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Early prediction of treatment failure in severe community-acquired pneumonia: The PRoFeSs score

José Manuel Pereira [a,b,*], Olga Laszczyńska [c], Ana Azevedo [c,d,e], Carla Basílio [a], Conceição Sousa-Dias [a,1], Paulo Mergulhão [a,b], José Artur Paiva [a,b]

[a] Emergency and Intensive Care Department, Centro Hospitalar São João EPE, Porto, Portugal
[b] Faculdade de Medicina da Universidade do Porto, Porto, Portugal
[c] EPIUnit - Institute of Public Health, University of Porto, Portugal
[d] Hospital Epidemiology Centre, Centro Hospitalar São João EPE, Porto, Portugal
[e] Department of Public Health and Forensic Sciences and Medical Education, University of Porto Medical School, Portugal

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ABSTRACT

Purpose: To identify a single/panel of biomarkers and to provide a point score that, after 48 h of treatment, could early predict treatment failure at fifth day of Intensive Care Unit (ICU) stay in severe community-acquired pneumonia (SCAP) patients.
Materials and methods: Single-center, prospective cohort study of 107 ICU patients with SCAP. Primary outcome included death or absence of improvement in Sequential Organ Failure Assessment score by ≥2 points within 5 days of treatment. Biomarkers were evaluated within 12 h of first antibiotic dose (D1) and 48 h after the first assessment (D3).
Results: A model based on Charlson's score and a panel of biomarkers (procalcitonin on D1 and D3, B-natriuretic peptide on D1, D-dimer and lactate on D3) had good discrimination for primary outcome in both derivation (AUC 0.82) and validation (AUC 0.76) samples and was well calibrated ($X^2 = 0.98$; df = 1; $p = .32$). A point score system (PRoFeSs score) built on the estimates of regression coefficients presented good discrimination (AUC 0.81; 95% Confidence Interval 0.72–0.89) for primary outcome.
Conclusions: In SCAP, a combination of biomarkers measured at admission and 48 h later may early predict treatment failure. PRoFeSs score may recognize patients with poor short-term prognosis.

1. Introduction

Community-acquired pneumonia (CAP) remains one of the leading causes of hospital admission and represents a burden to the health care system [1]. Severe community-acquired pneumonia (SCAP), usually defined as CAP admitted to an Intensive Care Unit (ICU), is associated with high morbidity and mortality, particularly in patients needing mechanical ventilation (around 30%) [2].

Although most CAP patients respond to treatment, some still fail to respond [3]. Treatment failure is usually defined as a clinical evolution with worsening of clinical status, dissemination of infection, including extrapulmonary extension of infection (e.g. empyema, meningitis, endocarditis) and signs of systemic inflammatory response, development of complications or death in spite of antimicrobial therapy [3-5]. The reported incidence of treatment failure among hospitalized patients with CAP ranges from 2.4% to 31% for early failure and from 3.9% to 11% for late failure [6].

Timely prediction of treatment failure may be relevant for the selection and implementation of early and appropriate rescue strategies. More than 80% of clinical failure in CAP patients seems to be directly related to pneumonia and the associated systemic inflammatory response and only an early identification of non-responders allows the use of a rescue therapy that may positively impact on outcome [7]. Biomarkers may help to identify those patients who fail to respond to treatment but, until now, no single or panel of biomarkers were validated as markers of treatment failure [8].

The goals of this study were to identify a single or a panel of biomarkers that could allow early prediction of treatment failure and to

Abbreviations: AUC, area under the Receiver Operating Characteristics curve; BNP, B-type Natriuretic Peptide; CAP, community-acquired pneumonia; CI, confidence Interval; COPD, Chronic Obstructive Pulmonary Disease; CRP, C-reactive protein; CXR, chest radiograph; CT, computed tomography; ICU, Intensive Care Unit; OR, odds ratio; P25-P75, 25th to 75th percentile; PCT, procalcitonin; PSI, Pneumonia Severity Index; ROC, receiver operating characteristics; SAPS, Simplified Acute Physiology Score; SD, standard deviation; SOFA, Sequential Organ Failure Assessment; WBC, White Blood Cell count.

* Corresponding author at: Emergency and Intensive Care Department, Centro Hospitalar São João EPE, Faculdade de Medicina da Universidade do Porto, Al Prof Hernâni Monteiro, 4200-319 Porto, Portugal.
E-mail addresses: jmcrpereira@yahoo.com, jmcrpereira@gmail.com (J.M. Pereira), anazev@med.up.pt (A. Azevedo).
[1] Deceased.

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provide a point score to estimate the individual risk of a composite outcome at fifth day of ICU stay in SCAP patients.

2. Material and methods

2.1. Study design

This was a single center, observational, prospective cohort study of patients with severe CAP recruited using convenience sampling when admitted to 28 level 3 critical care beds of the Intensive Care Department of a tertiary care university hospital in Portugal between December 2008 and March 2012. The study was approved by the local Ethics committee. Despite its observational nature, written informed consent was obtained from every patient or patient representative prior to inclusion in the study.

CAP was diagnosed when in addition to suggestive clinical features (e.g. cough, fever, sputum production, pleuritic chest pain), a demonstrable infiltrate was present in chest radiograph (CXR) or computed tomography (CT) scan [1]. Severe CAP was defined according to Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) criteria [9]. In order to be included into this study, severe CAP patients had to be ≥18 years old and had to be enrolled within 12 h after the first antibiotic dose. Antibiotic therapy prescription was to the discretion of the ICU attending physician. Patients who died within 3 days after enrolment were excluded.

The primary outcome established for this analysis included death or no improvement in the Sequential Organ Failure Assessment (SOFA) score [10] by at least two points within 5 days of treatment. A secondary outcome was defined as death or absence of SOFA improvement of at least two points or worsening of pulmonary infiltrate on the fifth day of treatment compared to hospital admission.

