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

Results from the German competence network CAPNETZ

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Abstract

Aim of this study was to investigate the prognostic value of procalcitonin (PCT) compared to the established inflammatory markers C-reactive protein (CRP) and leukocyte count (WBC) alone and in combination with the CRB-65 score in patients with community acquired pneumonia (CAP).

We enrolled 1671 patients with proven CAP. PCT, CRP, WBC and CRB-65 score were determined on admission. 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 to levels in survivors. In ROC analysis for survival, the AUC for PCT and CRB-65 was comparable (0.80, 95% CI 0.75–0.84 vs. 0.79, 95% CI 0.74–0.84, n.s.), **but each** significantly higher compared to CRP (0.62, 95% CI 0.54–0.68, $p < 0.01$) and WBC (0.61, 95% CI 0.54–0.68, $p < 0.01$). **PCT indentified low risk patients across CRB-classes 0, 1 and 2 as well as 3 and 4.**

In conclusion, 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 to CRP and WBC. **PCT can independently identify patients at low risk of death within CRB-65 risk classes.**

Key words : community acquired pneumonia – CRB-65 score – C-reactive protein – leukocytes – mortality – procalcitonin – prognosis

Introduction

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-score or the CRB-65-score are currently advocated as preferred scores because of their simplicity and applicability in the ambulatory setting [7,11].

Several inflammatory markers, e.g. leucocyte counts (WBC) and C-reactive protein (CRP) 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. It rapidly increases 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 our study was to investigate the predictive value of PCT compared to the established inflammatory markers WBC and CRP and the clinical CRB-65 score. Moreover, we studied whether the combined use of CRB-65 and PCT might prove 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 (CAPNETZ, http://www.capnetz.de) [1]. The network comprises 10 local clinical centres (LCC) throughout Germany. These centres represent hospitals and physicians in private practise at all levels of health-care provision involved in therapy of CAP. 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 is obtained from every patient prior to inclusion in the network study.

Study population

Inclusion criteria are age ≥ 18 years, a new pulmonary infiltrate diagnosed by chest x-ray together with at least one clinical symptom (fever, cough, purulent sputum, focal chest signs, dyspnoea, pleuritic pain). Exclusion criteria are conditions of systemic immune deficiency, active tuberculosis or hospitalisation less than four weeks prior to infection. The decision where to treat the patient is left to the discretion of the attending physician. No attempt is made to implement standardized criteria neither for the assessment of pneumonia severity nor for the decision to hospitalize.

All patients are assessed at first presentation and during follow-up according to a standardized data sheet. After 14 days and 180 days all patients or relatives are 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 this study included October 1, 2002 to September 30, 2005. For the purpose of this study, patients who died within 28 days were regarded as non-survivors.

Microbiological investigation

The laboratory work-up 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 [20].

Determination of PCT, CRP and leukocyte count

Leukocyte count (WBC) 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 until measurement. The assay requires 50 µl of serum, EDTA or heparin plasma, has a functional assay sensitivity (defined as lowest value with an interassay CV <20%) of 0.06 ng/mL and a lower detection limit of 0.02 ng/mL. 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 ≥ 30/min, systolic blood pressure < 90 mm Hg or diastolic blood pressure ≤ 60 mmHg, and age ≥ 65 years [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 ± SD or median and interquartile range in parenthesis unless stated otherwise. Statistical analysis was performed using **R version 2.5** and Graph Pad Prism 4.0. Two group nonparametric comparisons were calculated by the Mann-Whitney U-test. For multigroup comparisons, Kruskal-Wallis one-way analysis of variance test was used. Frequency comparison was done using the χ^2-test. To compare the predictive value of WBC, CRP, CRB-65 score, PCT, and the predicted probability derived from a logistic regression model including CRB-65 and PCT we constructed Receiver-operating-characteristics (ROC) curves using MedCalc statistical software and determined the area under the curve (AUC). 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 ratio and 95% confidence interval (CI) for risk factors and significance level for χ^2 (WALD test) are given. Levels of PCT were normalized by log transformation. To test if PCT adds predictive value to CRB-65 we used the likelihood ratio χ^2 test for nested models**.** Kaplan Meier survival curves were generated to visualize the distribution of times from baseline to death, and logrank test was performed to compare the survival curves between groups. All statistical tests were 2-tailed and a p-value < 0.05 was considered statistically significant.

