yrs of age) patients admitted by an emergency department (ED) physician to a 900-bed university hospital (Hospital Universitario Miguel Servet, Zaragoza, Spain) with a diagnosis of CAP were prospectively recruited within 24 h of their arrival. CAP was defined as an acute disease with a radiological infiltrate that was not previously present and not due to another known cause, and was associated with symptoms of lower respiratory tract infection. Exclusion criteria were: 1) severe immunodepression (HIV infection or severe haematological diseases); 2) immunosuppressive therapy (prednisone or equivalent dose of >20 mg daily for >2 weeks or any immunosuppressive regime therapy (azathioprine, cyclosporine, cyclophosphamide and/or other immunosuppressant drugs)); 3) leukopenia (<1,000 leukocytes per mm^3) or neutropenia (<500 neutrophils per mm^3) and/or chemotherapy in the previous year; 4) pulmonary abscess (radiological cavitation), aspiration pneumonia and obstructive pneumonia; 5) possible nosocomial origin (<30 days from hospital discharge); and 6) known active neoplasia. The study was approved by the Ethics Committee (Instituto Aragonés de Ciencias de la Salud, Zaragoza) and every patient gave informed consent. All patients were followed up during their hospital stay and those with a definitive diagnosis other than CAP were excluded (fig. 1).

During the study period, a sex- and age-matched control group was collected from subjects admitted to Orthopaedic Surgery, Digestive and Neurology Departments (Hospital Universitario Miguel Servet, Zaragoza, Spain). None of them had any suspicion of infectious or respiratory disease, immunosuppression, known neoplasia or recent trauma.

Data collection
The following variables were recorded: age; sex; anti-influenza vaccination <1 yr prior to the study; antipneumococcal vaccination <5 yrs prior to the study; tobacco consumption (nonsmoker, ex-smoker or current smoker, and pack-yrs of exposure in smokers); alcohol consumption (nondrinker, ex-drinker or <80 or >80 g alcohol per day in current drinkers); previous pneumonia; and previous recent (1 month) antibiotic treatment. In addition, at admission, the following were recorded: days of duration of disease; symptoms prior to infection; myalgia; CAP signs and symptoms; vital constants at the ED (respiratory and heart rates, arterial pressure and oxygen saturation); number of hours in the ED; arterial blood gas determinations (when performed); number of lobes involved and type of radiological condensation (alveolar, interstitial or mixed); and the presence of pneumothorax, atelectasis or bleeding.

PSI and CURB-65 scores were calculated for all patients. All patients were admitted to the hospital for ≥24 h.

Adherence to Spanish antibiotic guidelines [17] and time of first dose after arrival at the hospital were also recorded. After discharge, patients were followed up and mortality was recorded at 30, 90 and 180 days, and 1 yr after inclusion in the study, when possible.

Data on CAP evolution and complications during hospitalisation were assessed, as were antibiotics (doses and treatment length, and first dose time), and days of admission, intensive care unit (ICU) admission, oxygen and mechanical ventilation (MV) requirements, and clinical stability. Complications included respiratory failure, need for MV, shock, left cardiac failure, renal failure, pleural effusion and others. Intrahospital mortality, causes of exitus and therapeutic failure were recorded. After 30 days, a clinical examination, blood analysis including a second serological sample, and chest radiography were performed.

Short-term mortality was defined as death due to any cause within the first 30 days. Mid- and long-term mortality were
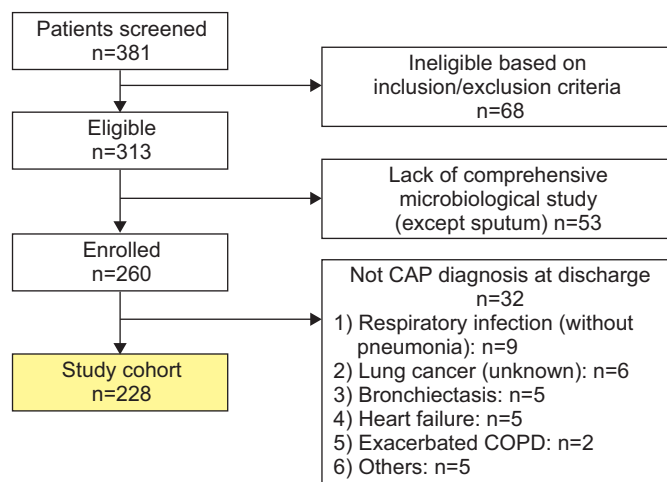

FIGURE 1. Flow diagram for patient enrolment or exclusion in the study. CAP: community-acquired pneumonia; COPD: chronic obstructive pulmonary disease.

TABLE 1	Baseline characteristics of the 228 community-acquired pneumonia patients on admission
Age yrs	73 (63–80)
Age ⩾65 yrs	162 (71.1)
Males	139 (61)
Smoking status	
Current smokers	55 (24.1)
Exposure pack-yrs	30 (11–60)
Ex-smoker	89 (39.0)
Exposure pack-yrs	48 (30–75)
Coexisting illnesses	
Neoplastic disease, not active	30 (13.2)
Heart disease	84 (36.8)
Cerebrovascular disease	47 (20.6)
COPD	72 (31.6)
Liver disease	7 (3.1)
Renal disease	35 (15.4)
Chronic renal disease	27 (11.8)
Diabetes mellitus	44 (19.3)
Bronchiectasis	11 (4.8)
Clinical findings	
Antibiotic pre-treatment	64 (28.1)
Pre-enrolment duration of symptoms days	3.5 (2–6)
Altered mental status	27 (11.8)
Pulse >125 beats·min^{-1}	20 (8.8)
Respiratory rate ⩾30 breaths·min^{-1}	43 (18.9)
Systolic BP <90 mmHg	26 (11.4)
Diastolic BP <60 mmHg	46 (20.2)
Body temperature <35 or >40°C	3 (1.3)
Radiographic findings	
Unilobar radiograph	190 (83.3)
Multilobar/bilateral radiograph	38 (16.7)
Pleural effusion	53 (23.2)
PSI	
Score	102.9±40.0
Class I	19 (8.3)
Class II	30 (13.2)
Class III	40 (17.5)
Class IV	85 (37.3)
Class V	54 (23.7)
CURB-65 score	
0	33 (14.5)
1	60 (26.3)
2	86 (37.7)
3	32 (14.0)
4	12 (5.3)
5	5 (2.2)
Aetiology	
Typical bacterial	57 (25.0)
Viral/atypical bacterial	57 (25.0)
Mixed bacterial plus viral	41 (18.0)
Unknown	73 (32.0)

Data are presented as median (interquartile range), n (%) or mean±SD. COPD: chronic obstructive pulmonary disease; BP: blood pressure; PSI: Pneumonia Severity Index; CURB-65: confusion (abbreviated mental test score of ⩽8), urea ⩾7 mol·L^{-1}, respiratory rate ⩾30 breaths·min^{-1}, blood pressure <90 mmHg systolic or <60 mmHg diastolic, and age ⩾65 yrs.

defined as death due to any cause up to 180 days and 1 yr, respectively, after inclusion in the study.