2.2. Data collection

The following parameters were collected within the first 24 h of ICU admission: age, gender, co-morbidities, presence of septic shock and/or acute respiratory distress syndrome and empiric antibiotic therapy, Charlson score [11], Simplified Acute Physiology Score (SAPS) II [12] and Pneumonia Severity Index (PSI) [13]. SOFA score was calculated on daily basis. The duration of mechanical ventilation, length of ICU and hospital stay and mortality (ICU and hospital) were also recorded.

2.3. Microbiologic evaluation

At the point of inclusion into the study, two pairs of blood cultures were collected. Blood cultures were processed using an automated microbiology growth and detection system (BACTEC). If there was bacterial growth, samples were Gram stained and subcultured. Endotracheal aspirate was taken from every patient whenever possible to test for bacteria according to standard procedures. Representative specimen originating from the lower respiratory tract was validated by the criteria of >25 granulocytes and <10 epithelial cells per low power field (total magnification ×100). Urine samples were collected, whenever possible, and tests for *Legionella pneumophila* and *Streptococcus pneumoniae* with antigens. Real-time polymerase chain reaction was used to evaluate the presence of respiratory virus in nasopharyngeal swab and bronchoalveolar lavage when clinically and epidemiologically indicated. Pleural fluid was also collected whenever available. Identification of microorganisms and susceptibility testing was performed according to hospital routine methods.

2.4. Biomarkers determination

Biomarkers considered were: white blood cells (WBC), C-reactive protein (CRP), lactate (LAC), procalcitonin (PCT), D-dimer (DD), B-type natriuretic peptide (BNP) and cortisol (COR), all assessed within 12 h (denoted as D1) of first antibiotic dose for a severe CAP episode and 48 h after the first assessment (D3).

Biomarkers determination were done according to standard procedures. WBC was obtained using an automated blood counter Sysmex® XE-5000 (Emilio de Azevedo Campos, Porto, Portugal). Serum CRP (Olympus AU5400® automated clinical chemistry analyzer - Beckman-Coulter®, Izasa, Porto, Portugal) and DD (STA®Rack Evolution, Roche) were measured by immunoturbidimetric assays. CRP measurement range is 0.2–480 mg/l with a coefficient of variation (CV) at 10 mg/l lower than 3.5%. DD quantitative range is 0.27–20 μg/ml with a CV of 3.2%. A chemiluminescent microparticle immunoassay was used for the quantitative determination of BNP (Architect i2000® automated analyzer - Abbott, Lisboa, Portugal) with a measurement range from 10 to 5000 pg/ml and an intra-assay CV at 100 pg/ml lower than 5.0%. Cortisol was measured by way of an electrochemiluminescent immunoassay using a Cobas® e411 automated analyzer (Roche®, Lisboa, Portugal). Its measurement range is 0.018–63.4 μg/dl with a CV at 20 μg/dl lower than 2.0%. According to the manufacturer's recommendations, samples were further diluted in order to determine biomarkers serum levels in case they were above the upper limit of measurement range.

PCT serum levels were determined using a highly sensitive immunoassay (miniVidas [bioMérieux]) based on ELFA (Enzyme-Linked Fluorescent Assay). The assay has a limit of detection of 0.03 ng/ml and a quantitative range of 0.05 and 200 ng/ml. If the serum value was higher than the upper limit of detection (200 ng/ml), we used this value for data analysis and the same methodology was used when it was lower than the lower limit of detection (0.05 ng/ml).

2.5. Chest imaging evaluation

An independent radiologist evaluated chest images (either CXR or CT), classifying pulmonary infiltrates as worse or not worse by the 5th day compared to the baseline.

2.6. Statistical analysis

Continuous variables are presented as mean and standard deviation (SD) or median and 25th–75th percentile (P25-P75) and compared using *t*-test or Mann-Whitney *U* test, as appropriate. Categorical variables are presented as proportions and compared using χ^2 or Fisher's Exact test. To create a predictive model, biomarkers levels were used in absolute values, measured at two time points (D1 and D3), or taking the relative change (RC) in biomarkers` values between D1 and D3 (RC = (D3–D1)/D1).

Among all biomarkers studied, 19 values were missing: in 17 patients one measurement and in one patient two were missing. To account for missing data, we used multiple imputation through chained equations ($n = 5$) [14], in which we estimated the missing values using the linear regression models controlled for age, sex, Charlson index and all available biomarkers in day 1 and day 3. We repeated the procedure of imputation five times, yielding 5 different datasets with imputed missing values. In each of the created dataset, we fitted the logistic regression model to predict established endpoints generating regression coefficients and standard errors. Obtained estimates were pooled across the imputed datasets according to Rubin's rules to produce a single set of estimates [15]. A backward strategy was applied to select variables for the final model using the likelihood ratio test to examine improvement in the fit over a model with fewer predictors. We found no highly correlated variables using the Spearman correlation coefficient.

For each of established outcomes, we built three models with different combinations of biomarkers data: Model 1) absolute values D1 and D3; Model 2) absolute values D1 and RC; and Model 3) absolute values D3 and RC. Among 6 models developed, two final models (one for each outcome) were chosen based on the discriminative power through the

area under the receiver operating characteristic curve (AUC). The calibration was assessed through the Hosmer-Lemeshow test, and possible over-fitting was evaluated by the leave-one-out cross validation method [16]. The later was preferred over k-fold cross-validation due to the limited number of patients in our study. Briefly, the model was trained on all minus one patient and subsequently was tested on the individual that had been left out. This process was repeated until every individual in the dataset had been used once as an unseen test individual. The precision of the models was further evaluated by non-parametric bootstrap analysis. For bootstrapping, 999 datasets were sampled with replacement within each of the 5 imputed datasets, and each bootstrap dataset had the same size of the original dataset ($n = 107$). The bootstrap regression coefficients and the respective 95% CI were compared with the parameters estimates from the original models. Moreover, the predictive model ability was corrected for optimism bias (which appears when the same data source is used to develop the model and assess its predictive ability) by calculating the performance measures over the predictions from bootstrap datasets applied to the original data set.

