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Utility of procalcitonin, C-reactive protein and white blood cells alone and in combination for the prediction of clinical outcomes in community-acquired pneumonia

Abstract

Background: The added value of biomarkers, such as procalcitonin (PCT), C-reactive protein (CRP), and white blood cells (WBC), as adjuncts to clinical risk scores for predicting the outcome of patients with community-acquired pneumonia (CAP) is in question. We investigated the prognostic accuracy of initial and follow-up levels of inflammatory biomarkers in predicting death and adverse clinical outcomes in a large and well-defined cohort of CAP patients.
Methods: We measured PCT, CRP and WBC on days 1, 3, 5, and 7 and followed the patients over 30 days. We applied multivariate regression models and area under the curve (AUC) to investigate associations between these biomarkers, the clinical risk score CURB-65, and clinical outcomes [i.e., death and intensive care unit (ICU) admission].
Results: Of 925 patients with CAP, 50 patients died and 118 patients had an adverse clinical outcome. None of the initial biomarker levels significantly improved the CURB-65 score for mortality prediction. Follow-up biomarker levels showed significant independent association with mortality at days 3, 5, and 7 and with improvements in AUC. Initial PCT and CRP levels were independent prognostic predictors of adverse clinical outcome, and levels of all biomarkers during the course of disease provided additional prognostic information.
Conclusions: This study provides robust insights into the added prognostic value of inflammatory markers in CAP. Procalcitonin, CRP, and to a lesser degree WBC provided some prognostic information on CAP outcomes, particularly when considering their kinetics at days 5 and 7 and when looking at adverse clinical outcomes instead of mortality alone.

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Introduction

Community-acquired pneumonia (CAP) continues to be a worldwide health problem, particularly as a leading source of infections with high mortality [1]. The incidence of CAP in Europe ranges from 1.2 to 11.6 cases per 1000 population per year [2] with rates of hospitalization ranging from 40% to 60% [3]. Although the elderly and patients with comorbidities have a 10-fold higher risk for CAP, sporadic viral pneumonia can sometimes be fatal in over 50% of younger patients 10–39 years of age [4, 5].

Diagnosis, severity assessment, and prediction of outcome in patients with CAP are challenging and often based on clinical experience, and not on scientific evidence. Clinical severity scores, such as the pneumonia severity index (PSI), the 'confusion, urea, respiratory, and blood pressure' (CURB) score, and its modification the CURB-65 (CURB plus age >65), may provide a more

objective initial severity assessment for mortality prediction and are thus recommended by guidelines [6]. However, these scores have important limitations, such as only moderate prognostic accuracy, validation only for mortality but not for other adverse clinical outcomes, and lack of inclusion of novel biomarkers reflecting the inflammatory response and/or infection severity. Several smaller studies have suggested that the addition of biomarkers, such as C-reactive protein (CRP) [7] and procalcitonin (PCT) [8] may further improve these scores. However, most previous studies had small sample sizes and/or were limited to measurement of biomarkers only once upon admission.

The aim of the current analysis was to take advantage of a large multicenter cohort to investigate the prognostic value of levels of these biomarkers and white blood cells (WBC) both at admission and during follow-up as adjuncts to the CURB65 score for prediction of mortality and adverse clinical outcomes.

Materials and methods

Setting and study population

The present study analyzed data from the procalcitonin guided antibiotic therapy and hospitalization in patients with lower respiratory tract infections (ProHOSP) study using 925 patients with radiologically confirmed CAP. A detailed description of this study has been published elsewhere [9, 10] and is also available in the clinicaltrials.gov database (NCT00350987). Full ethical approval for this trial was obtained from all Local Ethical Committees, and all patients gave written informed consent.

In brief, patients with lower respiratory tract infections (LRTI) including CAP admitted to emergency departments at 1 out of 6 hospitals in Switzerland between December 2006 and March 2008 were consecutively included. A study website provided information on the evidence-based management of all patients based on the most recent guidelines [6, 11]. For all patients with CAP, the study protocol explicitly specified the need for X-ray confirmation and for collection of two sets of pre-treatment blood cultures. Thus, two pairs of blood cultures for both aerobic and anaerobic conditions were collected and processed using an automated colorimetric detection system (BacT/ALERT, bioMerieux, Durham, NC, USA) in three hospitals and an equivalent blood culture system (BACTEC Becton-Dickinson, Cockeysville, MD, USA) in the other three hospitals [12]. If blood culture bottles indicated bacterial growth, samples were Gram stained and subcultured. The correct identification of the pathogen was achieved according to routine laboratory procedures. There was no recommendation for or against viral testing as the main trial focus was on bacterial CAP.

Inclusion criteria for patients were: written informed consent, age ≥18 years, and admission from the community or a nursing home with the main diagnosis of CAP. Exclusion criteria were the inability to provide written informed consent, insufficient German language

skills, active intravenous drug use, previous hospitalization within 14 days, severe immunosuppression other than that induced by corticosteroids, accompanying chronic infection or endocarditis, and severe medical co-morbidity where death was imminent. Diagnosis of CAP required the presence of at least one respiratory symptom (cough with or without sputum production, dyspnea, tachypnea, or pleuritic chest pain) in addition to one auscultatory finding or sign of infection (core body temperature >38.0 °C, shivers, or white blood count >10 g/L or <4 g/L cells) and a new infiltrate on chest radiograph [6].