Sample collection and processing

Determination of leukocyte count, CRP, PCT and MR-proADM

Venous blood samples were collected from CAP patients and controls on admission to the ED, within 6 h of arrival. Serum CRP was measured by immunoturbidimetry using the highly sensitive near-infrared particle immunoassay methodology (IMMAGE 800; Beckman Coulter, San Diego, CA, USA). The assay has an analytical detection limit of 0.06 mg·L^{-1} and a functional assay sensitivity of 0.11 mg·L^{-1}. PCT and MR-proADM concentrations were determined using sandwich immunoassays and time-resolved amplified cryptate emission measurement (PCT Sensitive KRYPTOR and MR-proADM KRYPTOR; BRAHMS, Hennigsdorf, Germany) as described in detail previously [18]. The analytical detection limits and functional assay sensitivities for the assays were 0.02 and 0.06 ng·mL^{-1} for PCT, and 0.05 and 0.25 nmol·L^{-1} for MR-proADM, respectively. Measurements of PCT and MR-proADM were performed in our laboratory (Servicio de Bioquímica Clínica, Hospital Universitario Miguel Servet) in a blinded fashion without knowing the clinical parameters and microbiological results.

Microbiological tests

Blood was drawn from CAP patients in the ED shortly after CAP diagnosis. Sputum was obtained when possible, before antibiotics were administered, and immediately sent for Gram staining and culture, and only samples containing a preponderance of leukocytes and a few squamous epithelial cells were considered acceptable. Another blood sample was obtained for the first serological *Mycoplasma pneumoniae* (complement fixation test; Virion Serion Institut, Wurzburg, Germany) and *Chlamydophila pneumoniae* (ELISA; Savyon Diagnostics Ltd, St Ashdod, Israel) tests. The second serological tests were performed on blood obtained during the 30-day follow-up visit. Urine was collected during the first 24 h and tested for *S. pneumoniae* and *Legionella pneumophila* antigens (BINAX Now; Binax, Portland, ME, USA).

Nasopharyngeal aspirates were obtained and processed for viral antigens using the direct fluorescence antibody (DFA) assay and two different viral PCR tests. DFA was performed for influenza virus A and B, parainfluenza virus 1, 2 and 3, adenovirus (AdV), human metapneumovirus (hMPV), and respiratory syncytial virus (RSV) (D3 Double Duet DFA Respiratory Virus Screening and ID Kit; Diagnostic Hybrids, Athens, OH, USA). The first PCR was a multiplex reverse transcriptase (RT) nested PCR assay for 14 respiratory viruses (influenza virus A, B and C, RSV A and B, AdV, coronavirus 229E and OC43, enterovirus, parainfluenza virus 1, 2, 3 and 4, and rhinovirus) [19]; the second test was a commercial RT-PCR kit, the ResPlex II Plus Panel (Qiagen LiquiChip System; Qiagen GmbH, Hamburg, Germany) [20] for detection of 18 viruses (influenza virus A and B, RSV A and B, parainfluenza virus 1, 2, 3 and 4, hMPV A and B, enterovirus (coxsackievirus/echovirus), rhinovirus, AdV B and E, coronavirus NL63, HKU1, 229E and OC43, and bocavirus). Nucleic acids had been extracted from nasopharyngeal aspirates immediately after their reception.
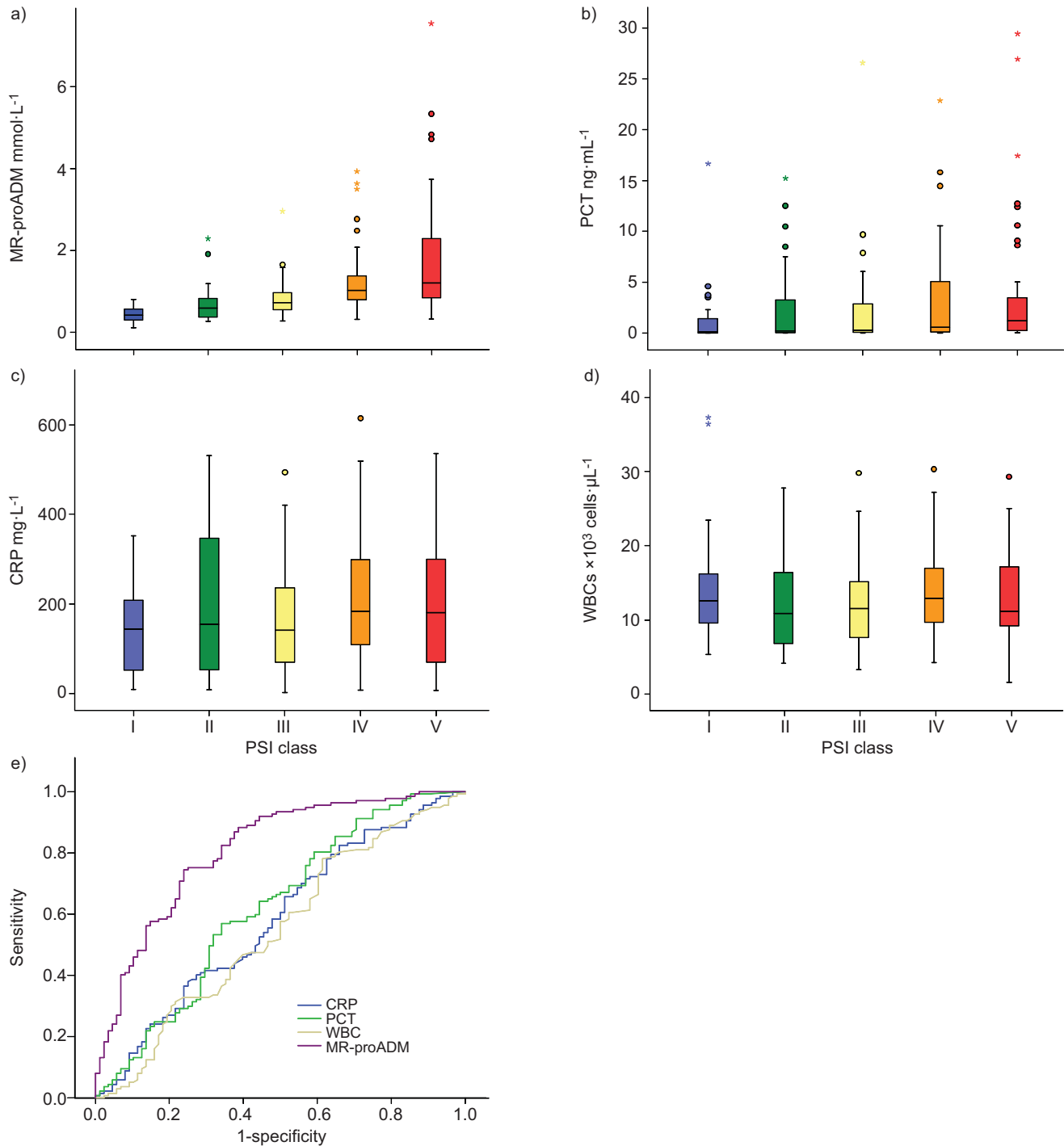
FIGURE 2. Biomarkers and Pneumonia Severity Index (PSI) severity score. Distribution of a) midregional (MR) proadrenomedullin (proADM), b) procalcitonin (PCT), c) C-reactive protein (CRP) and d) white blood cells (WBCs) by PSI classes. MR-proADM was the only biomarker able to distinguish between all different risk classes of PSI. When patients were classified into low- (I–III) and high-risk (IV–V) PSI classes, median levels of MR-proADM (p<0.0001), PCT (p=0.002) and CRP (p=0.025) were significantly higher in high- (IV–V) than in low-risk classes (I–III). Analogous results were not found for WBCs (p=0.183). e) Receiver operating characteristic analysis to assess the power of these biomarkers in order to discriminate between low- (PSI I–III) and high-risk (PSI IV–V) community-acquired pneumonia (CAP), showed an MR-proADM area under the curve (AUC) (0.811, 95% CI 0.753–0.869) that was significantly higher than the AUCs of PCT (0.620, 95% CI 0.542–0.697) and CRP (0.588, 95% CI 0.511–0.665) (p<0.0001 and p<0.0001, respectively). Therefore, MR-proADM presented the best AUC and may be considered a good predictor of CAP severity.