For the outcome for which best model performance estimates were obtained, a simple-integer point score was developed based on estimates of the regression coefficients of the multiple logistic regression model [17]: each predictor in the final model was organized into categories to which the number of points was determined based on respective β parameters. A total point score for each patient, reflecting the probability of the outcome, was computed by adding all points for the documented predictive variables.

Finally, we evaluated the discriminative ability (area under the ROC curve) and calibration of the developed risk score (Hosmer-Lemeshow test).

Sensitivity analysis was performed to examine whether exclusion of patients with virus isolates had impact on predictors selection.

All analyses were performed using R version 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria) or Stata 11.1 (Stat Corp., College Station, TX).

3. Results

3.1. Patients' characteristics and SCAP etiology

During the study period, 181 SCAP patients were admitted to the ICU of which 107 were included in the final analysis (Fig. S1). The mean age of the overall cohort was 62 years (SD = 15.7) and 60.7% were male. Median SAPS II and SOFA scores in the first 24 h after ICU admission were 52 (P25-P75: 39–61) and 10 (P25-P75: 8–12), respectively. Co-morbidities were present in 69.2% of the patients and the most frequent were diabetes mellitus and chronic respiratory pulmonary disease (COPD). Septic shock and invasive mechanical ventilation were present at admission in 73.8% and 89.7% of the patients, respectively.

Severe CAP was microbiologically documented in 62 (57.9%) cases of whom 9.7% were polymicrobial. As expected, *Streptococcus pneumoniae* ($n = 34$) was the leading pathogen followed by Influenza virus ($n = 9$) and *Enterobacteriaceae* ($n = 6$). Positive blood cultures were documented in 21 patients (19.6%) and *Streptococcus pneumoniae* was recovered from the blood in 14 of them (66.7%).

All patients received ATS/IDSA guidelines concordant antibiotic therapy [9] and 4 out of 62 patients with microbiologically documented SCAP received inappropriate empirical antibiotic therapy. A macrolide was part of the initial empirical antibiotic therapy in 98.2% of the cases.

Up to the fifth day of the ICU stay, 36 patients did not improve in SOFA score by at least two points, two patients died (death between the 3rd and 5th day) and 25 had worse radiological findings.

Table 1 shows characteristics of all patients included in the study and according to primary and secondary outcomes.

3.2. Biomarkers

Biomarkers' median serum levels on D1 and D3 and their relative change are presented in Table 2. Apart from C-reactive protein, median biomarkers serum levels were significantly different between D1 and D3. In our cohort, except for DD, they were significantly higher on D1 than on D3. PCT serum levels were lower than 0.05 ng/ml in two patients (one patient for PCT D1 and one for PCT D3) and in five patients they were higher than 200 ng/ml (2 patients for PCT D1 and 3 for PCT D3). No patient with acute kidney injury presented a PCT serum above the upper limit of detection.

Patients with treatment failure according to our primary outcome, compared to those who responded to treatment, showed an increase in median WBC count from D1 to D3 and smaller decrease in CRP, PCT and lactate. Cortisol decreased more in this group of patients while D-dimers increased more sharply. BNP kinetics was similar in both responding and non-responding patients.

Similar results were observed in patients who did not respond to therapy according to our secondary outcome except for WBC and CRP. WBC levels remained virtually unchanged in non-responders while a decrease was observed in responders. Median change of CRP from D1 to D3 was similar in both groups.

3.3. Predictive models

The best performance for primary outcome was obtained in the model 1 using absolute values of D1 and D3. The discriminatory power of the model accounted for AUC 0.82; (95% Confidence Interval [CI] 0.74–0.91) vs. AUC 0.72; 95% CI 0.63–0.82 and AUC 0.81; 95% CI 0.71–0.90 for model 2 and model 3, respectively. Moreover, the model was well calibrated ($X^2 = 0.98$; df = 1; $p = .32$). The performance estimated in a validation cohort remained good (AUC 0.76; 95% CI 0.66–0.86). The risk of primary outcome increased with higher Charlson score, PCT D3, D-Dimer D3 and LAC D3 values and was inversely related with BNP D1 and PCT D1 concentration in the derivation cohort (Table 3).

Regarding the secondary outcome the best performance was obtained in Model 2 (AUC 0.80; 95% CI 0.72–0.88 vs. AUC 0.75; 95% CI 0.66–0.85 and AUC 0.72; 95% CI 0.93–0.82 for models 1 and 3). In the validation sample the AUC was 0.74 (95% CI 0.65–0.84). The risk of the secondary outcome was associated with the lactate D1 and increasing value of lactate, WBC and DD between D1 and D3. On the contrary, higher BNP D1 and increase in PCR and cortisol were inversely related with the outcome (Table 3). This model was also well calibrated ($X^2 = 1.01$; df = 1; $p = .38$).

Fig. 1 shows AUC for both predictive models in the derivation and validation samples. Parameter estimates, and performance measures of the original models were consistent to those of the bootstrap, indicating robustness and stability of the models (Table S1).

In the sensitivity analysis in which patients with documented viral pneumonia were excluded ($n = 9$) there were fewer predictors selected for the final models, although those included were the same as in the main analysis and with a similar effect of outcomes (PCT1*10, odds ratio [OR] = 0.55; PCT3*10, OR = 1.75 and DD3*10, OR = 1.85 for the primary outcome; LAC1, OR = 1.42; BNP1*100, OR = 0.97; LAC change, OR = 13.82; WBC change, OR = 1.03; PCR change, OR = 0.71 and COR change, OR = 0.38 for the secondary outcome).

3.4. Score

Based on estimates of the regression coefficients of the multiple logistic regression model, a point score system [PRoFeSs – **PR**ediction **o**f **F**ailur**e** in **S**CAP **s**core) for risk of the primary outcome was obtained (Table S2). The six variables included were divided into categories and points were assigned to each of them (Table 4). The discriminatory power of this score, assessed by the area under the ROC curve was

Table 1
Main demographic and clinical characteristics of the study sample.

