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ORIGINAL PAPER

Low C-reactive protein values at admission predict mortality in patients with severe community-acquired pneumonia caused by *Streptococcus pneumoniae* that require intensive care management

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Abstract
Purpose To identify risk factors associated with mortality in patients with severe community-acquired pneumonia (CAP) caused by *S. pneumoniae* who require intensive care unit (ICU) management, and to assess the prognostic values of these risk factors at the time of admission.
Methods Retrospective analysis of all consecutive patients with CAP caused by *S. pneumoniae* who were admitted to the 32-bed medico-surgical ICU of a community and referral university hospital between 2002 and 2011. Univariate and multivariate analyses were performed on variables available at admission.
Results Among the 77 adult patients with severe CAP caused by *S. pneumoniae* who required ICU management, 12 patients died (observed mortality rate 15.6 %). Univariate analysis indicated that septic shock and low C-reactive protein (CRP) values at admission were associated with an increased risk of death. In a multivariate model, after adjustment for age and gender, septic shock [odds ratio (OR), confidence interval 95 %; 4.96, 1.11–22.25; $p = 0.036$], and CRP (OR 0.99, 0.98–0.99 $p = 0.034$) remained significantly associated with death. Finally, we assessed the discriminative ability of CRP to predict mortality by computing its receiver operating characteristic curve. The CRP value cut-off for the best sensitivity and specificity was 169.5 mg/L to predict hospital mortality with an area under the curve of 0.72 (0.55–0.89).
Conclusions The mortality of patients with *S. pneumoniae* CAP requiring ICU management was much lower than predicted by severity scores. The presence of septic shock and a CRP value at admission <169.5 mg/L predicted a fatal outcome.

Keywords Septic shock · *Streptococcus pneumoniae* · Prognostic · Pneumonia · C-reactive protein · Biomarkers

Introduction

Up to 10 % of all patients hospitalized with community-acquired pneumonia (CAP) require intensive care unit (ICU) management [1, 2]. Despite improvement in its

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general management, CAP is still a common cause of death in western countries [3, 4]. The main pathogen isolated from CAP patients requiring hospital management is *Streptococcus pneumonia* [5–7]. The burden of invasive pneumococcal infections is high. In the United Sates, there were 8,000 cases of pneumococcal bloodstream infections and 106,000–175,000 cases of pneumonia caused by pneumococcal infections that required hospitalization per year in 2000 [8]. Moreover, there were rising incidences of pneumococcal infections in infants (<1 year) and the elderly (>65 years) in whom rates may be as high as 30 cases/100,000 per year [8].

The epidemiology of nonsevere pneumonia caused by *S. pneumoniae* has been well studied [2, 7], but few data have been collected regarding patients developing severe forms of infection and requiring ICU management. In a recent prospective study of 1166 patients with severe CAP who were admitted to ICUs across 17 European countries, *S. pneumoniae* was the most commonly isolated organism (29 % of cases), and it was the most common cause of bacteremia and empyema [7]. Some studies suggested a correlation between the presence of co-morbidities and poor outcomes [4, 9], but others did not [5, 6]. A recent large prospective study in France indicated that death was influenced by the presence of septic shock and organ failure [10] rather than comorbidities.

In patients requiring ICU management, early identification of those with more severe outcomes would allow for more tailored therapeutic strategies. In this study, we aimed to examine the risk factors associated with mortality in patients with severe *S. pneumoniae* CAP requiring ICU management, and to assess their prognosis at the time of admission. We retrospectively analyzed the risk factors potentially associated with fatal outcomes in a cohort of patients with a severe form of *S. pneumoniae* CAP who were admitted to our medico-surgical 32-bed ICU over the last decade.

Methods

Patient population

We retrospectively included all consecutive adults ≥18 years of age who were admitted with severe CAP caused by *S. pneumoniae* to our 32-bed medico-surgical ICU at the Centre Hospitalier Universitaire Vaudois (CHUV), a community and referral university hospital, between January 2002 and December 2011. Patients with meningitis and/or invasive ear, nose, and throat (ENT) infections were excluded from the analysis. The present research has been performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments. The Institutional Review Board "Commission cantonale d'éthique de la recherche sur l'être humain" granted retrospective access to the data without need for individual informed consent.

