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Procalcitonin predicts patients at low risk of death from community-acquired pneumonia across all CRB-65 classes

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ABSTRACT: The aim of the present study was to investigate the prognostic value, in patients with community-acquired pneumonia (CAP), of procalcitonin (PCT) compared with the established inflammatory markers C-reactive protein (CRP) and leukocyte (WBC) count alone or in combination with the CRB-65 (confusion, respiratory rate $\geqslant$30 breaths·min^{-1}, low blood pressure (systolic value $<$90 mmHg or diastolic value $\leqslant$60 mmHg) and age $\geqslant$65 yrs) score.

In total, 1,671 patients with proven CAP were enrolled in the study. PCT, CRP, WBC and CRB-65 score were all determined on admission and patients were followed-up for 28 days for survival.

In contrast to CRP and WBC, PCT levels markedly increased with the severity of CAP, as measured by the CRB-65 score. In 70 patients who died during follow-up, PCT levels on admission were significantly higher compared with levels in survivors. In receiver operating characteristic analysis for survival, the area under the curve (95% confidence interval) for PCT and CRB-65 was comparable (0.80 (0.75–0.84) *versus* 0.79 (0.74–0.84)), but each significantly higher compared with CRP (0.62 (0.54–0.68)) and WBC (0.61 (0.54–0.68)). PCT identified low-risk patients across CRB classes 0–4.

In conclusion, procalcitonin levels on admission predict the severity and outcome of community-acquired pneumonia with a similar prognostic accuracy as the CRB-65 score and a higher prognostic accuracy compared with C-reactive protein and leukocyte count. Procalcitonin levels can provide independent identification of patients at low risk of death within CRB-65 (confusion, respiratory rate $\geqslant$30 breaths·min^{-1}, low blood pressure (systolic value $<$90 mmHg or diastolic value $\leqslant$60 mmHg) and age $\geqslant$65 yrs) risk classes.

KEYWORDS: Community-acquired pneumonia, CRB-65 (confusion, respiratory rate $\geqslant$30 breaths·min^{-1}, low blood pressure (systolic value $<$90 mmHg or diastolic value $\leqslant$60 mmHg) and age $\geqslant$65 yrs) score, C-reactive protein, mortality, procalcitonin, prognosis

Community-acquired pneumonia (CAP) is the most common potentially fatal infectious disease throughout the Western industrialised countries [1, 2]. Guidelines for the management of adult patients with CAP recommend a severity-based approach to diagnosis and treatment. Prognostic scores for CAP have been developed to assess pneumonia severity in order to validate clinical judgement and to guide decisions about treatment settings [3–10]. In Europe, the CURB (confusion, urea >7 mmol·L^{-1}, respiratory rate $\geqslant$30 breaths·min^{-1}, low blood pressure (systolic value <90 mmHg or diastolic value $\leqslant$60 mmHg) and age $\geqslant$65 yrs) score or the CRB-65 (confusion, respiratory rate $\geqslant$30 breaths·min^{-1}, low blood pressure (systolic value <90 mmHg or diastolic value $\leqslant$60 mmHg) and age $\geqslant$65 yrs) score are currently advocated as preferred scores due to their simplicity and applicability in the ambulatory setting [7, 11].

Several inflammatory markers, such as leukocyte (WBC) counts and C-reactive protein (CRP) levels, are traditionally used in the evaluation of pulmonary infections. However, the value of these markers remains very limited. Recently, procalcitonin (PCT) has emerged as a promising alternative. Its level increases rapidly in bacterial infections but remains low in viral diseases. High plasma concentrations of PCT are typically seen in sepsis, meningitis and pneumonia [12–17]. PCT also seems to be a prognostic factor in sepsis and pneumonia [18, 19].

Thus, the aim of the present study was to investigate the predictive value of PCT compared

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with the established inflammatory markers WBC and CRP, and the clinical CRB-65 score. Moreover, the combined use of CRB-65 and PCT was studied in order to determine if it was superior to CRB-65 alone in predicting short-term death from CAP.