	Total	Primary outcome			Secondary outcome		
	$n = 107$	Yes	No	*p*-Value	Yes	No	*p*-Value
		$n = 38$	$n = 69$		$n = 55$	$n = 52$	
Age (years)[a]	62.0 (15.7)	63.0 (17.2)	59.0 (14.7)	.231	59.2 (16.8)	62.4 (14.4)	.301
Male, *n* (%)	65 (60.7)	22 (57.9)	43 (62.3)	.809	36 (65.5)	29 (55.8)	.408
Charlson score[b]	3 (1–5)	3 (2–5)	3 (1–5)	.750	3 (1–5)	4 (1–6)	.173
Co-morbidities, *n* (%)	74 (69.2)	31 (81.6)	43 (62.3)	.065	40 (72.7)	34 (65.4)	.540
Diabetes mellitus	29 (27.1)	8 (21.1)	21 (30.4)	.296	12 (21.8)	17 (32.7)	.205
COPD	27 (25.2)	11 (28.9)	16 (23.2)	.512	13 (23.6)	14 (26.9)	.696
Alcohol abuse	14 (13.1)	7 (18.4)	7 (10.1)	.224	9 (16.4)	5 (9.6)	.301
Neurologic disease	13 (12.1)	4 (10.5)	9 (13.0)	.768	5 (9.1)	8 (15.4)	.319
Cancer	11 (10.3)	4 (10.5)	7 (10.1)	1.00	5 (9.1)	6 (11.5)	.677
Congestive heart failure	10 (9.3)	5 (13.2)	5 (7.2)	.315	5 (9.1)	5 (9.6)	.926
Chronic renal failure	10 (9.3)	2 (5.3)	8 (11.6)	.489	5 (9.1)	5 (9.6)	.926
SAPS II score[b]	52 (39–61)	56 (40–61)	48 (39–61)	.327	55 (41–61)	49 (38–61)	.520
SOFA score[b]	10 (8–12)	9 (7–12)	10 (9–12)	.160	10 (8–12)	10 (8–12)	.623
PSI score[b]	154 (124–180)	159 (131–186)	152 (120–174)	.236	155 (125–178)	153 (125–179)	.911
Septic shock at admission, *n* (%)	79 (73.8)	25 (65.8)	54 (78.3)	.240	38 (69.1)	41 (78.8)	.354
Worst PaO_2/FiO_2 at admission[b]	76.0 (61.4–106.4)	75.0 (60.5–116.8)	76.0 (63.5–103.5)	.730	72.5 (58.0–100.5)	78.2 (65.9–108.1)	.244
Mechanical ventilation, *n* (%)	96 (89.7)	36 (94.7)	60 (87.0)	.321	52 (94.5)	44 (84.6)	.117
Microbiological documentation, *n* (%)	62 (57.9)	22 (57.9)	40 (58.0)	.994	33 (60.0)	29 (55.8)	.805
Microorganisms, *n* (%)							
Streptococcus pneumoniae	34 (31.8)	12 (31.6)	22 (31.9)	.974	17 (30.9)	17 (32.7)	.843
Influenza virus	9 (8.4)	2 (5.2)	7 (10.1)	.487	4 (7.3)	5 (9.6)	.737
Enterobacteriaceae	6 (5.6)	2 (5.3)	4 (5.8)	1.000	3 (5.5)	3 (5.8)	1.000
Legionella pneumophila	5 (4.7)	2 (5.3)	3 (4.3)	1.000	3 (5.5)	2 (3.8)	1.000
Staphylococcus aureus	5 (4.7)	2(5.3)	3 (4.6)	1.000	4 (7.3)	1 (1.9)	.364
Haemophilus influenza	3 (2.8)	0 (0.000)	3 (4.3)	.551	0 (0.000)	3 (5.8)	.111
Pseudomonas aeruginosa	3 (2.8)	1 (2.6)	2 (2.9)	1.000	1 (1.8)	2 (3.8)	.611
Combined antibiotic therapy, *n* (%)	106 (99.1)	37 (97.4)	69 (100)	.761	54 (98.2)	52 (100)	1.000
Inappropriate empiric antibiotic therapy, *n* (%)	4 (3.7)	2 (5.3)	2 (2.9)	.614	3 (5.5)	1 (1.9)	.618
Duration of mechanical ventilation (days)[b]	10 (6–21)	13 (8–24)	10 (6–21)	.280	16 (8–25)	10 (7–16)	.080
Length of stay (days)[b]							
ICU	12 (9–22)	13 (9–24)	11 (8–20)	.250	16 (9–27)	11 (9–16)	.061
Hospital	22 (15–35)	21 (13−30)	22 (16–36)	.321	23 (16–36)	21 (14–32)	.579
Mortality (%)							
ICU	22.4	18 (47.4)	6 (8.7)	<.001	21 (38.2)	3 (5.8)	<.001
Hospital	27.1	19 (50.0)	10 (14.5)	<.001	22 (40.0)	7 (13.5)	.002

COPD- Chronic Obstructive Pulmonary Disease; ICU- Intensive Care Unit; IDSA/ATS- Infectious Diseases Society of America/American Thoracic Society; LOS- Length of stay; PaO2/FiO2 ratio - ratio of arterial oxygen partial pressure to fractional inspired oxygen; PSI- Pneumonia Severity Index; SAPS- Simplified Acute Physiology Score; SOFA - Sepsis-related Organ Failure Assessment.

[a] Data presented as mean (SD).

[b] Data presented as median (25th–75th percentile).

0.81 (95% CI 0.72–0.89) just like the predictive model (Fig. 2) and it was also well calibrated ($X^2 = 2.88$; df = 1; $p = .09$).