Data collection

For each patient, we recorded the age, sex, and severe comorbidities according to the standard definitions used in the severity score. Clinical variables (heart and respiratory rate, blood pressure, etc.) and usual biological values (as determined by the accredited Laboratory of the Service of Biomedicine of the CHUV) were extracted from the computerized information system (Metavision, iMDsoft, Israel). C-reactive protein (CRP) levels were measured using the Tina-quant® CRP method on a Modular P apparatus (Roche Diagnostics, Mannheim, Germany). Severity of illness was evaluated on the first ICU day using the Simplified Acute Physiology Score (SAPS) II [11] and the Acute Physiology and Chronic Health Evaluation II (APACHE II) score [12]. Organ dysfunction at 24 h was evaluated by the Sepsis-related Organ Failure Assessment (SOFA) score [13].

Definitions and types of infection

We define sepsis, severe sepsis, and septic shock according to criteria proposed by the 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference [14]. Community-acquired infection was defined as an infection manifesting before or within 48 h after hospital admission, whereas nosocomial infection was defined as an infection occurring at least 48 h after hospital admission. Nosocomial and healthcare-associated pneumonia were excluded. Patients with concomitant pneumococcal meningitis, invasive ENT infections, or endocarditis were not included. Microbiologically documented, severe CAP infections caused by *S. pneumoniae* were diagnosed according to the adapted American Thoracic Society definition [15].

Statistical analysis

Continuous variables are reported as the mean and standard deviation (SD) or as medians and interquartile ranges (IQR) as indicated. Categorical variables are reported as frequencies. APACHE II, SAPS II, and SOFA scores are expressed as medians and IQR. Comparison of continuous variables between survivors and nonsurvivors was carried out using the Student's *t* test for parametric values, and the Mann–Whitney *U* test for nonparametric values. Fisher's exact test was used to compare categorical variables.

We assessed the independent predictors of hospital mortality at the time of admission and 24 h after admission with logistic regression models in which we included all variables with a *P* value ≤0.1 from the univariate analysis.

Severity scores are computed after 24 h in the ICU, so they were not included in the models assessing the predictors of hospital mortality at time of admission. Age and gender were included in all models as clinically relevant variables for mortality, excepted for models containing severity scores; indeed the variable age is already used to compute those scores. Given the potential impact of frailer elderly patients, we completed the statistical analysis with age as a categorical variable (age group >65 years vs ≤65 years).

We assessed the discriminative ability of CRP to predict mortality by computing its receiver operating characteristic (ROC) curve. The cut-off for the best sensitivity and specificity was derived from the curve coordinates. The area under the curve (AUC) was reported with 95 % confidence intervals (CI 95 %), as well as the *P* value for the difference with the reference line.

A two-sided *P* value <0.05 was considered statistically significant. We used the statistical software SPSS (version 19, IBM Company, USA) for data processing and analyses.

Results

Patient characteristics

From January 2002 to December 2011, 22,226 patients were admitted to the 32-bed medico-surgical ICU. Among them, 84 presented with invasive *S. pneumoniae* infections, including 77 patients with severe CAP and seven with meningitis.

Outcomes

Among the 77 patients with severe *S. pneumoniae* CAP requiring ICU management, 12 patients died (15.6 %) (Table 1). Compared to the mortality predicted by the APACHE II scores (32.2 %) and the SAPS II (39.2 %), we observed a lower hospital mortality rate (15.6 %). This trend hold true for elderly >65 years (22.2 %). This corresponded to a standardized mortality ratio (SMR) of 0.48 and 0.40 for APACHE II and SAPS II, respectively. Comorbidity was present in a high proportion of patients, but we did not observe any correlation between comorbidity and the outcome.

The microbiological characteristics, the severity of the infection, and the supportive measures required to treat the patients are presented in Table 2. Septic shock, APACHE II score, SAPS II, SOFA score at 24 h, and the presence of multiple organ failure were correlated with a fatal outcome. In contrast, successful noninvasive ventilation and a high initial CRP value were correlated with survival.

Pneumococcal coverage was adequate in all patients (Table 1). Among initial treatment, combined antibiotics were given in 45 (69 %) of survivors and in 11 (92 %) of non-survivors ($P = 0.163$).