MATERIALS AND METHODS

Setting

CAPNETZ represents a German competence network for the study of CAP [1, 20]. The network comprises 10 local clinical centres (LCC) throughout Germany. These centres represent hospitals and physicians in private practice at all levels of health care provision involved in CAP therapy. Within CAPNETZ, all new CAP cases are reported *via* a network of sentinel practices and hospitals to the study monitor of the corresponding LCC.

The CAPNETZ project was approved by the local ethical committee. Written informed consent was obtained from every patient prior to inclusion in the network study.

Study population

The inclusion criteria were: age $\geqslant$18 yrs, a new pulmonary infiltrate diagnosed by chest radiograph together with at least one of the following clinical symptoms: fever, cough, purulent sputum, focal chest signs, dyspnoea and pleuritic pain. The exclusion criteria were conditions of systemic immune deficiency, active tuberculosis or hospitalisation $<$4 weeks prior to infection. The decision of where to treat the patient was left to the discretion of the attending physician. No attempt was made to implement standardised criteria for the assessment of pneumonia severity or for the decision to hospitalise.

All patients were assessed at first presentation and during follow-up, according to a standardised data sheet. After 14 and 180 days all patients or relatives were contacted either personally or *via* telephone for a structured interview on outcome parameters (*e.g.* resolution of symptoms, length of antimicrobial therapy and death).

The recruitment period for the present study was October 1, 2002 to September 30, 2005. For the purpose of the present study, patients who died within 28 days of involvement were regarded as nonsurvivors.

Microbiological investigation

The laboratory procedure for CAPNETZ patients has been previously described [1]. Briefly, it included sputum samples and pharyngeal aspiration with Gram stain and culture, blood samples for serological testing for *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*, and a urine sample for the detection of *Streptococcus pneumoniae* and *Legionella pneumophila* serogroup 1. Detection of respiratory pathogens was performed according to standard methods and established microbiological guidelines [21].

Determination of PCT, CRP and leukocyte count

WBC count was determined by the hospital laboratory. Serum CRP was measured by nephelometry with a commercially available assay (Behring Diagnostics, Marburg, Germany). Serum PCT was determined by an immunofluorescent assay (B.R.A.H.M.S PCT sensitive Kryptor; B.R.A.H.M.S AG, Henningsdorf, Germany). All serum samples for PCT testing were centrally stored at -70°C in the CAPNETZ material bank in Ulm, Germany, until measurement. The assay requires 50 μL of serum, EDTA or heparin plasma, has a functional assay sensitivity (defined as the lowest value with an interassay coefficient of variation $<$20%) of 0.06 ng·mL^{-1} and a lower detection limit of 0.02 ng·mL^{-1}. Laboratory measurements were performed in a blinded fashion without knowledge of the microbiological results or the clinical status of the patient.

Determination of CRB-65

The CRB-65 score consists of four variables: confusion, respiratory rate $\geqslant$30 breaths·min^{-1}, systolic blood pressure $<$90 mmHg or diastolic blood pressure $\leqslant$60 mmHg, and age $\geqslant$65 yrs [3, 5]. One point is given for each parameter present, which results in CRB-65 scores of 0–4. The CRB-65 score was calculated with patient data obtained at admission.

Statistics

Continuous variables are expressed as mean$\pm$SD or median (interquartile range), unless otherwise stated. Two group nonparametric comparisons were calculated by the Mann–Whitney U-test. For multigroup comparisons, Kruskal–Wallis one-way ANOVA was used. Frequency comparison was performed using the Chi-squared test. To compare the predictive value of WBC, CRP, CRB-65 score and PCT, and the predicted probability derived from a logistic regression

TABLE 1 Distribution of CRB-65 (confusion, respiratory rate $\geqslant$30 breaths·min^{-1}, low blood pressure (systolic value $<$90 mmHg or diastolic value $\leqslant$60 mmHg) and age $\geqslant$65 yrs) risk classes and associated 28-day mortality

CRB-65 risk class	Total	Hospitalised patients	Patients with known outcome	28-day mortality
0	557	262 (47.0)	538	2 (0.4)
1	608	445 (73.2)	587	22 (3.7)
2	275	258 (93.8)	229	27 (11.8)
3	58	57 (98.3)	44	8 (18.2)
4	10	10 (100.0)	6	4 (66.7)
Total	1508	1032 (68.4)	1404	63 (4.5)

Data are presented as n or n (%).