The total score ranges from −31 to +39. The estimated risk is lower than 2% for scores ≤ −5 points and 99% for scores ≥23 points (Table S3). The best relationship between sensitivity and specificity was observed at a cut-off of 3 points. At this cut-off, the score presented a sensitivity of 79% (95% CI 63–90) and a specificity of 71% (95% CI 59–81). The positive and negative predictive values were 60% (95% CI 45–74) and 86% (95% CI 74–94), respectively.

Since established primary endpoint referred mainly to the change in SOFA score between the first and the fifth day of treatment, likely it is, at least partially, predictable from SOFA evolution in first 3 days. In the secondary analysis, we evaluated the added predictive value of PRoFeSs score in patients who improved (by at least two points) and did not improve in terms of SOFA between D1 and D3 (Fig. 3). In the former group, scoring above 3 points in PRoFeSs score explicitly distinguished patients at risk of the outcome (33.3% vs 3.0%, $p = .013$). Similarly, in the patients whose SOFA did not improve up to the third day, the threshold of 3 points separated patients into groups of the significantly different risk of the endpoint: 29.2% vs 71.4%, $p = .003$.

4. Discussion

The most important findings of this study are: (1) A combination of biomarkers (absolute value and relative change), measured on day 1 and 48 h after the first assessment, can be used to early predict treatment failure in SCAP; (2) A new score, the PRoFeSs score, applicable in clinical practice, seems to help to identify SCAP patients with poor short-term prognosis; and (3) PROFESS score, at its best cut-off, in patients with and without improvement in SOFA at D3, further discriminates between responders and non-responders to treatment.

The IDSA/ATS guidelines [9] states that the lack of a clear-cut and validated definition in the literature makes nonresponse difficult to study and the lack of response varies according to the site of treatment. Several authors addressing the issue of treatment failure in hospitalized CAP patients used variables such as need of vasopressors or mechanical ventilation, radiographic progression and death as surrogates of treatment failure [18-21], mainly in the first 5 days [22]. Nevertheless, this definition does not seem to be appropriate for a SCAP population, such as ours, in which the rate of mechanical ventilation and vasopressor support is very high (89.7% and 73.8%, respectively). In such patients, apart from death, worsening of SOFA score may be the best way to define treatment failure. In fact, in critically ill patients, independently of the initial score, absence of improvement in SOFA score during the first days (48–72 h) of ICU admission is associated with a worse prognosis [23-27]. This may help to define which patients may benefit from a change in therapeutic strategy or to identify patients in whom continuing therapy is likely to be futile [28]. Rescue strategies include not only antibiotic therapy but also the implementation of immunomodulatory therapies such as steroids, immunoglobulins, monoclonal antibodies

Table 2
Biomarkers characteristics.

	Total		Primary outcome				Secondary outcome			
	(*n* = 107)		Yes (*n* = 38)		No (*n* = 69)		Yes (*n* = 55)		No (*n* = 52)	
	Median	Range	Median	Range	Median	Range	Median	Range	Median	Range
White blood cells (cells × 10^9L)										
D1	15,640	430 to 114,970	14,805	660 to 34,580	15,640	430 to 114,970	13,360	430 to 35,100	15,765	1790 to 114,970
D3	12,800	2260 to 49,160	15,665	3890 to 30,950	12,400	2260 to 49,160	12,640	2260 to 30,950	12,945	2740 to 49,160
Change[a]	−9	−86 to 6563	9	−77 to 3034	−14	−86 to 6563	−1	−77 to 6563	−14	−86 to 460
C-reactive protein (mg/L)										
D1	229.5	5.4 to 646.1	221.5	24.0 to 646.1	230.5	5.4 to 549.3	213.4	24.0 to 646.1	240.1	5.4 to 549.3
D3	181.0	26.2 to 644.5	183.8	37.8 to 644.5	181.0	26.2 to 482.1	201.1	26.2 to 644.5	178.8	43.9 to 482.1
Change[a]	−16	−82 to 1098	−8	−77 to 149	−19	−82 to 1098	−15	−82 to 149	−18	−75 to 1098
Lactate (mmol/L)										
D1	3.41	0.85 to 15.88	3.67	1.13 to 15.88	3.41	0.85 to 13.39	4.27	1.13 to 15.88	2.90	0.85 to 13.28
D3	1.80	0.40 to 9.85	2.06	0.84 to 9.85	1.53	0.40 to 5.71	2.06	0.84 to 9.85	1.41	0.40 to 2.72
Change[a]	−45	−91 to 337	−33	−87 to 337	−53	−91 to 101	−39	−89 to 337	−53	−91 to 101
Procalcitonin (ng/mL)										
D1	9.42	0.01 to 200.00	8.29	0.01 to 133.84	10.33	0.08 to 200.00	11.09	0.01 to 200.00	9.11	0.08 to 139.06
D3	6.13	0.01 to 200.00	6.19	0.01 to 200.00	6.13	0.07 to 200.00	7.27	0.01 to 200.00	4.82	0.07 to 56.43
Change[a]	−36	−85 to 2681	−14	−85 to 578	−43	−85 to 2681	−25	−85 to 578	−44	−85 to 2681
D-dimer (μg/mL)										
D1	3.21	0.44 to 35.45	3.50	0.50 to 35.45	3.11	0.44 to 25.00	3.21	0.50 to 35.45	3.21	0.44 to 25.00
D3	4.54	0.43 to 76.19	8.17	0.43 to 76.19	3.97	0.92 to 39.96	6.61	0.43 to 76.19	3.81	0.92 to 39.96
Change[a]	57	−87 to 1192	117	−87 to 1192	31	−75 to 830	117	−87 to 1192	19	−75 to 644
BNP (pg/mL)										
D1	424.1	11.9 to 8922.8	516.3	11.9 to 3040.5	402.2	13.5 to 8922.8	482.7	11.9 to 3040.5	393.3	13.5 to 8922.8
D3	250.2	10.0 to 9872.0	320.4	24.7 to 2855.8	232.8	10.0 to 9872.4	241.7	10.0 to 2855.8	250.2	12.0 to 9872.4
Change[a]	−30	−91 to 1090	−28	−91 to 1090	−30	−89 to 806	−32	−91 to 1090	−25	−87 to 806
Cortisol (μg/dL)										
D1	84.0	8.2 to 552.7	136.2	14.9 to 552.7	66.4	8.2 to 546.8	88.8	12.6 to 552.7	73.9	8.2 to 546.8
D3	39.3	3.1 to 368.5	44.0	7.5 to 252.7	33.1	3.1 to 368.5	39.3	7.5 to 252.7	38.7	3.1 to 368.5
Change[a]	−33	−96 to 1063	−40	−96 to 112	−31	−92 to 1063	−42	−96 to 243	−29	−92 to 1063