Patients with CAP were divided into three groups: bacterial, viral/atypical and mixed. *S. pneumoniae* and other Gram-positive and -negative bacteria classically considered producers of CAP, as well as *L. pneumophila*, were included as ''bacterial''. *M. pneumoniae* and *C. pneumoniae* were considered ''atypical'' and added to the viral group [7, 16]. One or more typical bacteria

TABLE 2	30-day complications	
30-day complication		**Patients n**
Respiratory failure without hypercapnia		81
Respiratory acidosis		11
MV		8
ICU admission		7
Nosocomial pneumonia		1
Pleural effusion		30
Empyema		2
Pneumothorax		2
Death		13
Left cardiac failure		37
New hyperglycaemia/diabetes mellitus decompensation		31
Acute renal failure		13
Tract urinary infection		15
Tachyarrythmias		12
Septic shock		11
Confusional syndrome		12
Acute gastroenteritis		7
Coronary acute syndrome		4
Cardiogenic shock		1
Cerebellum infarction		1
Complete AV blockade		1
Pericardial effusion		1
Endocarditis		1
Hypertensive crisis		1
LLE cellulitis		1
Coagulopathy		1
Fournier gangrene		1
Haemoptysis (oral anticoagulants)		1
Right arterial iliofemoral obstruction		1
Right psoas haematoma		1
Rectorrhagia		1
Total complications		**310**

Numbers of patients who suffered each type of complication of a total of 146 patients with complications are shown. MV: mechanical ventilation; ICU: intensive care unit; AV: atrioventricular; LLE: left lower extremity.

TABLE 3	Univariate and multivariate logistic regression analyses			
Variable	**Univariate**		**Multivariate**	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
Aetiology		0.059		
Bacterial	1.35 (0.65–2.80)	0.423		
Viral	0.804 (0.39–1.64)	0.547		
Mixed	2.93 (1.14–7.53)	0.025		
PSI	2.08 (1.61–2.69)	**0.000**		
CURB-65	1.99 (1.49–2.69)	**0.000**	1.60 (1.15–2.22)	**0.005**
MR-proADM	3.51 (1.86–6.63)	**0.000**	2.24 (1.18–4.24)	**0.014**
CRP	1.04 (1.01–1.06)	**0.002**		
PCT	1.07 (0.99–1.14)	0.058		
WBCs	1.01 (0.96–1.05)	0.837		
AUC (95% CI)			0.729 (0.659–0.799)	

PSI: Pneumonia Severity Index; CURB-65: confusion (abbreviated mental test score of $\leqslant 8$), urea $\geqslant 7$ mol·L^{-1}, respiratory rate $\geqslant 30$ breaths·min^{-1}, blood pressure <90 mmHg systolic or <60 mmHg diastolic, and age $\geqslant 65$ yrs; MR: midregional; proADM: proadrenomedullin; CRP: C-reactive protein; PCT: procalcitonin; WBC: white blood cell; AUC: area under the curve. Dependent variable: complications. Bold indicates statistically significant p-values.

(and *L. pneumophila*) in association with one or more viruses or atypical bacteria were considered ''mixed'' CAP.

Statistical analysis

Baseline and follow-up characteristic data are presented as n (%) for categorical variables, and as mean±SD or median (inter-quartile range (IQR)) for continuous variables, as appropriate.

Frequency comparison was performed by Chi-squared test or Fisher's exact test, when appropriate, for qualitative variables. Correlations were analysed using the Spearman rho correlation analysis. Two-group comparisons were performed using the Wilcoxon/Mann–Whitney U-test and multigroup comparisons using the Kruskal–Wallis test.

We constructed receiver operating characteristic (ROC) curves and determined the area under the curve (AUC). The AUC and its 95% confidence intervals were estimated for each biomarker and compared using a nonparametric method. Sensitivity, specificity, positive and negative predictive values, and

positive- and negative-likelihood ratios (LHR+ and LHR-, respectively) were calculated for each cut-off value of the biomarkers.

Bonferroni correction of critical p-values was applied when performing a high number of comparisons. In order to avoid a lot of spurious positives, the alpha value was lowered to account for the number of comparisons being performed.

Logistic regression was used to analyse the effect of adding biomarkers to the PSI and CURB-65 score for short-, mid- and long-term mortality. The accuracy of these models at predicting mortality was compared with the accuracy of the PSI or CURB-65 score by comparing their AUCs.

We used two different tests to determine whether there was an association between different aetiologies and MR-proADM. First, we performed a nonparametric test to evaluate the association between each group of the categorical variable (aetiology) and the quantitative variable (MR-proADM) by means of the Mann–Whitney U-test. We also transformed the MR-proADM levels into a categorical variable (MR-proADM quartiles) and performed a comparison with aetiology using the Chi-squared test.

All tests were two-tailed and p-values <0.05 were considered to indicate statistical significance, applying Bonferroni correction when appropriate. All statistical analyses were performed using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA), except the comparisons of the AUCs, which were carried out using MedCalc version 11.4.2.0 (MedCalc Software, Mariakerke, Belgium).

RESULTS

Patients and controls

260 patients with a diagnosis of CAP were included in the study. Of these patients, 32 (12.3%) were excluded because

they had an alternative diagnosis. A total of 228 subjects constituted the study cohort, with a median age of 73 yrs (IQR 63–80 yrs) (table 1).

Each patient received antibiotic therapy according to Spanish Respiratory Society Guidelines [17] and an initial dose was administered within 6 h of arriving in the ED in 192 (84.2%) subjects with CAP. All biomarkers were available on admission in 225 (99%) subjects. 139 (60.96%) patients were identified as being at high risk by PSI (classes IV and V) and 135 (59.2%) by CURB-65 score ($\geqslant$2).