Results

Patients

The study population comprised 1671 patients with a mean age of 61 ± 18 years (range 18 to 98 years), and 55 % were male. 1113 patients (66.6 %) were hospitalised, 558 (33.4 %) were treated as outpatients. The causative pathogen was found in 472 patients (28.2 %) [typical bacterial infection: n= 219 (13.1%), atypical bacterial infection n= 205 (12.3%), viral infection n= 48 (2.9%) mixed infections with two or more pathogens n= 58 (3.5%)]. Patients with typical bacterial CAP showed higher PCT levels compared to patients with atypical bacterial or viral CAP. At 28 days follow-up, 125 patients (7.5 %) were lost to follow-up and 70 patients died. Thus, the mortality rate of the remaining population of 1546 patients (545 patients treated as outpatients, 1001 hospitalized patients) was 4.5 %. The mortality rates of outpatients were significantly lower than that of hospitalized patients (n = 2 (0.4%) versus n = 68 (6.8%), p <0.0001).

Pneumonia severity and mortality

A total of 1508 data sets were complete for calculation of CRB-65. The distribution of CRB-65 scores and its association with mortality in outpatients and hospitalized patients is given in table 1. Increasing severity of CAP according to CRB-65 was not associated with a pronounced gradual increase of WBC (figure 1c) or CRP values (figure 1b). Conversely, PCT levels increased significantly with increasing severity of CAP ($p < 0.0001$, figure 1a). The median (interquartile range) PCT levels were 0.10 ng/mL (0.07-0.21 ng/mL) in CRB-65 class 0, 0.15 ng/mL (0.09-0.52 ng/mL) in class 1, 0.29 ng/mL (0.12-1.80 ng/mL) in class 2, 0.77 ng/mL (0.22-10.17 ng/mL) in class 3, and 3.33 ng/mL (0.51-9.58 ng/mL) in class 4).

Table 1. Distribution of CRB-65 risk classes and associated 28 day mortality

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

Hospitalisation

The decision to hospitalize was highly associated with an increasing CRB-65 score (table 1). Accordingly, patients who were hospitalized had significantly higher levels of WBC (median (interquartile range) 12.3 (9.2-16.2) vs. 9.0 (6.9-12.1) G/L, $p < 0.0001$), CRP (124.0 (51.6-225.2) vs. 35.0 (8.9-100.5) mg/L, $p < 0.0001$), and PCT (0.24 (0.11-1.08) vs. 0.08 (0.06-0.12) ng/mL, $p < 0.0001$). Patients with prior antimicrobial treatment showed significantly lower levels of PCT (0.10 (0.06-0.18) vs. 0.17 (0.09-0.76) ng/mL, $p < 0.0001$), CRP (74.0 (19.0-160.5) vs. 97.4 (34.0-207.0) mg/L, $p < 0.0001$) and WBC (9.9 (7.4-13.6) vs. 11.6 (8.6-15.4) G/L, $p < 0.0001$) compared to 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 to those in survivors (0.88 (0.32-3.38) vs. 0.13 (0.08-0.38) ng/mL, $p < 0.0001$, figure 2a). The respective values for CRP were 132.8 (79.0-232.3) vs. 85.4 (25.1-192.0) mg/L, $p = 0.0006$ (figure 2b) and for WBC 13.7 (9.1-18.8) vs. 11.0 (8.1-14.8) G/L, $p = 0.0014$ (figure 2c).