BNP, brain-type natriuretic peptide; D1, day 1; D3, day 3. Primary endpoint: death/SOFA; Secondary endpoint: death/SOFA/Chest evaluation.
[a] Expressed in percent.

or extracorporeal cytokine removal therapies. Yet, it must be highlighted that, at this moment, there is not strong evidence that modulating host response definitely improves outcome in SCAP. Regarding antimicrobial therapy, to change the class of the antibiotic or the way we deliver it (e.g. from intermittent to continuous or prolonged infusion) and to increase its dose are some procedures that can be adopted if treatment failure is identified.

Table 3
Estimates of the models for composite primary and secondary endpoints.

	B	Adjusted odds ratio (95% CI)	*p*-Value for model fit[a]
Primary endpoint			
Intercept	−3.037	0.048 (0.009–0.267)	
Charlson score (points)	0.285	1.330 (1.059–1.669)	.021
BNP D1 (100 × pg/mL)	−0.051	0.950 (0.901–1.001)	.047
PCT D1 (10 × ng/mL)	−0.559	0.572 (0.355–0.922)	.003
PCT D3 (10 × ng/mL)	0.492	1.635 (0.993–4.692)	.016
D-Dimer D3 (10 × μg/mL)	0.781	2.184 (1.352–3.530)	.001
Lactate D3 (mmol/L)	0.670	1.954 (1.093–3.498)	.030
Secondary endpoint			
Intercept	−0.914	0.401 (0.161–0.997)	
Lactate D1 (mmol/L)	0.308	1.360 (1.072–1.728)	.003
BNP D1 (100 × pg/mL)	−0.041	0.959 (0.915–1.006)	.036
Lactate change[b]	0.165	1.179 (1.013–1.373)	.016
CRP change[b]	−0.054	0.947 (0.900–0.998)	.004
WBC change[b]	0.015	1.015 (0.986–1.045)	.027
D-Dimer change[b]	0.029	1.029 (1.004–1.055)	.017
Cortisol change[b]	−0.059	0.943 (0.871–1.021)	.017

BNP, Brain-type Natriuretic Peptide; CRP, C-Reactive Protein; D1, day 1; PCT, Procalcitonin; WBC, White Blood Cells.
Primary endpoint: death/SOFA; Secondary endpoint: death/SOFA/Chest evaluation.
[a] *p*-Value for likelihood ratio test between the presented model and one that excludes each predictor. A *p*-value < .05 indicates that the exclusion of the respective predictor would result in a significantly poorer model.
[b] Change reflects an increase by 10% in the biomarker from day 1 to day 3.

Recently, it has been recognized that, in SACP patients, an excessive proinflammatory response is associated with both deleterious effects and worse prognosis [29,30]. Yet, few studies assessed the utility of biomarkers, or their kinetics, for treatment failure prediction, especially in SCAP patients.

The two most studied biomarkers in SCAP are CRP and PCT. CRP absolute levels and kinetics after 3–4 days of treatment can help to identify treatment failure in this group of patients. Menendez et al. found that a CRP level ≥219 mg/l on day 1 has an independent predictive value for treatment failure. Furthermore, CRP levels on day 1 and day 3 were associated with early and late treatment failure respectively [19]. Regarding CRP kinetics, by day 3, a reduction inferior to 50% to 60% of the initial value is associated with an increased risk of having received inappropriate empiric antibiotic therapy, an increased risk of ICU/30-day mortality, complicated pneumonia and need for mechanical ventilation and/or inotropic support [31-35]. The ability to rule out severe complications is mainly due to the high negative predictive value of CRP kinetics after 72 h treatment [31].

PCT has prognostic value in CAP. Levels above 2 ng/ml have been associated with an increased incidence of bacteremia, multiorgan failure and mortality [36]. A relationship between PCT concentration and clinical resolution has been identified [37] and PCT levels on day 1 and day 3 have been independently associated with treatment failure [19,20,31,38]. Previous studies on PCT kinetics demonstrated that an increase in this biomarker from day 1 to day 3 in SCAP is associated with worse prognosis [38] while a decrease is observed in patients without