13 (5.8%) out of 224 CAP patients followed up for 30 days after admission died. The cause of death of 12 of these patients was the initial CAP or its complications and one patient died due to cardiogenic shock. A further seven patients had died at 90 days (20 out 220 patients, 9.1%) and their causes of death were: Alzheimer's disease (two patients), dilated cardiomyopathy (one patient), new CAP (one patient), complications of initial CAP (one patient) and unknown causes (two patients). Six more had died at 180 days (26 out of 218, 11.9%), because of chronic obstructive pulmonary disease (COPD) (two patients), ischaemic heart disease, pulmonary fibrosis, new CAP and vascular dementia (one patient each). At 1 yr of follow-up, four more patients had died (18 out 150 patients, 12%), and their causes of death included new CAP (two patients), renal failure and Alzheimer's disease (one patient), and small bowel neoplasm (one patient). Excluding 30-day mortality, all but one patient (at 90 days) died due to causes other than the initial CAP. Thus, the number of patients studied at each timepoint was 228 patients at admission, 224 at 30 days, 220 at 90 days, 218 at 180 days and 150 patients at 1 yr.

The control group was composed of 70 age- and sex-matched subjects. Comorbidities in this group were similar to those of CAP patients. Nasopharyngeal aspirates were obtained in 60 controls for viral search, including both PCR tests. We did not obtain paired blood samples for serological studies in these subjects.

Biomarker levels and CAP severity

Levels of MR-proADM on admission increased significantly with increasing severity of CAP according to the PSI (p<0.0001) and CURB-65 scores (p<0.0001). In terms of severity assessment, correlation coefficients (CCs) between MR-proADM and PSI and CURB-65 scores were higher (CC 0.562 and 0.561, respectively) than those of PCT (CC 0.228 and 0.283), and there was a good correlation between both clinical scores (CC 0.718). MR-proADM was the only biomarker able to distinguish between all different PSI score risk classes (p<0.05) (fig. 2a–d). ROC analysis to discriminate between low-risk (PSI I–III) and high-risk (PSI IV–V) CAP showed that MR-proADM was the best biomarker (fig. 2e).

The optimal cut-off for MR-proADM was 0.646 nmol·L^{-1}, with a sensitivity of 92.1%, specificity of 55.1%, positive predictive value of 76.2% and negative predictive value of 80.3%. With this cut-off, of 139 patients classified by PSI score as high-risk (classes IV and V), 128 (92%) would have been correctly classified by MR-proADM levels, whereas only 11, according to PSI score, would have been ''wrongly'' considered as low-risk CAP (PSI I–III). 10 of these 11 patients were elderly (68–95 yrs of age); seven of them had a CURB-65 score of 1, one had a score of 2 and three had a score of 3. All the patients had comorbidities. Seven patients developed complications, but radiological resolution was achieved in all 11 and they are all still alive.

Complications and mortality

Complications in CAP patients

146 (64%) patients suffered 310 significant complications within 30 days of admission (table 2). We found significantly

TABLE 4	Levels of biomarkers according to short-, mid- and long-term mortality				
Mortality	**Patients n**	**Biomarker**			
		CRP mg·L^{-1}	WBCs ×10^3 cells·µL^{-1}	PCT ng·mL^{-1}	MR-proADM nmol·L^{-1}
30-day	224				
Survivors	211	156.4 (89.0–286.9)	11.85 (8.4–16.83)	0.41 (0.09–3.50)	0.856 (0.592–1.911)
Deaths	13	238.3 (123.4–332.5)	14.7 (6.5–17.8)	1.174 (0.477–6.69)	2.341 (1.188–4.226)
p-value		0.262	0.914	0.123	**<0.0001**
90-day	220				
Survivors	200	155.8 (89.1–287.3)	11.9 (8.4–16.6)	0.376 (0.09–3.53)	0.839 (0.578–1.158)
Deaths	20	228.9 (77.6–283.0)	10.5 (8.0–17.9)	1.024 (0.21–3.18)	1.731 (1.072–2.515)
p-value		0.535	0.915	0.151	**<0.0001**
180-day	218				
Survivors	192	155.6 (89.8–287.2)	11.75 (8.4–16.4)	0.373 (0.085–3.63)	0.838 (0.578–1.139)
Deaths	26	228.9 (91.1–287.4)	14.7 (8.2–18.7)	1.004 (0.13–2.94)	1.476 (1.056–2.43)
p-value		0.391	0.519	0.158	**<0.0001**
1-yr	150				
Survivors	132	144.7 (71.7–253.0)	11.65 (8.3–16.4)	0.255 (0.076–4.41)	0.772 (0.50–1.03)
Deaths	18	251.9 (181.0–323.3)	16.1 (10.5–21.9)	1.134 (0.429–6.68)	1.238 (1.044–2.471)
p-value		0.030	0.060	0.069	**<0.0001**

Data are presented as median (interquartile range), unless otherwise stated. CRP: C-reactive protein; WBC: white blood cell; PCT: procalcitonin; MR: midregional; proADM: proadrenomedullin. Bonferroni correction was applied (p$\leqslant$0.003125). Bold indicates statistically significant p-values.

Biomarker	Patients n	ROC analysis	
		AUC (95% CI)	p-value
30-day mortality	224		
CRP*,#,¶		0.593 (0.525–0.658)	0.294
WBC*,#,¶		0.509 (0.442–0.577)	0.927
PCT*,#,¶		0.627 (0.560–0.691)	0.089
MR-proADM		0.859 (0.807–0.902)	**<0.0001**
PSI		0.858 (0.805–0.901)	**<0.0001**
PSI + MR-proADM#		0.914 (0.869–0.948)	**<0.0001**
CURB-65		0.851 (0.798–0.895)	**<0.0001**
CURB-65 + MR-proADM		0.900 (0.853–0.936)	**<0.0001**
90-day mortality	220		
CRP*,#,¶		0.542 (0.474–0.609)	0.561
WBC*,#,¶		0.507 (0.439–0.576)	0.926
PCT*,#,¶		0.597 (0.529–0.663)	0.108
MR-proADM		0.825 (0.768–0.873)	**<0.0001**
PSI		0.811 (0.753–0.860)	**<0.0001**
PSI + MR-proADM#		0.862 (0.809–0.905)	**<0.0001**
CURB-65		0.832 (0.776–0.879)	**<0.0001**
CURB-65 + MR-proADM¶		0.879 (0.828–0.919)	**<0.0001**
180-day mortality	218		
CRP*,#,¶		0.552 (0.483–0.619)	0.412
WBC*,#,¶		0.540 (0.471–0.607)	0.567
PCT*,#,¶		0.585 (0.517–0.652)	0.114
MR-proADM		0.792 (0.732–0.844)	**<0.0001**
PSI		0.781 (0.720–0.834)	**<0.0001**
PSI + MR-proADM#		0.822 (0.765–0.871)	**<0.0001**
CURB-65		0.802 (0.743–0.853)	**<0.0001**
CURB-65 + MR-proADM¶		0.845 (0.790–0.891)	**<0.0001**
1-yr mortality	150		
CRP¶		0.658 (0.576–0.734)	0.030
WBC*,#,¶		0.636 (0.553–0.713)	0.086
PCT*,#,¶		0.641 (0.558–0.718)	0.054
MR-proADM		0.803 (0.731–0.864)	**<0.0001**
PSI		0.793 (0.719–0.855)	**<0.0001**
PSI + MR-proADM#		0.828 (0.758–0.885)	**<0.0001**
CURB-65		0.829 (0.759–0.886)	**<0.0001**
CURB-65 + MR-proADM		0.870 (0.806–0.920)	**<0.0001**

TABLE 5 Receiver operating characteristic (ROC) analysis results for short-, mid- and long-term mortality

AUC: area under the curve; CRP: C-reactive protein; WBC: white blood cells; PCT, procalcitonin; MR: midregional; proADM: proadrenomedullin; PSI: Pneumonia Severity Index; CURB-65: confusion (abbreviated mental test score of ≤8), urea ≥7 mol·L⁻¹, respiratory rate ≥30 breaths·min⁻¹, blood pressure <90 mmHg systolic or <60 mmHg diastolic, and age ≥65 yrs; PSI + MR-proADM: logistic regression model combining MR-proADM levels with PSI risk score; CURB-65 + MR-proADM: logistic regression model combining MR-proADM levels with CURB-65 risk score. Bonferroni correction was applied (p≤0.00156). Bold indicates statistically significant p-values. *: p<0.05 for comparison of AUCs with that of MR-proADM; #: p<0.05 for comparison of AUCs with that of PSI; ¶: p<0.05 for comparison of AUCs with that of CURB-65.