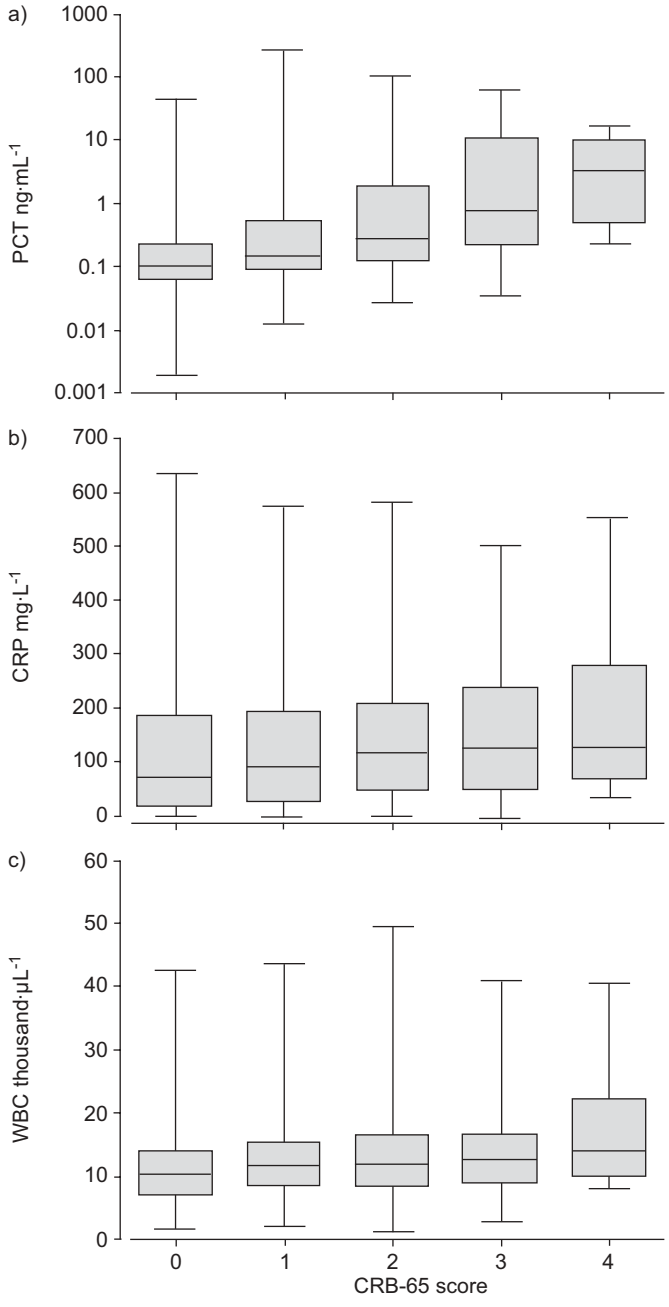

FIGURE 1. Admission levels of a) procalcitonin (PCT), b) C-reactive protein (CRP) and c) leukocyte (WBC) count in community-acquired pneumonia patients classified into CRB-65 (confusion, respiratory rate $\geqslant$30 breaths·min^{-1}, low blood pressure (systolic value $<$90 mmHg or diastolic value $\leqslant$60 mmHg) and age $\geqslant$65 yrs) classes 0–4. Boxes represent 25th–75th percentiles, with horizontal lines and whiskers indicating median values and range, respectively.