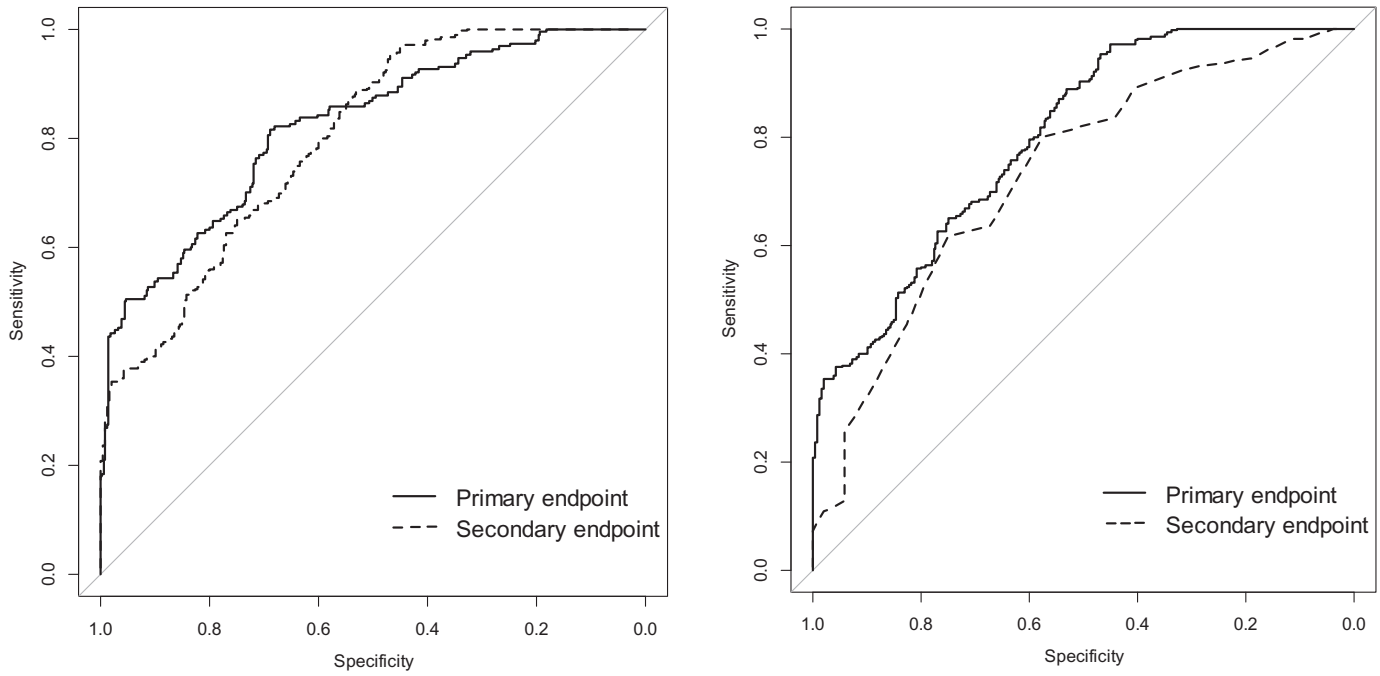

Fig. 1. AUC for models: in the derivation sample (left), in the cross-validation sample (right). Primary endpoint: death/SOFA; Secondary endpoint: death/SOFA/Chest evaluation.

complications [39]. Moreover, a decline in PCT serum levels of at least 30% between day 2 and day 3 is not only associated with good outcome but also with appropriateness of first-line empirical antibiotic therapy [40].

Table 4
Point scoring system for risk of composite primary endpoint within 5-day stay in ICU.

Variables	Categories	Points
Charlson score (points)	0–1	0
	2–3	2
	4–5	3
	6–10	6
Lactate D3 (mmol/l)	≤1.10	0
	1.11–1.35	1
	1.36–1.80	2
	1.81–2.49	3
	2.50–3.49	5
	≥3.50	11
PCT D1 (ng/ml)	≤2.17	0
	2.18–7.23	−1
	7.24–9.42	−2
	9.42–15.40	−3
	15.41–27.20	−4
	27.21–47.90	−7
	47.91–76.10	−10
	≥76.11	−26
PCT D3 (ng/ml)	≤2.93	0
	2.94–8.64	1
	8.65–19.40	2
	19.41–27.40	4
	27.41–49.20	6
	≥49.21	12
D-dimer D3 (μg/ml)	≤3.04	0
	3.05–7.17	1
	7.18–9.14	2
	9.15–18.50	3
	18.51–32.6	7
	≥32.61	10
BNP D1 (pg/ml)	≤227.0	0
	227.1–809.0	−1
	809.1–2140.0	−2

BNP, Brain-type Natriuretic Peptide; D1, day 1; D3, day 3; PCT, Procalcitonin.

In our study, we observed that the higher the PCT level on D1, the lower the chance of treatment failure at D5. But, on D3, the higher the PCT levels the higher the odds of primary outcome.

Several reasons can be evoked to justify the difference between our results and those previously published: we included only patients with severe community-acquired pneumonia admitted to an Intensive Care Unit, presenting on admission multiple organ failure (median SOFA score of 10) and already under mechanical ventilation and vasopressor support on admission in 89.7% and 73.8% of the cases, respectively; our primary outcome was different from previous endpoints; although there was a wide range of values, median PCT values on D1, in both

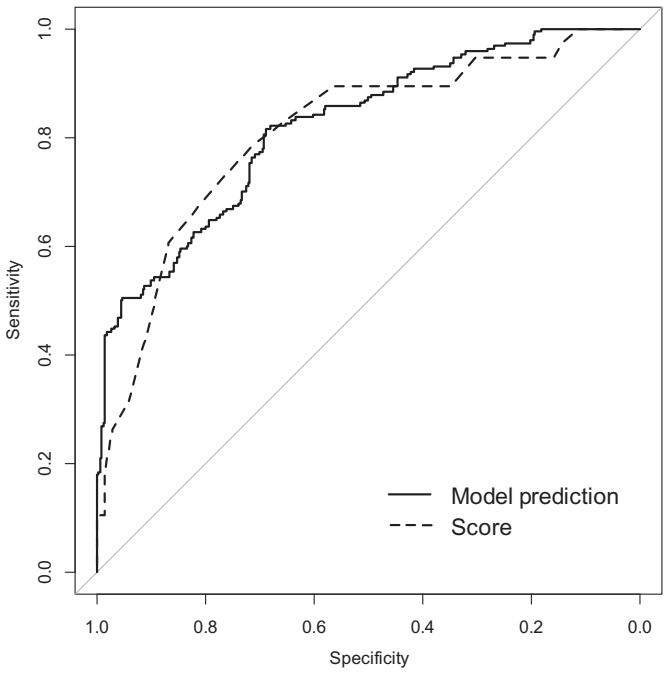

Fig. 2. AUC for composite primary endpoint: model prediction vs. score.