Outcome prediction at 24 h after admission

In the multivariate analysis, the APACHE II (OR 1.13, CI 95 % 1.02–1.25; $P = 0.021$), SAPS II (OR 1.06, CI 95 % 1.01–1.11, $P = 0.024$), and SOFA (OR 1.54, CI 95 % 1.16–2.05, $P = 0.003$) severity scores at 24 h predicted death. Each score was included in a separate multivariate logistic regression model adjusted for gender, CRP and septic shock, adding age in the analysis with SOFA. When age is included, as a categorical variable (age group >65 vs ≤65), SOFA (OR 1.6; CI 95 % 1.18–2.23, $P = 0.030$) remained significant to predict mortality.

Outcome prediction at time of admission

Severity scores include the worst values of a high number of physiological variables and can only be computed after 24 h, so they were not included in this analysis. After adjustment for age and gender, septic shock (OR 4.96; CI 95 % 1.11–22.25, $P = 0.036$) and a low CRP value (OR 0.99; CI 95 % 0.98–099, $P = 0.034$) predicted death. When age was included as categorical variable (age >65 vs ≤65), septic shock (OR 5.42; CI 95 % 1.18–24.9, $P = 0.030$), and a low CRP value (OR 0.99; CI 95 % 0.98–099, $P = 0.023$) remained significant.

Procalcitonin (PCT)

Among the 20 patients (26 %) for whom PCT measurements within 24 h of admission were available, the median PCT value was 20.8 ng/ml (IQ: 4.4–40.4). No statistical difference was found between survivors (14 patients, median 7.4 ng/ml (IQR: 3.5–55.1) and non-survivors (6 patients, median 36.5 ng/ml (IQR 16.3–40.4) ($P = 0.35$; Mann–Whitney).

CRP

Two-thirds of the patients who died (8 of 12) presented with CRP lower third, with values below 158 mg/L, (Fig. 1). Three quarters of these eight patients (6 of 8) presented with CRP values below 133 mg/L. Table 3 presents patient's characteristics according to CRP terciles. We assessed the discriminative ability of CRP to predict mortality by computing its ROC curve. The ROC curve of an admission CRP value <169.5 mg/L predicted mortality with a sensitivity of 75 %, a specificity of 72 % (1–0.277), a positive predictive value of 33 %, and a negative predictive value of 94 %. The AUC was 0.72 (CI 95 % 0.55–0.89, $P = 0.018$) (Fig. 2).

Table 1 Characteristics of the patients with severe pneumonia caused by *S. pneumoniae*