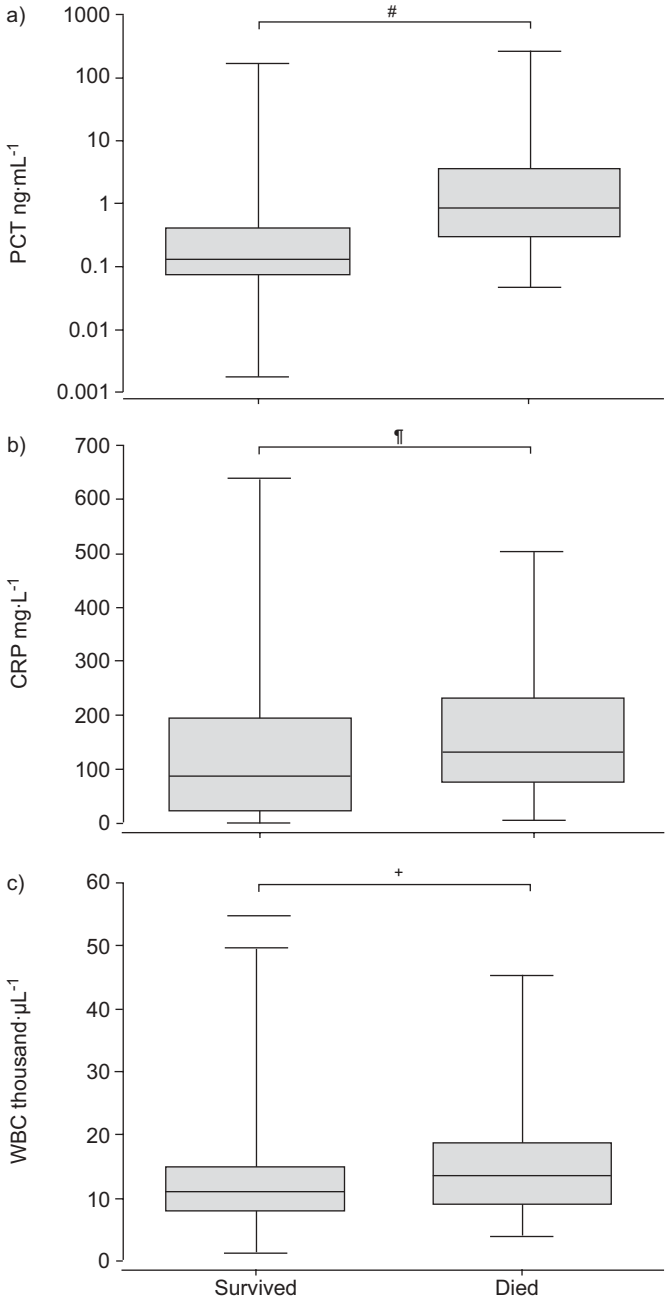

FIGURE 2. Admission levels of a) procalcitonin (PCT), b) C-reactive protein (CRP) and c) leukocyte (WBC) count in community-acquired pneumonia patients who survived and who died. Boxes represent 25th–75th percentiles, with horizontal lines and whiskers indicating median values and range, respectively. #: $p<0.0001$; ¶: $p=0.0006$; +: $p=0.0014$.

model including CRB-65 and PCT, receiver operating characteristic (ROC) curves were constructed and the area under the curve (AUC) determined. The outcome variable was survival within 28 days. The operative characteristics of CRB-65 and PCT were assessed calculating sensitivity, specificity, predictive values and the likelihood ratio. The relationship of different variables with survival was assessed by Cox proportional hazards analysis (single predictor and multivariable analysis). Hazard ratios and 95% confidence intervals (CIs) for risk factors and significance level for Chi-squared (Wald) test are provided. Levels of PCT were normalised by log transformation. In order to test whether PCT adds predictive value to CRB-65, the likelihood ratio Chi-squared test for nested models was used. Kaplan–Meier survival curves were generated to visualise the distribution of times from baseline to death, and a log-rank test was performed in order to compare