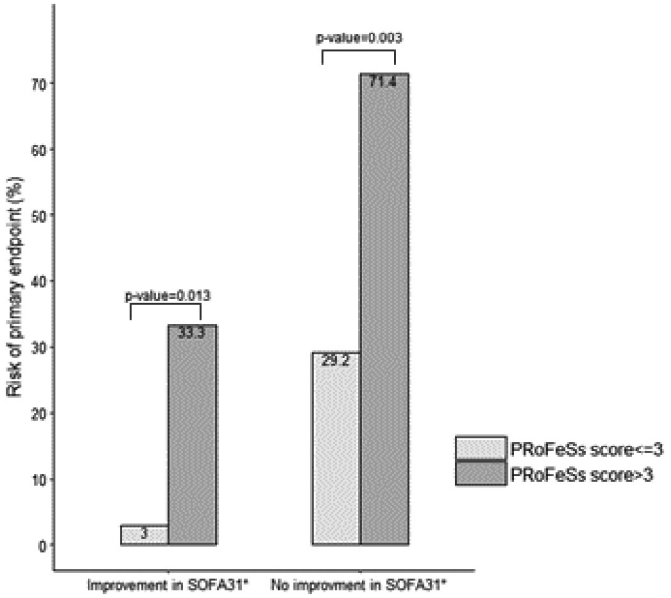

Fig. 3. Risk of primary endpoint according to PRoFeSs score at is best cut-off in patients with and without improvement in SOFA at D3. *Improvement in SOFA score by at least two points between the first and the third day of treatment.

responders and non-responders, were higher than previously suggested cut-off levels predictors of outcome.

Other biomarkers are being studied to assess their role in the management of CAP patient. Pro-adrenomedullin and BNP on admission showed to be good predictors of treatment failure [41,42]. We also demonstrated, in a small number of SCAP patients ($n = 19$), that a decrease in mid-regional pro-adrenomedullin serum levels in the first 48 h after ICU admission was a good predictor of clinical response and better outcome [43]. Baseline level of cortisol seems to be significantly higher in non-survivors confirming the interference of infection in adrenal function supporting the value of this biomarker as good predictor of mortality [44]. D-Dimers have been associated with radiological pneumonia extension [45] and hospital mortality [46]. Furthermore, significantly higher levels are found in SCAP early treatment failure [47].

Until now, no single or panel of biomarkers have been able o identify patients at higher risk of poor short-term outcome or who may benefit from coadjuvant anti-inflammatory treatment. Based on our results, we developed a model that showed a good discriminatory power for our primary outcome in both derivation (AUC 0.82) and validation (AUC 0.76) cohort. However, for a model to have clinical value, it must also have a good discriminatory power and be well calibrated. Calibration is often considered the most important property of a model and reflects the extent to which it correctly estimates the absolute risk. Poorly calibrated models will underestimate or overestimate the outcome of interest [48]. Our model, besides presenting a good discriminatory power, was also well calibrated supporting its value in clinical practice.

To our knowledge, this is the first score developed to early predict treatment failure in SCAP patients. Based on 6 variables, available in daily practice, it is easy to calculate, presents a good discriminatory power (AUC 0.81) and may be a useful tool for ICU physicians in the management of SCAP.

Previously, a clinical score to predict 28-day hospital mortality based in a large retrospective study of SCAP patients was proposed [49]. However, adverse outcomes such as multiple organ failure were not assessed, and it must be emphasized that 28-day mortality may not be related to SCAP itself. This CLCGH scoring system, that included serum creatinine, WBC, CRP, Glasgow coma scale and serum bicarbonate, showed a good discrimination power (AUC 0.889) to predict 28-day mortality but similar to SOFA score (AUC 0.864). On the contrary, our score, at its best cut off, could further discriminate between responders and non-responders in patients with and without improvement in SOFA score on D3.

One limitation of previous studies of biomarkers of treatment failure is that although their mean value is statistically different in responders and non-responders, the wide range of biomarker values makes it difficult to define an absolute cut-off to predict outcome. In our score, different categories were created for each biomarker which may increase its accuracy to predict treatment failure and this may be a strength of this study. Our study has also other strengths: all patients were prospectively enrolled, all biomarkers were collected within 12 h after the first antibiotic dose in patients without prior antibiotic, we used only biomarkers available in daily clinical practice and both inflammation/infection, coagulation and stress biomarkers were included.

However, some limitations also merit consideration. First, this was an observational, single center study. Second, blood samples were not collected daily. We chose to obtain those samples on day 1 and 3 in order to carry our research into current clinical practice.

Third, even though all patients were admitted to ICU, the small number of patients included in this cohort may determine the precision of the final estimates. The inclusion of 6 and 7 variables in the final models within the sample of 38 and 55 outcome events, respectively, raises concern about possible overfitting. However, the good predictive performance of the models remained satisfactory after cross-validation, the method to assess overfitting commonly used in small samples. Although the ideal methods for assaying the biomarkers may have not been used, which may be considered a limitation, we used tests with good precision and agreement between them. Finally, treatment failure definition used in this study has not been validated. In fact, at this moment, several definitions for failure in hospitalized patients with CAP have been used in the literature [50], most of them unsuitable for critically ill patients. We chose to use some variables previously used, such as early mortality and pulmonary infiltrate worsening, and we add SOFA score evolution due to its relationship with short term prognosis in this group of patients.

5. Conclusions

A group of biomarkers that may be helpful to early (after 48 h of ICU admission) identify SCAP patients with a high risk of poor outcome at the 5th day of ICU admission was identified. We suggest that the PRoFeSs score is a promising tool for the management of these patients, namely, helping to estimate the risk of treatment failure. Furthermore, this score can be a useful tool to select patients to be included in future studies to evaluate the usefulness of an early intervention with new therapies in CAP patients with a complicated course.

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None.

Declaration of competing interests

The authors declare that they have no competing interests.

Authors' contributions

JMP and JAP conceived and designed the study. JMP, CB, PM and CSD had substantial contribution to the acquisition of the data. OL and AA performed statistical analysis. JMP and OL drafted the article. All authors revised it critically for important intellectual content and gave final approval of the version submitted for publication.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2019.05.020.

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