In the ROC analysis, the AUCs were as follows. PSI: 0.729 (95% CI, 0.659–0.800); MR-proADM: 0.706 (95% CI, 0.636–0.776); CURB-65: 0.693 (95% CI, 0.619–0.767); PCT: 0.635 (95% CI, 0.557–0.714); CRP: 0.618 (95% CI, 0.542–0.694). No significant differences were found when the AUCs for PSI and MR-proADM were compared (p=0.547).

The optimal cut-off for predicting complications for MR-proADM was 0.833 nmol·L⁻¹ (sensitivity 67.35%; specificity 66.23%; LHR+ 1.99; LHR- 0.49). The multivariate analysis selected only CURB-65 and MR-proADM as predictors of complications (table 3).

Short-, mid- and long-term mortality
Table 4 shows that MR-proADM was the only biomarker able to discriminate between patients who died at 30, 90 and 180 days, and 1 yr (p<0.0001). ROC analysis showed that the AUC for MR-proADM was significantly higher than those for PCT, CRP and WBC, and similar to those for the PSI and CURB-65 scores (table 5). Logistic regression models combining MR-proADM levels with either PSI or CURB-65 risk scores showed significant effects (p<0.05).

The optimal cut-off for predicting 30-day mortality for MR-proADM was 1.066 nmol·L⁻¹, with sensitivity of 92.3%, specificity of 67.46%, LHR+ of 2.84 and LHR- of 0.11. Only the AUC of model combining MR-proADM with PSI differed from the AUC of PSI alone (p=0.0002). For 90- and 180-day mortality, the combination of MR-proADM levels with either PSI or CURB-65 scores yielded significant effects (p<0.05).

For 1-yr mortality, only a model combining MR-proADM and PSI discriminated mortality better than the PSI score alone (p=0.0392). Logistic regression models combining CRP with clinical scores or MR-proADM levels did not yield significant effects (table 5 and fig. 3).

The multivariate analysis of mortality at 30 and 180 days selected CURB-65 and MR-proADM as predictors (table 6).

Aetiology
The causative pathogen was found in 155 (68%) patients: bacterial infection in 57 (25.0%) patients, viral/atypical bacterial infection in 57 (25.0%) and mixed (bacterial plus virus/atypical) infection in 41 (17.98%) (table 7). All 60 controls with viral study had a negative DFA assay, and genomes of AdV and parainfluenza virus 4 were found in three and one subject, respectively (four out of 60, 6.7%).

Biomarker levels and aetiology
Levels of biomarkers in CAP patients with different aetiologies are shown in table 8. PCT was the only biomarker that showed significant differences (p<0.0001) between bacterial (median 2.402 ng·mL⁻¹) and viral/atypical CAP (median 0.272 ng·mL⁻¹). PCT was also the only biomarker that distinguished viral/atypical from mixed pneumonia (median 1.568 ng·mL⁻¹; p=0.007). None of the biomarkers discriminated between bacterial and mixed aetiology.

We did not find any association between aetiology and MR-proADM (p>0.05). Table 8 shows that MR-proADM levels were similar in all three aetiological groups.

higher levels of MR-proADM (p<0.0001), PCT (p=0.001) and CRP (p=0.004), and higher PSI (p<0.0001) and CURB-65 (p<0.0001) scores in patients with complications.
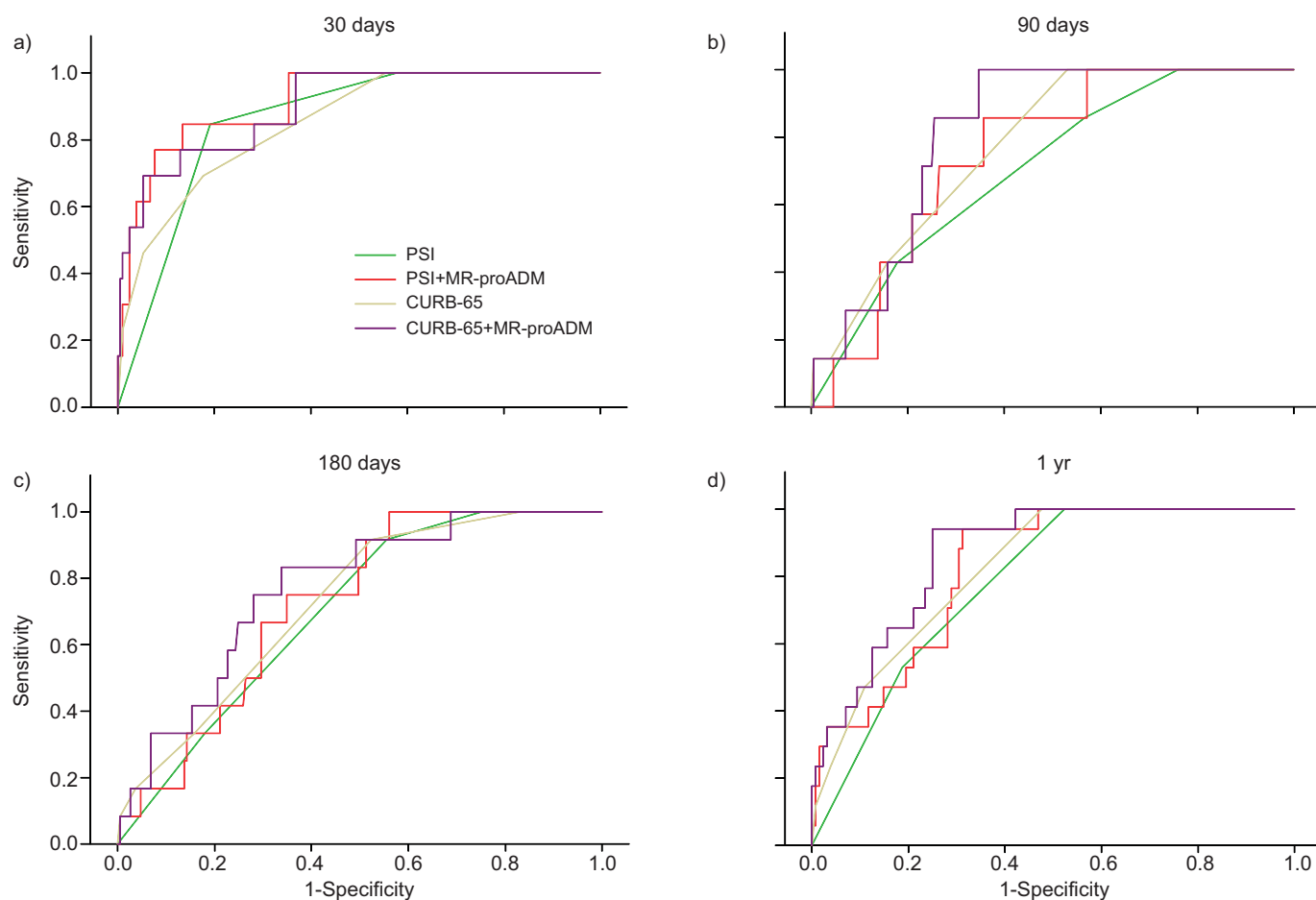
FIGURE 3. Receiver operating characteristic curves for short-, mid- and long-term mortality comparing Pneumonia Severity Index (PSI)/CURB-65 score (confusion (abbreviated mental test score of ≤8), urea ≥7 mol·L⁻¹, respiratory rate ≥30 breaths·min⁻¹, blood pressure <90 mmHg systolic or <60 mmHg diastolic, and age ≥65 yrs) with the corresponding logistic regression models (PSI/CURB-65 score plus midregional (MR) proadrenomedullin (proADM)). a) Mortality at 30 days: combining MR-proADM with PSI significantly improved the prognostic accuracy of PSI alone (area under the curve (AUC) 0.858), with an AUC of 0.914 (p=0.0002). However, the AUC of the model combining MR-proADM and CURB-65 (0.900), although higher, did not differ from the AUC of CURB-65 alone (0.851; p=0.097). Mortality at b) 90 and c) 180 days: combination of MR-proADM levels with either PSI or CURB-65 risk score improved the prognostic accuracy over that of the PSI and CURB-65 scores alone (p<0.05). d) Mortality at 1 yr: combining MR-proADM levels with PSI risk score (AUC 0.828) better discriminated mortality at 1 yr than PSI score alone (0.793; p=0.0392). However, the AUC of the model combining MR-proADM and CURB-65 (0.870, 95% CI 0.806–0.920), although higher, did not differ from the AUC of CURB-65 alone (0.829; p=0.089).