The accuracy of WBC, CRP, PCT and CRB-65 to predict death at 28 days according to receiver operating characteristics is given in figure 3. The AUC was highest for PCT (0.80, 95% CI 0.75 to 0.84), which was not significantly different compared to CRB-65 score (0.79,

95% CI 0.74 to 0.84, n.s.). However, the AUC for CRP (0.62, 95% CI 0.54 to 0.68, $p < 0.01$) and WBC (0.61, 95% CI 0.54 to 0.68, $p < 0.01$) were significantly lower compared to PCT and CRB-65 score. The combined use of CRB-65 and PCT even improved the accuracy to predict death (AUC for the combined model 0.83, 95% CI 0.77 to 0.88, $p < 0.01$ compared to 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 0.228 ng/mL with a sensitivity of 84.3 % (95% CI 73.6% to 91.9%), a specificity of 66.6 % (95% CI 64.1% to 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 analysis are given in Table 2. As detailed, in univariable analyses increased PCT, WBC, CRP, and CRB-65 displayed significant hazard ratios. In multivariable Cox proportional-hazards regression analyses, only PCT and CRB-65 remained as independent predictors of 28-days mortality. Using the likelihood ratio χ^2 test for nested models, PCT was shown to add significant value to CRB-65 (χ^2 24.05; p<0.0001).**

Table 2. Univariable and Multivariable Cox Proportional Hazard Model for Various Variables.

	Univariable Model for Survival				Multivariable Model for Survival			
Variables	**d. f.**	**Chi square**	**Hazard Ratio (95% CI)**	**p**	**d. f.**	**Chi square**	**Hazard Ratio (95% CI)**	**p**
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 (CRB-65 1: CRB-65 0)			10.25 (2.41-43.58)				6.69 (1.56-28.65)	
CRB-65 (CRB-65 2 : CRB-65 0)			31.56 (7.51-132.71)				18.92 (4.47-80.04)	
CRB-65 (CRB-65 3,4 : CRB-65 0)			71.46 (15.99-319.43)				31.12 (6.79-142.59)	

IQR = interquartile range; d. f. = degrees of freedom

Figure 4 shows Kaplan-Meyer curves of 1671 CAP patients who were stratified into 4 groups according to quartiles of PCT. 28-days mortality was significantly higher in patients with increased baseline PCT levels (Logrank Test p<0.0001).

Figure 5 shows Kaplan Meier survival curves of low risk patients (CRB-65 0), patients at intermediate risk (CRB 1-2) and high risk patients (CRB-65 3-4), each stratified according to a PCT cut-off level of 0.228 ng/mL. Mortality was significantly different according to PCT with a threshold of ≤ 0.228 ng/mL in all three risk groups. Patients in all three groups at risk with PCT values ≤ 0.228 ng/mL 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 to WBC and CRP. Moreover, the additional use of PCT using a threshold of ≤ 0.228 ng/mL was able to predict patients at very low risk of death within all three risk groups defined by CRB-65.

Recent guidelines about the management of adult CAP are build up upon pneumonia severity assessment as the starting point of all crucial treatment decisions such as hospitalisation, ICU admission and choice of antimicrobial treatment [3-5,8,10]. 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 > 7mmol/l, Respiratory rate ≥ 30/min, systolic blood pressure < 90 mm Hg or diastolic pressure ≤ 60 mmHg. One point is given for each feature present which results in CURB scores 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 that includes only clinical variables. Blood urea is replaced by age ≥ 65 years. A recent analysis of the CAPNETZ study group validated the CURB, CRB and CRB-65 scores for the prediction of death from CAP in the hospital and outpatient setting [11]. Analysis was done for 1343 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 who could also demonstrate the equivalence of CURB and CRB-65 compared to the pneumonia severity index (PSI) proposed by Fine [4,6]. 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. Our study confirms the findings of previous studies that PCT is a good predictor of pneumonia severity [16,18,19,21]. 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 to 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 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 ≤ 0.228 ng/mL 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 our study is very close to a PCT threshold of 0.25 ng/mL found by Christ-Crain et al. which allowed to discourage antimicrobial treatment in patients with suspected lower respiratory tract infections [22,23]. Obviously, there is a subgroup of patients with CAP which exerts an only minimal inflammatory response and seems to be perfectly able to cope with their infection. The mechanisms behind this observation deserve further study. Of note, patients with antimicrobial pretreatment were found to have lower PCT values.