	All patients ($n = 77$)	Alive ($n = 65$)	Dead ($n = 12$)	P value*
Demographics				
Age (years), mean (SD)	55.7 (16.8)	54.7 (16.8)	61.2 (16.2)	NS
>65 years, *n* (%)	27 (35.1)	21 (32.3)	6 (50)	NS
Male gender, *n* (%)	56 (72.2)	46 (70.7)	10 (83.3)	NS
Underlying conditions				
Cardiovascular disease, *n* (%)	50 (64.9)	42 (64.6)	8 (66.6)	NS
Ischemic heart disease, *n* (%)	16 (20.8)	12 (18.5)	4 (33.3)	NS
Valvular heart disease, *n* (%)	2 (2.6)	2 (3.1)	0 (0)	NS
Heart failure, *n* (%)	5 (6.5)	4 (6.2)	1 (8.3)	NS
Arrhythmia, *n* (%)	10 (13)	9 (13.8)	1 (8.3)	NS
HTA	24 (31.2)	20 (30.8)	4 (33.3)	NS
COPD, *n* (%)	14 (18.2)	13 (20)	1 (8.3)	NS
Sleep apnea syndrome, *n* (%)	4 (5.2)	4 (6.2)	0 (0)	NS
Liver disease, *n* (%)	23 (29.9)	17 (26.2)	6 (50)	NS
Cirrhosis, *n* (%)	9 (11.7)	6 (9.2)	3 (25)	NS
Hepatitis, *n* (%)	12 (15.5)	10	2 (16.7)	NS
Renal disease, *n* (%)	9 (11.7)	8 (12.3)	1 (8.3)	NS
Neurological disease, *n* (%)	20 (26)	16 (24.6)	4 (33.3)	NS
Epilepsy	6 (7.8)	6 (9.2)	0 (0)	NS
Stroke	5 (6.5)	3 (4.6)	2 (16.7)	NS
Cancer, *n* (%)	16 (20.8)	12 (18.5)	4 (33.3)	NS
HIV, *n* (%)	9 (11.7)	7 (10.8)	2 (16.7)	NS
Substance abuse, *n* (%)	24 (31.2)	18 (27.7)	6 (50)	NS
Splenectomy, *n* (%)	3 (3.9)	2 (3.1)	1 (8.3)	NS
Initial antibiotic treatment, *n* (%)				
Combined treatment	56 (72.3)	45 (69.2)	11 (91.7)	NS
Betalactam and macrolide	43 (55.8)	34 (52.3)	9 (75)	NS
Betalactam and carbapenem	6 (7.8)	5 (7.7)	1 (8.3)	NS
Betalactam and glycopeptide	1 (1.3)	1 (1.5)	0 (0)	NS
Carbapenem and glycopeptide	5 (6.5)	4 (6.2)	1 (8.3)	NS
Glycopeptide and macrolide	1 (1.3)	1 (1.5)	0 (0)	NS
Monotherapy	21 (27.3)	20 (30.7)	1 (8.3)	NS
Carbapenem monotherapy	1 (1.3)	1 (1.5)	0 (0)	NS
Betalactam monotherapy	20 (26)	19 (29.2)	1 (8.3)	NS
Risk factors for *S. pneumoniae* infection				
Past pneumococcal infection, *n* (%)	2 (2.6)	2 (3.1)	0 (0)	NS
Active smoker, *n* (%)	25 (32.5)	21 (32.3)	4 (33.3)	NS
Obesity (BMI > 30 kg/m^2), *n* (%)	6 (7.8)	6 (9.2)	0 (0)	NS
BMI, mean (SD)	24.7 (5.1)	24.1 (4.3)	24.8 (5.3)	NS

COPD chronic obstructive pulmonary disease, *HIV* human immunodeficiency virus, *BMI* body mass index, *NS* not significant (dead vs alive)

* Fisher's exact test or student's *t* test (alive vs dead)

Discussion

CAP caused by *S. pneumoniae* has a large burden and is associated with high mortality [10, 16]. Interestingly, we report a lower than expected mortality in our cohort of CAP patients with *S. pneumoniae* infections requiring ICU management. Indeed, trends toward decreased mortality rates of severe sepsis patients were recently reported by others [17]. These lowered mortality rates may be accounted for by implementation of aggressive management of severe infections over the last decade, as recommended by international guidelines [18].

As with other types of severe infections, the shock and severity scores assessed at 24 h also predicted death in our cohort. Interestingly, our data showed that among patients with CAP caused by *S. pneumoniae* that required ICU management, the presence of septic shock and a low initial serum CRP level at admission correlated with a fatal

Table 2 Severity of the infection and the supportive measures required to treat the patients

	All patients ($n = 77$)	Alive ($n = 65$)	Dead ($n = 12$)	P value[#]
Sepsis, *n* (%)	22 (28.6)	20 (30.8)	2 (16.7)	NS
Severe sepsis, *n* (%)	20 (26)	19 (29.2)	1 (8.3)	NS
Septic shock, *n* (%)	34 (44.2)	25 (38.5)	9 (75)	0.03
Severity scores				
APACHE II, median (IQR)	19 (13)	18 (13)	28.5 (11)	0.004
SAPS II, median (IQR)	47 (20)	42 (26)	59.5 (10)	0.002
Organ dysfunctions				
SOFA at 24 h, median (IQR)	8 (5)	8 (4)	13 (3)	<0.0001
MOF, *n* (%)	14 (18.2)	8 (12.3)	6 (50)	0.006
Acute renal failure[a], *n* (%)	31 (44.3)	25 (41.7)	6 (60)	NS
DIC[a], *n* (%)	7 (10)	4 (6.7)	3 (30)	0.055
Respiratory failure				
ARDS[a], *n* (%)	3 (4.3)	2 (33.3)	1 (10)	NS
NIV, *n* (%)	46 (59.7)	43 (66.2)	3 (25)	0.01
NIV failure, *n* (%)	21 (27.3)	18 (27.7)	3 (25)	NS
Invasive ventilation, *n* (%)	58 (75.3)	47 (72.3)	11 (91.7)	NS
Duration of MV (days), median (IQR)	3 (8)	2 (8)	5.5 (11)	NS
ICU LOS (days), median (min–max)	8.6 (1–39)	8.6 (9)	8.5 (6.5)	NS
Microbiological documentation				
Positive sputum, *n* (%)	25 (32.5)	20 (30.8)	5 (41.7)	NS
Positive blood culture, *n* (%)	42 (54.5)	34 (52.3)	8 (66.7)	NS
Positive urinary antigen, *n* (%)	44 (57.1)	40 (61.5)	4 (33.3)	NS
Biological values at admission				
Leucocytes (g/L), mean (SD)	13.4 (9.5)	13.7 (9.5)	11.7 (9.8)	NS
Band forms, *n* (%)	34 (44.2)	26 (0.4)	8 (66.7)	NS
CRP (mg/L), mean (SD)	237 (140)	253 (137)	151 (128)	0.02