DISCUSSION

Our findings confirm that initial levels of MR-proADM in CAP patients have considerable predictive power for complications, and short-, mid- and long-term mortality of CAP. This predictive power of mortality was independent of the aetiology of CAP.

In our study, MR-proADM was the only biomarker able to distinguish between every PSI class (p<0.05), whereas PCT only discriminated the extreme levels of severity (class I–III from IV–V). MR-proADM was the best biomarker (AUC of 0.811), with an optimal cut-off of 0.646 nmol·L⁻¹. With this cut-off, 128 (92%) out of 139 patients in PSI classes IV and V would have been correctly classified. This cut-off could be used in the ED, in association with clinical severity scores, when deciding whether to admit patients with CAP to the hospital or manage them as outpatients. Previous studies found a good correlation between MR-proADM levels and PSI [11, 14] and CRB-65 (confusion (abbreviated mental test score of ≤8), respiratory rate ≥30 breaths·min⁻¹, blood pressure <90 mmHg systolic or

<60 mmHg diastolic, and age ≥65 yrs) [12] severity scores, whereas another study concluded that PCT can identify low-risk patients across CRB-65 classes [10].

146 (64%) of our patients suffered 310 significant complications within 30 days of admission, and showed significantly higher levels of MR-proADM, PCT and CRP, and significantly higher PSI and CURB-65 scores, although the best AUCs were those for PSI, MR-proADM and CURB-65; these AUCs were better than those for PCT and CRP. SCHUETZ et al. [13] found that MR-proADM had a greater discriminatory power than PSI and CURB-65 scores. These findings may be of use when deciding where to manage CAP, especially in subjects with low-range severity scores and high levels of biomarkers. The decision to treat these cases as outpatients should probably be reconsidered [13].

MR-proADM has shown to be an accurate biomarker for short-term mortality in CAP [11–14] and sepsis [21, 22]. In our study, the addition of MR-proADM levels to the PSI clinical severity score significantly improved 30-day prognostic accuracy.

TABLE 6	Univariate and multivariate logistic regression analyses					
Variable	30-day mortality			180-day mortality		
	Univariate	Multivariate		Univariate	Multivariate	
	p-value	OR (95% CI)	p-value	p-value	OR (95% CI)	p-value
Aetiology	0.159			0.267		
Bacterial	0.119			0.150		
Viral	0.124			0.150		
Mixed	0.135			0.168		
PSI	0.000			0.000		
CURB-65	0.000	2.80 (1.54–5.11)	0.001	0.000	2.37 (1.54–3.65)	0.000
MR-proADM	0.000	2.23 (1.31–3.79)	0.003	0.000	1.79 (1.15–2.78)	0.010
CRP	0.295			0.519		
PCT	0.045			0.259		
WBCs	0.929			0.654		
AUC (95% CI)		0.900 (0.853–0.936)			0.845 (0.790–0.891)	

PSI: Pneumonia Severity Index; CURB-65: confusion (abbreviated mental test score of $\leqslant 8$), urea $\geqslant 7$ mol·L^{-1}, respiratory rate $\geqslant 30$ breaths·min^{-1}, blood pressure <90 mmHg systolic or <60 mmHg diastolic, and age $\geqslant 65$ yrs; MR: midregional; proADM: proadrenomedullin; CRP: C-reactive protein; PCT: procalcitonin; WBC: white blood cells; AUC: area under the curve. Dependent variable: mortality. Bold indicates statistically significant p-values.

A Swiss group observed that a model including MR-proADM and PSI significantly increased the prediction accuracy over that of the PSI score alone for treatment failure [11], and 30-day mortality [13], whereas a German study found an improvement of prognostic power for the CRB-65 score after adding MR-proADM [12]. However, in the study by HUANG et al. [14], MR-proADM levels did not alter PSI-based risk assessment in most CAP patients, although this may be partly due to the high number of low-risk CAP patients (60.6%) in their cohort. Recently, ALBRICH et al. [23] reported, in a cohort of CAP and non-CAP lower respiratory tract infection patients, that a risk score based on CURB-65 classes enhanced by MR-proADM cut-off ranges improved prognostic assessment of this clinical score, in terms of death of any cause, ICU admission or complications within 30 days after enrolment.

Our optimal cut-off for MR-proADM for predicting 30-day mortality was 1.066 nmol·L^{-1}. CHRIST-CRAIN et al. [11] proposed a cut-off for short-term mortality (mean 6.9 weeks) of 1.8 nmol·L^{-1} and HUANG et al. [14] of 1.3 nmol·L^{-1} for 30-day mortality. This latter cut-off, which is higher than our value, was obtained from a lower-severity CAP cohort (60% were PSI I–III), but with surprisingly higher short-term mortality (6.4%) [14]. KRÜGER et al. [12] found a MR-proADM cut-off for short- and long-term mortality that was slightly lower than our value (0.959 nmol·L^{-1}), but severity was also lower in their cohort.