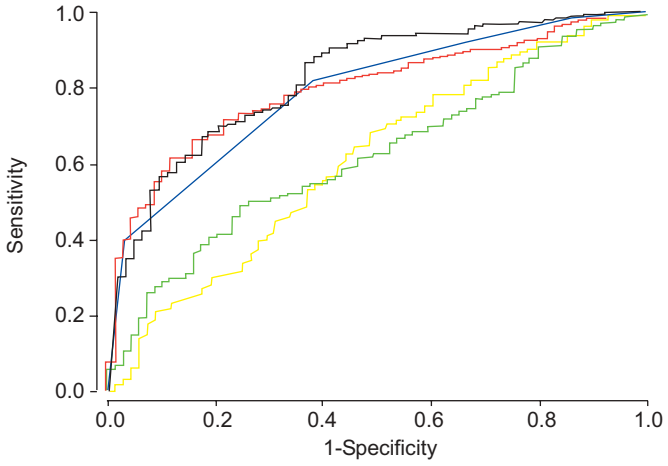

FIGURE 3. Receiver operating characteristic curves comparing leukocyte count (yellow; area under curve (AUC) 0.61), C-reactive protein (green; AUC 0.62), procalcitonin (red; AUC 0.80), CRB-65 (confusion, respiratory rate ⩾30 breath-s·min^{-1}, low blood pressure (systolic value <90 mmHg or diastolic value ⩽60 mmHg) and age ⩾65 yrs) score (blue; AUC 0.79) and the combined predicted probabilities from a binary logistic model including procalcitonin and CRB-65 (black; AUC 0.83) with respect to prediction of death at 28-day follow-up.

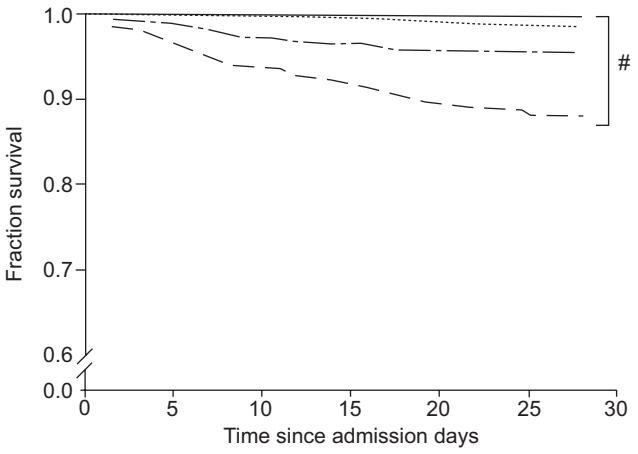

FIGURE 4. Kaplan–Meier curves for 28-day mortality with patients grouped according to quartiles of serum PCT. ——: 1st quartile; ·····: 2nd quartile; — – —: 3rd quartile; — — — 4th quartile. #: p<0.0001.

the survival curves between groups. All statistical tests were two-tailed and a p-value <0.05 was considered statistically significant.

RESULTS

Patients

The study population comprised 1,671 patients with a mean±SD (range) age of 61±18 (18–98) yrs of which 1,113 (66.6%) patients were hospitalised and 558 (33.4%) were treated as outpatients. Approximately 55% were male. The causative pathogen was found in 472 (28.2%) patients; of which, typical bacterial infection was found in 219 (13.1%); atypical bacterial infection in 205 (12.3%); viral infection in 48 (2.9%) and mixed infections with two or more pathogens in 58 (3.5%). Patients with typical bacterial CAP showed higher PCT levels compared with patients with atypical bacterial or viral CAP. At 28 days follow-up, 125 (7.5%) patients were lost to follow-up and 70 patients died. Thus, the mortality rate of the remaining population of 1,546 patients (545 patients treated as outpatients, 1,001 hospitalised patients) was 4.5%. The mortality rates of outpatients were significantly lower than those of hospitalised patients (n=2 (0.4%) *versus* n=68 (6.8%); p <0.0001).

Pneumonia severity and mortality

A total of 1,508 data sets were complete for calculation of CRB-65. The distribution of CRB-65 scores and its association with mortality in outpatients and hospitalised patients is provided in table 1. Increasing severity of CAP according to CRB-65 was not associated with a pronounced gradual increase of WBC (fig. 1c) or CRP values (fig. 1b). Conversely, PCT levels increased significantly with increasing severity of CAP (p<0.0001; fig. 1a). The median (interquartile range) PCT levels were: 0.10 (0.07–0.21) ng·mL^{-1} in CRB-65 class 0; 0.15 (0.09–0.52) ng·mL^{-1} in class 1; 0.29 (0.12–1.80) ng·mL^{-1} in class 2; 0.77 (0.22–10.17) ng·mL^{-1} in class 3; and 3.33 (0.51–9.58) ng·mL^{-1} in class 4.