ARDS Adult respiratory distress syndrome, *MOF* Multiple organ dysfunction (>3), *DIC* disseminated intra-vascular coagulation, *NIV* non-invasive ventilation, *MV* mechanical ventilation, *ICU LOS* ICU length of stay, *NS* not significant (dead vs alive)

[#] Fisher's exact test or student's *t* test or Mann–Whitney *U* test

[a] For 70 patients (60 alive and 10 dead)

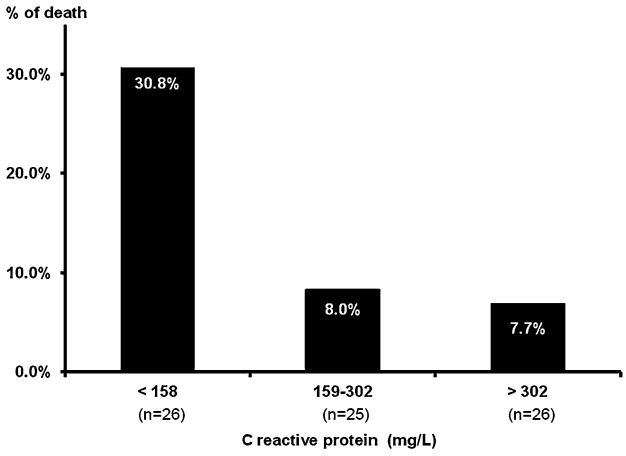

Fig. 1 CRP levels among patients with fatal outcomes. Proportion of patients who died according to terciles of CRP levels. Two-thirds of the patients who died (8 of 12) presented with a CRP level below 158 mg/L. Of these eight patients, three quarters (6 of 8) had a CRP value below 133 mg/L

outcome. This finding is unexpected and counterintuitive. Most clinicians would consider a priori that low CRP values may be associated with a less severe systemic inflammation response, which should reflect a better prognosis. However, data from animal studies suggest an association between CRP values and survival. In mice, administration of CRP within a few hours of a *S. pneumoniae* challenge led to a reduction in the concentration of bacteria in the blood, and consecutively lessened the severity of the infection [19, 20]. Over the study period, PCT values were only available for a small number of patients, precluding any conclusion about the absence of difference between survivors and non-survivors.

Several aspects may limit the interpretation of our data. We retrospectively analyzed a small cohort of patients admitted over one decade. Nevertheless, these patients can be considered as a homogenous cohort of severely ill patients requiring ICU management in an institution where the ratio between ICU and intermediate care beds is 1–3.