MR-proADM with PSI and CURB-65 scores separately distinguished mid- and long-term mortality from survival after CAP. Three studies found a correlation between long-term mortality and a high PSI score in the acute phase of CAP [4, 5, 15]. GUERTLER et al. [15] observed that a model including male sex, COPD, neoplastic disease and peak MR-proADM levels was significantly better at discriminating 18-month survivors from nonsurvivors than PSI. In our ROC analysis, the 1-yr

mortality AUC for PSI improved significantly after adding MR-proADM. In terms of short-term mortality, death in all but one of our patients who died after 30 days was due to causes other than the initial CAP, and the causes of death in our study were similar to those in other published studies [24, 25]. Four (23.5%) patients died during the year after admission due to a new case of pneumonia.

We found only significant relationship between MR-proADM (and clinical scores) and short- and long-term mortality. The limited number of patients could be a reason for the lack of prognostic power of PCT in our study, which has been found in other larger series [6]. It is not yet clear whether a relationship between high MR-proADM levels and lower long-term survival is because a worse general condition is associated with lower immune function, thereby facilitating the spread of respiratory infections, or because a more severe infection exacerbates the underlying chronic diseases of the patients, or both [15].

With regards to the aetiological agents detected, two findings deserve comment. First, we cannot be sure that the viruses detected really played a pathogenetic role in our CAP patients, instead of representing possible prolonged viral shedding or even a coincidental upper airway infection [26]; however, the different viral yield obtained from patients and controls can help us to conclude that, at least in an important number of cases, viruses were a true pathogen in our CAP patients. Secondly, the relatively high rate of *Pseudomonas aeruginosa* in our population may be due to the inclusion of patients with bronchiectasis.

We found that PCT was the best biomarker, when compared with CRP and MR-proADM, for discriminating CAP involving typical bacteria (bacterial and mixed groups) from viral (and atypical) CAP. PCT levels in CAP due to *M. pneumoniae* and *C. pneumoniae* have been found to be low, although severe CAP

TABLE 7	Aetiology of community-acquired pneumonia patients				
Bacterial	**Patients n**	**Viral/atypical**	**Patients n**	**Mixed**	**Patients n**
S. pneumoniae	27	AdV	14	*S. pneumoniae* + RV	6
L. pneumophila	4	RV	7	*S. pneumoniae* + AdV	4
E. coli	2	CoV	6	*S. pneumoniae* + RSV	2
S. marcescens	2	InfA	7	*S. pneumoniae* + hMPV	2
MRSA	2	RSV A	4	*S. pneumoniae* + InfA	2
A. denitrificans	1	InfB	2	*S. pneumoniae* + InfB	1
A. xylosoxidans	1	RSV A + CoV	2	*S. pneumoniae* + *S. aureus* + AdV	1
C. striatum	1	hMPV	1	*S. pneumoniae* + RV + InfA	1
E. cloacae	1	*M. pneumoniae*	1	*S. pneumoniae* + RV + InfB	1
H. influenzae	1	RSV B	1	*S. pneumoniae* + InfA + PIV4	1
E. faecalis	1	InfA + PIV1	1	*S. pneumoniae* + InfB + CoV	1
M. catarrhalis	1	AdV + InfA	1	*S. pneumoniae* + AdV + CoV	1
P. aeruginosa	1	AdV + RV	1	*S. pneumoniae* + *H. influenzae* + AdV + RV	1
S. aureus	1	AdV + CoV	1	*Corynebacterium* + hMPV	1
S. hominis	1	CoV + InfA	1	*S. hominis* + AdV	1
S. pneumoniae + *S. aureus*	2	EV + RV	1	*S. hominis* + *S. epidermidis* + AdV	1
S. pneumoniae + *H. influenzae*	1	InfA + RV	1	*E. coli* + RSV A + InfA	1
P. aeruginosa + *C. striatum*	1	InfA + RSV A	1	*H. influenzae* + AdV + RV	1
P. aeruginosa + *K. oxytoca*	1	InfB + RV	1	*H. influenzae* + AdV + InfA	1
P. aeruginosa + *L. pneumophila*	1	hMPV + RSV	1	*H. influenzae* + RV + RSV A + InfA	1
S. aureus + *P. multocida*	1	RV + InfB	1	*P. aeruginosa* + InfA	2
S. aureus + *E. faecium* + *S. pneumoniae*	1	hMPV + RSV + InfA	1	*S. epidermidis* + hMPV	1
H. influenzae + *S. marcescens*	1			*E. coli* + *M. pneumoniae*	1
E. coli + *C. striatum* + *A. baumannii*	1			*M. catarrhalis* + CoV	1
				M. morganii + CoV	1
				E. faecalis + PIV1	1
				H. parainfluenzae + PIV3	1
				S. maltophilia + AdV	1
				P. aeruginosa + RSV A + CoV	1
Total	57	**Total**	57	**Total**	41

Out of 228 patients, aetiology was known in 155 (67.98%) and unknown in 73 (32.02%). *S. pneumoniae*: *Streptococcus pneumoniae*; *L. pneumophila*: *Legionella pneumophila*; *E. coli*: *Escherichia coli*; *S. marcescens*: *Serratia marcescens*; MRSA: methicillin-resistant *Staphylococcus aureus*; *A. denitrificans*: *Alcaligenes denitrificans*; *A. xylosoxidans*: *Alcaligenes xylosoxidans*; *C. striatum*: *Corynebacterium striatum*; *E. cloacae*: *Enterobacter cloacae*; *H. influenzae*: *Haemophilus influenzae*; *E. faecalis*: *Enterococcus faecalis*; *M. catarrhalis*: *Moraxella catarrhalis*; *P. aeruginosa*: *Pseudomonas aeruginosa*; *S. aureus*: *Staphylococcus aureus*; *S. hominis*: *Staphylococcus hominis*; *K. oxytoca*: *Klebsiella oxytoca*; *P. multocida*: *Pasteurella multocida*; *A. baumannii*: *Acinetobacter baumannii*; AdV: adenovirus; RV: rhinovirus; CoV: coronavirus; Inf: influenza virus; hMPV: human metapneumovirus; RSV: respiratory syncytial virus; PIV: parainfluenza virus; *M. pneumoniae*: *Mycoplasma pneumoniae*; EV: enterovirus; *S. epidermidis*: *Staphylococcus epidermidis*; *M. morganii*: *Morganella morganii*; *H. parainfluenzae*: *Haemophilus parainfluenzae*; *S. maltophilia*: *Stenotrophomonas maltophilia*.

due to *L. pneumophila* may show higher values [16]. In our study, plasma levels of MR-proADM were similar among patients infected with the three groups of microorganisms, and we found no association between MR-proADM and aetiology. This indicates that initial values of MR-proADM do not depend on the causes of CAP.