Hospitalisation

The decision to hospitalise was highly associated with an increasing CRB-65 score (table 1). Accordingly, patients who were hospitalised had significantly higher levels of WBC (median (interquartile range) 12.3 (9.2–16.2) *versus* 9.0 (6.9–12.1) thousand·μL^{-1}; p<0.0001), CRP (124.0 (51.6–225.2) *versus* 35.0 (8.9–100.5) mg·L^{-1}; p<0.0001), and PCT (0.24 (0.11–1.08) *versus* 0.08 (0.06–0.12) ng·mL^{-1}; p<0.0001). Patients with prior antimicrobial treatment showed significantly lower levels of PCT (0.10 (0.06–0.18) *versus* 0.17 (0.09–0.76) ng·mL^{-1}; p<0.0001), CRP (74.0 (19.0–160.5) *versus* 97.4 (34.0–207.0) mg·L^{-1}; p<0.0001) and WBC (9.9 (7.4–13.6) *versus* 11.6 (8.6–15.4) thousand·μL^{-1}; p<0.0001) compared with those without prior antimicrobial treatment.

Prediction of death from CAP

Increasing CRB-65 scores were associated with increasing death rates (table 1). Median PCT levels on admission of nonsurvivors were significantly higher compared with those in survivors (0.88 (0.32–3.38) *versus* 0.13 (0.08–0.38) ng·mL^{-1}; p<0.0001; fig. 2a). The respective values for CRP were 132.8 (79.0–232.3) *versus* 85.4 (25.1–192.0) mg·L^{-1} (p=0.0006; fig. 2b) and for WBC 13.7 (9.1–18.8) *versus* 11.0 (8.1–14.8) thousand·μL^{-1} (p=0.0014; fig. 2c).

The accuracy of WBC, CRP, PCT and CRB-65 to predict death at 28 days according to ROC curves is provided in figure 3. The AUC (95% CI) was highest for PCT (0.80 (0.75–0.84)), which was not significantly different compared with CRB-65 score (0.79 (0.74–0.84); p=nonsignificant). However, the AUC for CRP (0.62 (0.54–0.68); p<0.01) and WBC (0.61 (0.54–0.68); p<0.01) were significantly lower compared with PCT and CRB-65 score. The combined use of CRB-65 and PCT even improved the accuracy to predict death (AUC (95% CI) for the combined model 0.83 (0.77–0.88); p<0.01 compared with CRB-65 alone).

Predictive potential of a combined use of CRB-65 and PCT

The optimal prognostic accuracy (minimal false-negative and false-positive results) for PCT to predict death was

TABLE 2 Univariable and multivariable cox proportional hazard model for various variables

Variables	Model for survival							
	Univariable				Multivariable			
	df	Chi–squared	Hazard ratio (95% CI)	p-value	df	Chi–squared	Hazard ratio (95% CI)	p-value
Log10PCT (per IQR increase)	1	66.3	2.36 (1.92–2.91)	<0.00001	1	18.0	1.79 (1.37–2.34)	<0.0001
WBC (per IQR increase)	1	15.7	1.48 (1.22–1.8)	0.00007	1	1.4	1.14 (0.92–1.43)	0.2374
CRP (per IQR increase)	1	10.1	1.58 (1.19–2.09)	0.00145	1	<0.05	1.01 (0.72–1.41)	0.9761
CRB-65	3	52.0		<0.00001	3	30.9		<0.0001
CRB-65 1/0			10.25 (2.41–43.58)				6.69 (1.56–28.65)	
CRB-65 2/0			31.56 (7.51–132.71)				18.92 (4.47–80.04)	
CRB-65 3,4/0			71.46 (15.99–319.43)				31.12 (6.79–142.59)	

df: degrees of freedom; CI: confidence interval; PCT: procalcitonin; IQR: interquartile range; WBC: leukocyte; CRP: C-reactive protein; CRB-65: confusion, respiratory rate $\geqslant$30 breaths·min^{-1}, low blood pressure (systolic value <90 mmHg or diastolic value $\leqslant$60 mmHg) and age $\geqslant$65 yrs.