The present study has some limitations. Firstly, we were unable to record which patients were treated in intermediate care units and the ICU. We therefore could not analyze the usefulness of PCT in predicting the admission to these units. Secondly, the number of outpatients was limited, and the use of PCT and in combination with CRB-65 clearly should be studied in this population. **Also** the number of patients at high risk was also small, raising the concern whether our observations can be expanded to this subgroup as well. Finally, since our analysis uses the same dataset to develop the predictive model and test the model, a validation in an independent patient cohort is mandatory**.** In contrast to the widespread used inflammatory markers WBC and CRP, PCT seems to be a valuable tool helping clinicians to assess disease severity in CAP. Most importantly, we think that the combined use of CRB-65

and PCT offers an important additional information to clinicians, allowing for the recognition of patients at very low risk of death despite increased CRB-65 score.

Contributors

Stefan Krüger helped planning the study, performed data processing and interpretation and wrote the manuscript. Norbert Suttorp, Reinhard Marre and Tobias Welte organized CAPNETZ and data processing, planned the study and helped with the manuscript. Santiago Ewig helped with data interpretation and with the manuscript. Jana Papassotiriou helped planning the study, performed data processing and interpretation and helped with the manuscript. Klaus Richter was involved in planning the study and statistical analysis. Heike von Baum organised microbiological work in the central study unit.

Conflict of interest

Jana Papassotiriou is employee of BRAHMS AG, the manufacturer of the assay B.R.A.H.M.S PCT sensitive KRYPTOR, B.R.A.H.M.S AG, Henningsdorf, Germany.

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[1] Markus Becker, Antje Kuhnke, Hartmut Lode, Malina Schmidt-Ioanas, Norbert Suttorp, (Berlin), Torsten Bauer, Santiago Ewig, Barbara Schlosser (Bochum), Matthias Pletz, Tobias Welte (Hannover), Klaus Dalhoff, Sven Pischke, Niels Schübel (Lübeck), Ingrid Huntemann, Joachim Lorenz (Lüdenscheid), Thomas Klante (Magdeburg), Tom Schaberg, Konstanze Voigt (Rotenburg), Stefan Krüger, Christian Schumann (Ulm), Berthold Jany, Uwe Ziegler (Würzburg), Torsten Illmann, Michael Wallner, Michael Weber (IT), Heike von Baum, Susanne Gonschior, Klaus Richter (main office) and all study nurses.

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Figures

Figure 1: Admission levels of PCT (a), CRP (b), WBC (c) in CAP patients classified into CRB-65 classes 0-4. Solid lines denote median values, boxes represent 25th to 75th percentiles and whiskers indicate the range.