TABLE 8	Levels of biomarkers in aetiological groups			
Aetiology	**Biomarker**			
	CRP mg·L⁻¹	**WBCs ×10³ cells·μL⁻¹**	**PCT ng·mL⁻¹**	**MR-proADM nmol·L⁻¹**
Bacterial	187.0 (101.9–340.5)	12.9 (9.75–17.9)	2.402 (0.243–5.688)	0.909 (0.669–1.506)
Viral/atypical	148.7 (105.1–258.15)	11.6 (8.4–16.35)	0.272 (0.074–1.63)	0.875 (0.606–1.155)
Mixed	260.0 (104.0–353.0)	11.2 (7.9–15.65)	1.568 (0.189–5.359)	0.949 (0.711–1.497)

Data are presented as median (interquartile range). CRP: C-reactive protein; WBC: white blood cell; PCT: procalcitonin; MR: midregional; proADM: proadrenomedullin.

There are two clinical implications of our study. First, MR-proADM is the best biomarker to predict short-term outcome in hospitalised CAP, whatever its aetiology. Secondly, it can be used to monitor the long-term follow-up of CAP patients discharged from hospital. Obviously, the final objective is to help to decrease mortality of CAP. These considerations are in line with a recent perspective article by EWIG and TORRES [27].

The limitations of our study merit consideration. The most important limitation is that this was a single-hospital study. Furthermore, we did not study biomarkers serially and their values may therefore change during the patient's course, thereby making it possible to better identify deterioration or improvement.

We conclude that plasma levels of MR-proADM, obtained within 6 h of arrival at the hospital, have considerable prognostic value, independently of the causal agent of CAP. Furthermore, our results confirm previous reports that MR-proADM has a similar short-, mid- and long-term predictive power to that of the PSI and CURB-65 scores, has a good correlation with them and, when added to these clinical scores, improves their prognostic accuracy.

STATEMENT OF INTEREST
Statements of interest for A.B. Lasierra and A. Torres, and for the study itself can be found at www.erj.ersjournals.com/site/misc/statements.xhtml

REFERENCES
1 Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med 1997; 336: 243–250.
2 Lim WS, van der Eerden MM, Laing R, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax 2003; 58: 377–382.
3 Capelastegui A, España PP, Quintana JM, et al. Validation of a predictive rule for the management of community-acquired pneumonia. Eur Respir J 2006; 27: 151–157.
4 Mortensen EM, Kapoor WN, Chang CC, et al. Assessment of mortality after long-term follow-up of patients with community-acquired pneumonia. Clin Infect Dis 2003; 37: 1617–1624.
5 Johnstone J, Eurich DT, Majumdar SR, et al. Long-term morbidity and mortality after hospitalization with community-acquired pneumonia: a population-based cohort study. Medicine (Baltimore) 2008; 87: 329–334.
6 Niederman MS. Biological markers to determine eligibility in trials for community-acquired pneumonia: a focus on procalcitonin. Clin Infect Dis 2008; 47: Suppl. 3, S127–S132.
7 Krüger S, Ewig S, Papassotiriou J, et al. Inflammatory parameters predict etiologic patterns but do not allow for individual prediction of etiology in patients with CAP – results from the German competence network CAPNETZ. Respir Res 2009; 10: 65.
8 Christ-Crain M, Stolz D, Bingisser R, et al. Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia: a randomized trial. Am J Respir Crit Care Med 2006; 174: 84–93.
9 Menéndez R, Martínez R, Reyes S, et al. Biomarkers improve mortality prediction by prognostic scales in community-acquired pneumonia. Thorax 2009; 64: 587–591.
10 Krüger S, Ewig S, Marre R, et al. Procalcitonin predicts patients at low risk of death from community-acquired pneumonia across all CRB-65 classes. Eur Resp J 2008; 31: 349–355.
11 Christ-Crain M, Morgenthaler NG, Stolz D, et al. Pro-adrenomedullin to predict severity and outcome in community-acquired pneumonia. [ISRCTNO4176397]. Crit Care 2006; 10: R96.
12 Krüger S, Ewig S, Giersdorf S, et al. Cardiovascular and inflammatory biomarkers to predict short- and long-term survival in community-acquired pneumonia. Results from the German competence network CAPNETZ. Am J Respir Crit Care Med 2010; 182: 1426–1434.
13 Schuetz P, Wolbers M, Christ-Crain M, et al. Prohormones for prediction of adverse medical outcome in community-acquired pneumonia and lower respiratory tract infections. Crit Care 2010; 14: R106.
14 Huang DT, Angus DC, Kellum JA, et al. Midregional proadrenomedullin as a prognostic tool in community-acquired pneumonia. Chest 2009; 136: 823–831.
15 Guertler C, Wirz B, Christ-Crain M, et al. Inflammatory response predict long-term mortality risk in community-acquired pneumonia. Eur Respir J 2011; 37: 1439–1446.
16 Haeuptle J, Zaborsky, Fiumefreddo R., et al. Prognostic value of procalcitonin in Legionella pneumonia. Eur J Clin Microbiol Infect Dis 2009; 28: 55–60.
17 Alfageme I, Aspa J, Bello S, et al. Normativas para el diagnostico y el tratamiento de la neumonía adquirida en la comunidad. Sociedad Española de Neumología y Cirugía Torácica (SEPAR) [Guidelines for the diagnosis and management of community-acquired pneumonia. Spanish Society of Pulmonology and Thoracic Surgery (SEPAR)]. Arch Bronconeumol 2005; 41: 272–289.
18 Morgenthaler NG, Struck J, Alonso C, et al. Measurement of midregional proadrenomedullin in plasma with an immunoluminometric assay. Clin Chem 2005; 51: 1823–1829.
19 Coiras MT, Aguilar JC, Garcia ML, et al. Simultaneous detection of fourteen respiratory viruses in clinical specimens by two multiplex reverse transcription nested-PCR assays. J Med Virol 2004; 72: 484–495.
20 Sample and Assay Technologies. ResPlex II handbook. Hamburg, Qiagen, 2010.
21 Christ-Crain M, Morgenthaler NG, Struck J, et al. Mid-regional pro-adrenomedullin as a prognostic marker in sepsis: an observational study. Crit Care 2005; 9: R816–R824.
22 Guignant C, Voirin N, Venet F, et al. Assessment of pro-vasopressin and pro-adrenomedullin as predictors of 28-day mortality in septic shock patients. Intensive Care Med 2009; 35: 1859–1867.
23 Albrich WC, Dusemund F, Ruegger K, et al. Enhancement of CURB65 score with proadrenomedullin (CURB65-A) for outcome prediction in lower respiratory tract infections: derivation of a clinical algorithm. BMC Infect Dis 2011; 11: 112.
24 Mortensen EM, Coley CM, Singer DE, et al. Causes of death for patients with community-acquired pneumonia. Results from the

Pneumonia Patient Outcomes Research Team Cohort Study. *Arch Intern Med* 2002; 162: 1059–1064.

25 Yende S, D'Angelo G, Kellum JA, *et al.* Inflammatory markers at hospital discharge predict subsequent mortality after pneumonia and sepsis. *Am J Respir Crit Care Med* 2008; 177: 1242–1247.

26 Ruuskanen O, Lathi E, Jennings LC, *et al.* Viral pneumonia. *Lancet* 2011; 377: 1264–1275.

27 Ewig S, Torres A. Community-acquired pneumonia as an emergency: time for an aggressive intervention to lower mortality. *Eur Respir J* 2011; 38: 253–260.