0.228 ng·mL^{-1}, with a sensitivity (95% CI) of 84.3% (73.6–91.9), a specificity (95% CI) of 66.6% (64.1–69.0), a positive likelihood ratio of 2.52 and a negative likelihood ratio of 0.24. Positive and negative predictive values were 10.7 and 98.9%, respectively. Results of uni- and multivariable Cox proportional hazards regression analyses are provided in table 2. As detailed, increased PCT, WBC, CRP, and CRB-65 displayed significant hazard ratios in univariable analyses. In multivariable Cox proportional hazards regression analyses, only PCT and CRB-65 remained as independent predictors of 28-day mortality. Using the likelihood ratio Chi-squared test for nested models, PCT was shown to add significant value to CRB-65 (Chi-squared 24.05; p<0.0001).

Figure 4 shows Kaplan–Meier curves of 1,671 CAP patients who were stratified into four groups according to quartiles of PCT. In patients with increased baseline PCT levels (log-rank test p<0.0001), 28-day mortality was significantly higher.

Figure 5 shows Kaplan–Meier survival curves of low-risk patients (CRB-65 0), patients at intermediate risk (CRB-65 1–2) and high-risk patients (CRB-65 3–4), each stratified according to a PCT cutoff level of 0.228 ng·mL^{-1}. Mortality was significantly different according to PCT, with a threshold of $\leqslant$0.228 ng·mL^{-1} in all three risk groups. Patients in all three groups at risk with PCT values $\leqslant$0.228 ng·mL^{-1} had a very low risk of death from CAP.

DISCUSSION

The current study demonstrated that PCT levels on admission predict the severity and outcome of CAP with a similar prognostic accuracy as the CRB-65 score and a higher prognostic accuracy compared with WBC and CRP levels. Moreover, the additional use of PCT using a threshold of $\leqslant$0.228 ng·mL^{-1} was able to predict patients at very low risk of death within all three risk groups defined by CRB-65.

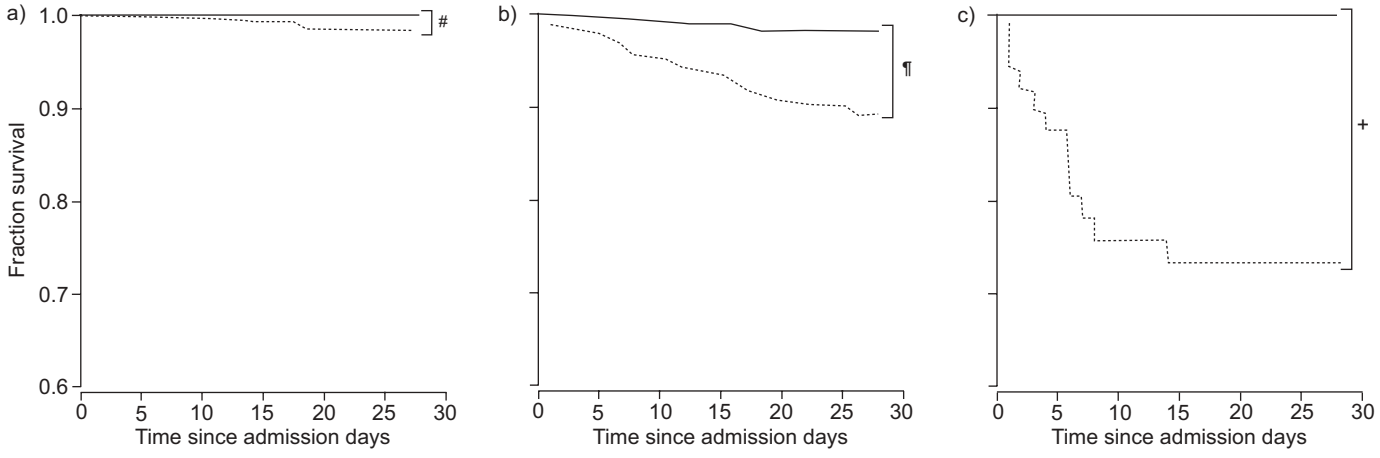

FIGURE 5. Kaplan–Meier analysis in patients classified into CRB-65 (confusion, respiratory rate $\geqslant$30 breaths·min^{-1}, low blood pressure (systolic value <90 mmHg or diastolic value $\leqslant$60 mmHg) and age $\geqslant$65 yrs) a) class 0, b) classes 1–2 and c) classes 3–4 according to procalcitonin levels below (———) and above (·····) a cutoff concentration value of 0.228 ng·mL^{-1}. #: p=0.0088; ¶: p<0.0001; +: p=0.0499.