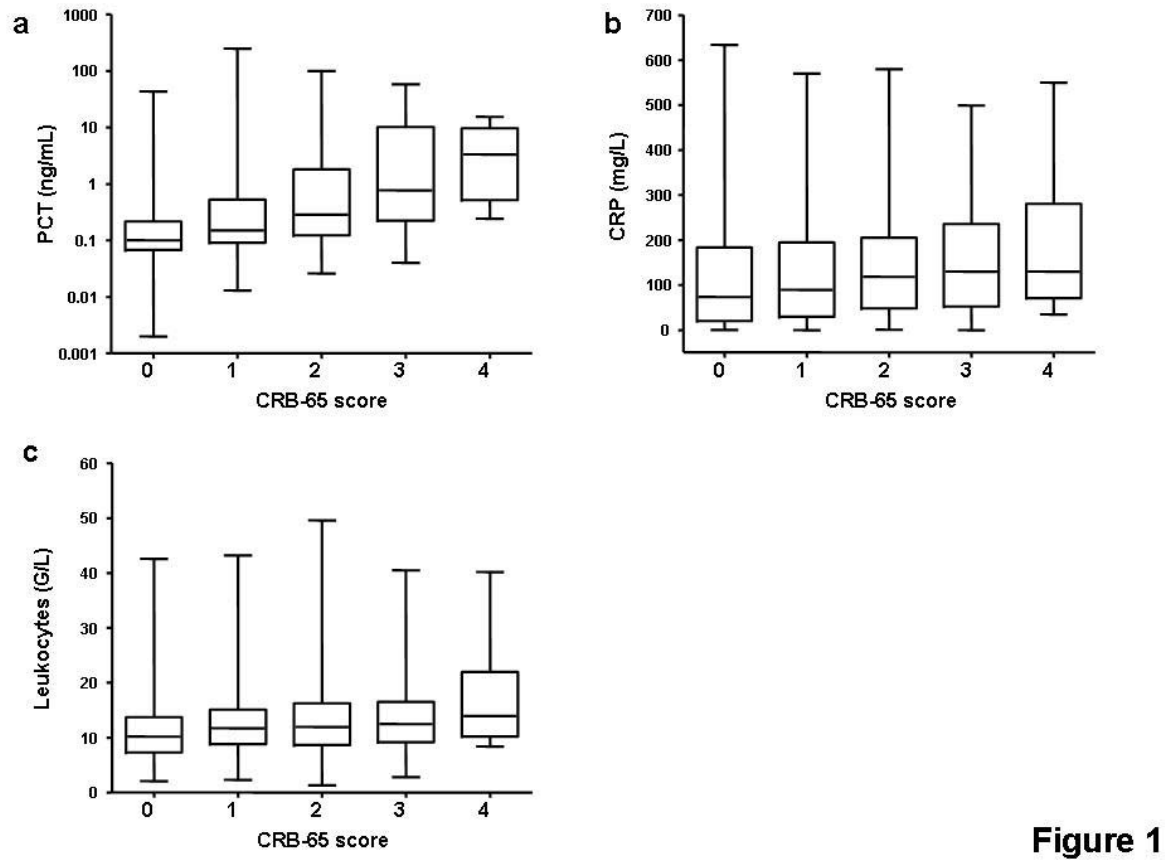

Figure 1

Figure 2: Box plots of admission levels of PCT (a), CRP (b), WBC (c) in CAP patients who survived and who died. Solid lines denote median values, boxes represent 25th to 75th percentiles and whiskers indicate the range.