Table 3 Characteristics of the patients according to CRP terciles

	CRP < 158 ($n = 26$)	CRP = 159–302 ($n = 25$)	CRP > 302 ($n = 26$)	*P* value*
Mortality, *n* (%)	8 (30.8)	2 (8)	2 (7.7)	0.032
Demographics				
Age (years), mean (SD)	57.4 (16)	52.4 (15.4)	57.4 (18.8)	NS
>65 years, *n* (%)	9 (34.6)	6 (24)	12 (46.2)	NS
Male gender, *n* (%)	18 (69.2)	20 (80)	18 (69.2)	NS
Underlying conditions				
Cardiovascular disease, *n* (%)	18 (69.2)	15 (60)	17 (65.4)	NS
COPD, *n* (%)	6 (23.1)	6 (24)	2 (7.7)	NS
Liver disease, *n* (%)	10 (38.3)	8 (32)	5 (19.2)	NS
Renal disease, *n* (%)	4 (15.4)	2 (8)	3 (11.5)	NS
Neurological disease, *n* (%)	6 (23.1)	8 (32)	6 (23.1)	NS
Cancer, *n* (%)	5 (19.2)	6 (24)	5 (19.2)	NS
HIV, *n* (%)	2 (7.7)	5 (20)	2 (7.7)	NS
Substance abuse, *n* (%)	9 (34.6)	9 (36)	6 (23.1)	NS
Splenectomy, *n* (%)	2 (7.7)	0 (0)	1 (3.8)	NS
Risk factors for *S. pneumoniae* infection				
Past pneumococcal infection, *n* (%)	1 (3.8)	1 (4)	0 (0)	NS
Active smoker, *n* (%)	9 (34.6)	9 (36)	7 (26.9)	NS
Obesity (BMI > 30 kg/m^2), *n* (%)	3 (11.5)	0 (0)	3 (11.5)	NS

COPD chronic obstructive pulmonary disease, *HIV* human immunodeficiency virus, *BMI* body mass index, *NS* not significant

* Fisher's exact test or one-way ANOVA

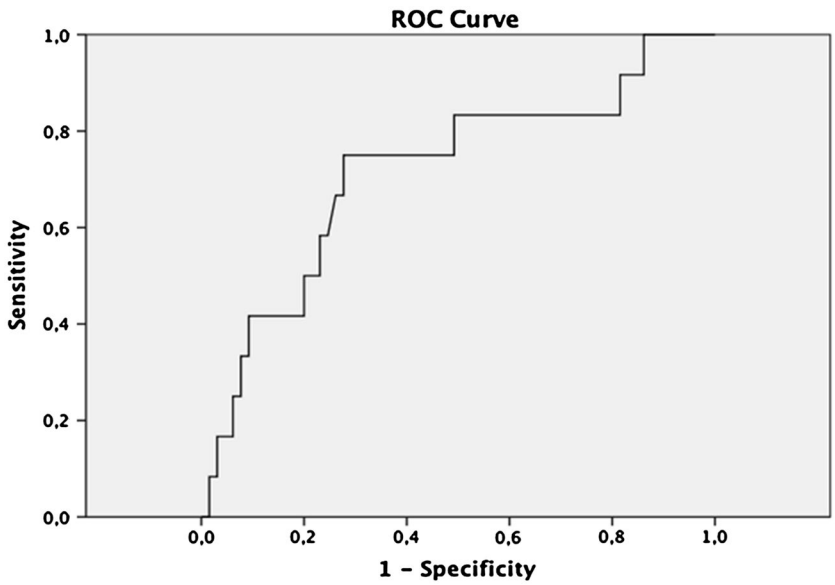

Fig. 2 Accuracy of CRP in outcome prediction. ROC curve of CRP levels in the prediction of hospital mortality. The AUC for a CRP value <169.5 mg/L is 0.716 (0.547–0.886)

The absences of electronic or computerized documentation of care preclude analyzing the impact of delay between hospital admission and first antibiotic administration on patient outcome. However, community-acquired pneumonia is characterized by an undefined and highly variable time between onset of the disease, clinical manifestations, and hospital admission. As such, the precise interval of time between onset of the disease and the first antibiotic administration is hard to determine, although highly relevant. This observation is only valid in the specific stetting of patients with severe pneumonia requiring ICU management. Our results should be considered as preliminary, but should be of sufficient interest to justify confirmation in larger cohorts of patients.

An eventual confirmation of a significant correlation between low initial CRP values and fatal outcomes may

be used to stratify patients with severe CAP caused by *S. pneumoniae*. Indeed, progressive ICU shortages (e.g., ICU-related costs, shortages of ICU physician, and nurses) may be responsible for the early ICU discharge of patients that are perceived to be at low risk of death, such as those with severe infection and a good perceived prognosis.

Conclusion

Since CRP values are almost universally available within a few hours of ICU admission, they may help to stratify patients with severe CAP due to *S. pneumoniae* according to their prognoses and to tailor their management accordingly.

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Conflict of interest All authors declare no potential conflicts of interest regarding their contribution to this study.

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