Recent guidelines about the management of adult CAP [3–5, 8, 10] are based upon pneumonia severity assessment as the starting point of all crucial treatment decisions, such as hospitalisation, intensive care unit admission and choice of antimicrobial treatment. Different scoring systems have been developed for a more objective assessment of CAP severity. Based on the modified severity assessment score of the British Thoracic Society, the simple CURB score was developed and extensively validated [3, 5, 6]. It consists of only four variables: confusion, urea >7 mmol·L^{-1}, respiratory rate $\geqslant 30$ breaths·min^{-1}, systolic blood pressure <90 mmHg or diastolic pressure $\leqslant 60$ mmHg. One point is given for each feature present, which results in CURB scores of 0–4. In a primary care setting, blood–urea results are not directly available; therefore, the CURB score has been modified to the CRB-65 score, which includes only clinical variables. Blood urea is replaced by age $\geqslant 65$ yrs. A recent analysis of the CAPNETZ study group [11] validated the CURB, CRB and CRB-65 scores for the prediction of death from CAP in the hospital and outpatient setting. Analysis was performed for 1,343 CAP patients and overall 30-day mortality was 4.3% (0.6% in outpatients and 5.5% in hospitalised patients). CURB and CRB-65 scores provided comparable predictions for death in CAP patients. Similar data were also reported by CAPELASTEGUI *et al.* [6], who could also demonstrate the equivalence of CURB and CRB-65 compared with the pneumonia severity index proposed by FINE *et al.* [4]. Thus, the use of the simple CURB or CRB-65 scores is now advocated by European respiratory physicians [7].

Readily measurable biomarkers that reflect the severity of CAP and outcome could be helpful as additional prognostic tools. The present study confirms the findings of previous studies that PCT is a good predictor of pneumonia severity [16, 18, 19, 22]. Patients with a higher CRB-65 score had significantly higher PCT levels. In contrast, CRP and WBC were not correlated to the severity of the disease.

Compared with CRB-65, PCT had an at least comparable predictive potential for death from pneumonia within 28 days. In fact, it was even slightly superior than that of CRB-65. However, both tools do not seem to measure the same thing. When patients were grouped according to three groups at risk, PCT at a threshold of $\leqslant 0.228$ ng·mL^{-1} was able to predict survivors within all three groups. Thus, the very high negative predictive potential of PCT at this threshold for death (98.9%) might be successfully used to discriminate patients who might be safely treated as outpatients despite an increased CRB-65 score.

Interestingly, the PCT threshold found in the present study is very close to a PCT threshold of 0.25 ng·mL^{-1} found by CHRIST-CRAIN *et al.* [22, 23] which discouraged antimicrobial treatment in patients with suspected lower respiratory tract infections. Obviously, there is a subgroup of patients with CAP that exert only a minimal inflammatory response and seem to be perfectly able to cope with infection. The mechanisms behind this observation deserve further study. Of note, patients with antimicrobial pre-treatment were found to have lower PCT values.

The present study has some limitations. First, whether or not patients were treated in intermediate care units or the intensive care unit was not recordable; therefore the usefulness of procalcitonin in predicting the admission to these units could not be analysed. Secondly, the number of outpatients was limited, and the use of procalcitonin alone and in combination with CRB-65 should clearly be studied in this population. Additionally, the number of patients at high risk was also small, raising the concern whether the present observations can be expanded to this subgroup as well. Finally, since the present analysis uses the same data set to develop the predictive model and test the model, a validation in an independent patient cohort is mandatory. In contrast to the widely used inflammatory markers leukocyte count and C-reactive protein level, procalcitonin levels seem to be a valuable tool in helping clinicians to assess disease severity in community-acquired pneumonia. Most importantly, the present authors believe that the combined use of CRB-65 (confusion, respiratory rate $\geqslant 30$ breaths·min^{-1}, low blood pressure (systolic value <90 mmHg or diastolic value $\leqslant 60$ mmHg) and age $\geqslant 65$ yrs) score and procalcitonin offers important additional information to clinicians, allowing for the recognition of patients at very low risk of death despite increased CRB-65 score.

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