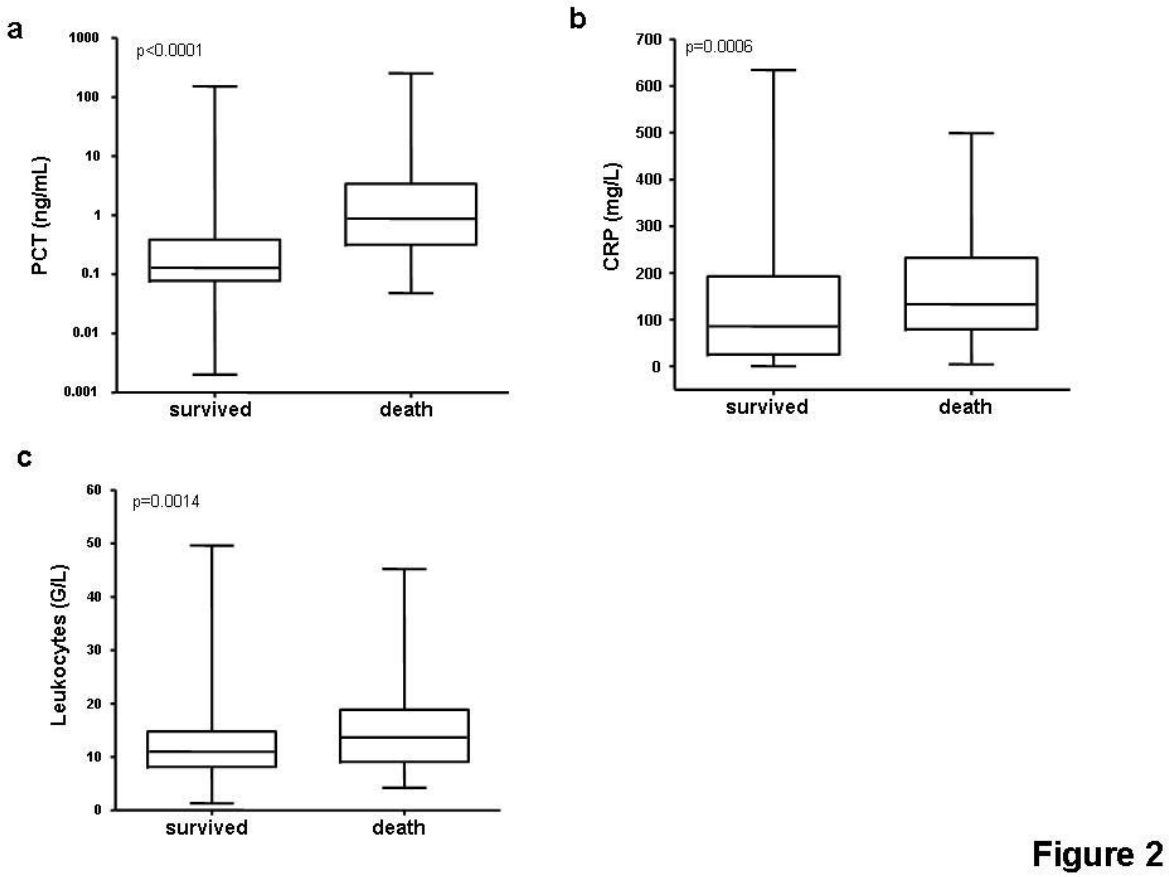

Figure 3: ROC curves comparing WBC (leucocytes), CRP, PCT, CRB-65 score, and the combined predicted probabilities from a binary logistic model including PCT and CRB-65 with respect to prediction of death at 28 days follow-up.

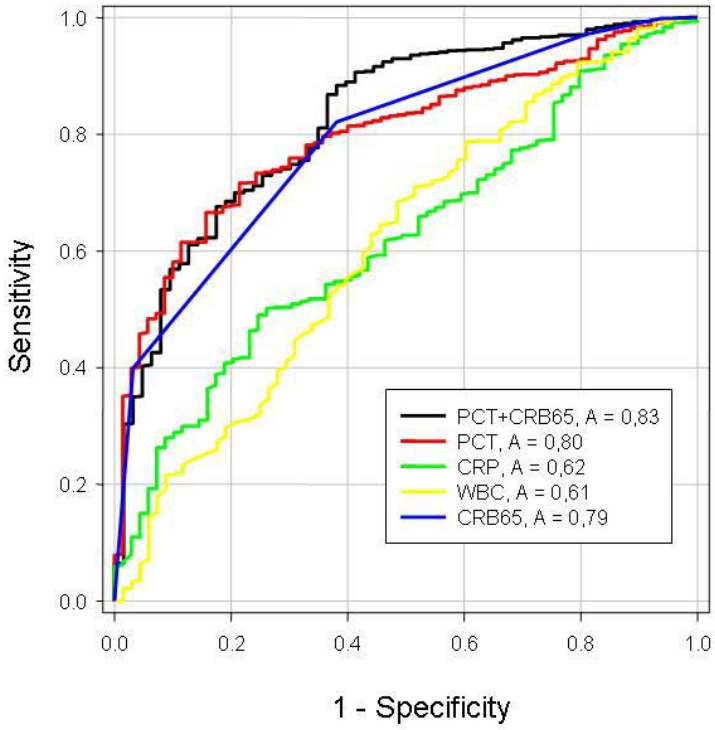

Figure 3

Figure 4: Kaplan-Meyer curves for 28-days mortality: patients grouped according to quartiles of serum PCT.

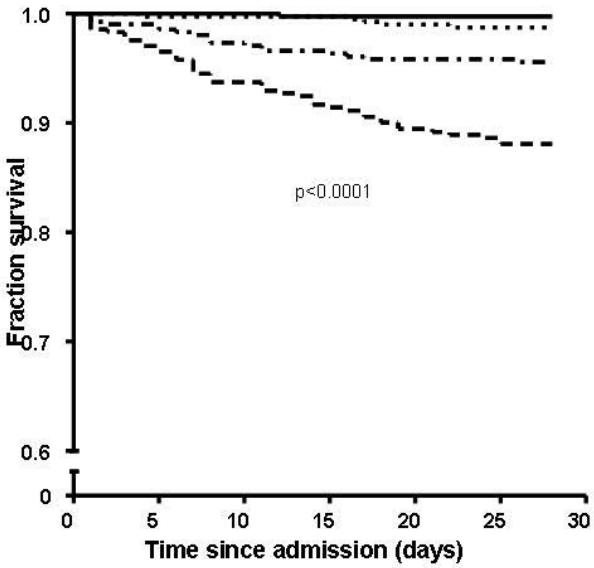

Figure 4

Figure 5: Kaplan-Meyer analysis in patients classified into CRB-65 class 0 (a), CRB-65 classes 1-2 (b) and CRB-65 classes 3-4 (c) according to PCT levels below (solid lines) and above (dotted lines) a cut-off concentration of 0.228 ng/mL.

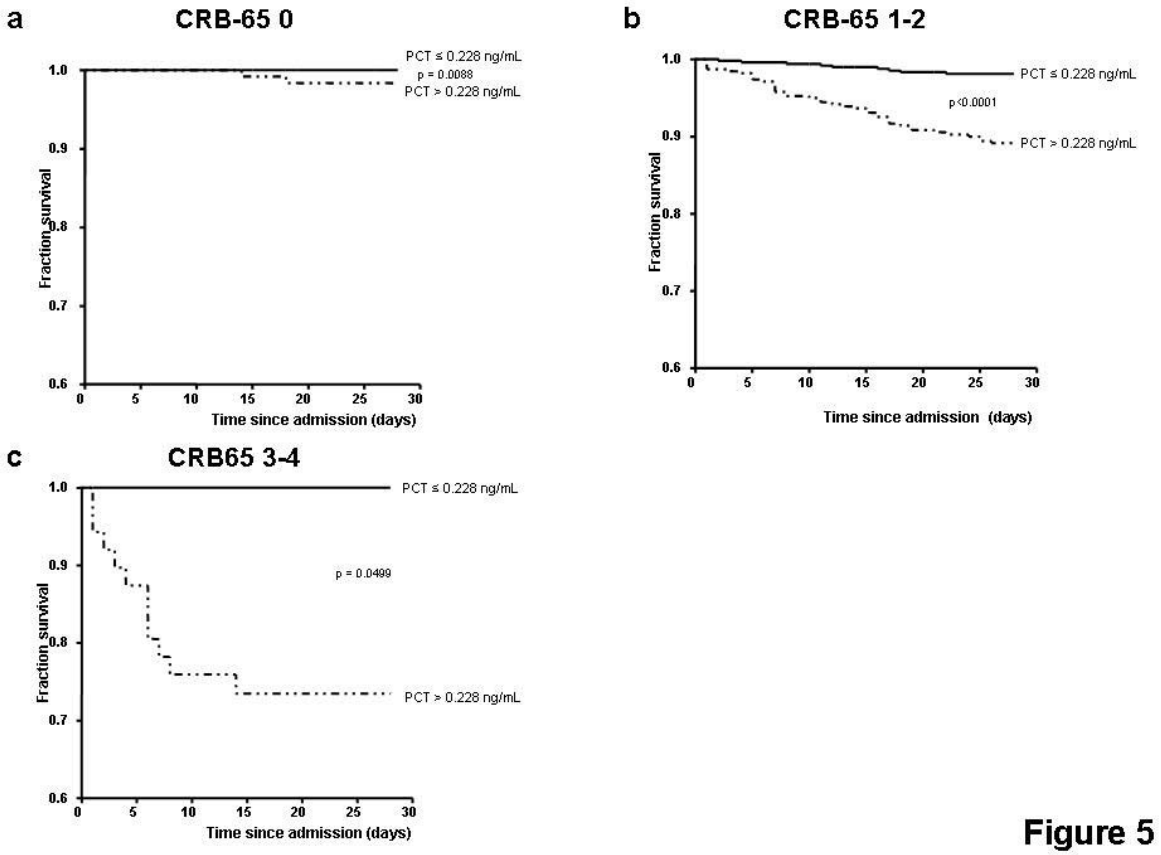
a
CRB-65 0
PCT ≤ 0.228 ng/mL
p = 0.0088
PCT > 0.228 ng/mL
Fraction survival
Time since admission (days)
b
CRB-65 1-2
PCT ≤ 0.228 ng/mL
p<0.0001
PCT > 0.228 ng/mL
Fraction survival
Time since admission (days)
c
CRB65 3-4
PCT ≤ 0.228 ng/mL
p = 0.0499
PCT > 0.228 ng/mL
Fraction survival
Time since admission (days)

Figure 5