In all patients, baseline assessments included collection of clinical data and vital signs, confirmation of the presence or absence of comorbid conditions, and a routine blood test. Patients were followed during the hospital stay and blood specimens were sampled for PCT, CRP, and WBCs upon hospital admission, on days 3, 5 and 7, and on the day of discharge. Serum PCT was measured with a highly sensitive time-resolved amplified cryptate emission (TRACE) technology assay (PCT Kryptor, B.R.A.H.M.S. AG, Hennigsdorf, Germany). The assay has a detection limit of 0.02 μg/L and a functional assay sensitivity of 0.06 μg/L (i.e., 3- to 10-fold above normal mean values). Serum CRP concentrations were determined by an enzyme immunoassay having a detection limit of <5 mg/dL (EMIT, Merck Diagnostica, Zurich, Switzerland). The CURB-65 score was calculated at admission in all patients as recommended [13, 14].

We performed blinded telephone interviews with all patients 30 days after inclusion for assessment of vital status and other secondary endpoints.

Statistical considerations and analysis

The primary endpoint of this analysis was all-cause mortality within 30 days. Secondary endpoints included serious adverse events defined as death or intensive care unit (ICU) admission.

Discrete variables are expressed as counts (percentage) and continuous variables as medians and interquartile ranges (IQR). Frequency comparison was done using the χ^2-test. The two-group comparison for continuous data was done with the Mann-Whitney U-test. We used univariate and multivariate logistic regression analysis to study the association between biomarker levels and outcome adjusting the models for the CAP severity score CURB-65 [15]. Area under the receiver-operating-characteristics curve (AUC) was calculated to assess overall discrimination using STATA 9.2 (Stata Corp, College Station, TX, USA). All statistical tests were two-tailed and p-values <0.05 were considered to indicate statistical significance.

Results

This analysis includes 925 patients with a final diagnosis of CAP. The median age was 73 years and most patients suffered from at least one comorbidity including chronic heart failure (17%), cerebrovascular disease (9%), diabetes (17%), and chronic renal failure (23%). Risk assessment on admission showed that 50.4% of patients were in the high-risk CURB-65 category with scores of ≥2 points. At the 30-day follow-up, 118 patients had a serious

adverse event defined as mortality (35 patients, 3.8%), ICU admission (68 patients, 7.4%) or both (15 patients, 1.6%). Table 1 shows pertinent patient characteristics of the overall cohort and categorized by survival status. Admission PCT levels were significantly higher in non-survivors as compared to survivors [0.83 ng/L (IQR 0.30–5.66) vs. 0.46 (IQR 0.15–2.61); p=0.023]. There was no difference between these two groups with regard to admission CRP and WBC levels.

We used univariate and multivariate logistic regression models to investigate associations between admission and follow-up biomarker levels and outcome (Table 2). In univariate analysis, admission PCT levels were significant predictors of 30-day mortality on admission [unadjusted odds ratio (OR) per unit increase of log transformed PCT 1.19 (95% CI 1.03–1.38); AUC 0.60]. However, this association was no longer significant after adjustment for the CURB-65 score. No significant association of admission CRP levels [unadjusted OR 1.01 (95% 0.77–1.33); AUC 0.45] or WBC counts [unadjusted OR 1.01 (95% 0.56–1.86); AUC 0.52] with outcome was found.

Consideration of follow-up biomarker levels and kinetics of the biomarkers from admission through days 3, 5, and 7 revealed all biomarkers as having a better association with outcome compared to initial levels alone (Table 2). The AUC of PCT was 0.61, 0.68, and 0.73 at days 3, 5 and 7, respectively, while the differences in AUC between admission and these three time points were 0.69, 0.65, and 0.71, respectively. The corresponding results for CRP were 0.62, 0.68, and 0.78 for days 3, 5 and 7, and 0.50, 0.44, and 0.62 for the differences, respectively. For WBC, the AUC values were 0.67, 0.65, and 0.77 on days 3, 5, and 7, respectively, while the respective differences were 0.67, 0.58, and 0.79.

Table 3 shows the results of a similar analysis for serious adverse events. In this case, the prognostic potential for all biomarkers was better compared to survival prediction and was also significant after adjusting for the CURB-65 score.

Table 1 Baseline characteristics of the study participants (n=925).

	All patients (925)	Survivors (875)	Non-survivors (50)	p-Value
Demographic characteristics				
Age, years	73 (59–82)	72 (57–82)	81 (75–85)	<0.0001
Sex (men), n (%)	544 (58.8)	511 (58.4)	33 (66.0)	0.28
Coexisting illnesses, n (%)				
Chronic heart failure	159 (17.2)	143 (16.3)	16 (32.0)	0.0043
Cerebrovascular disease	82 (8.9)	77 (8.8)	5 (10.0)	0.7718
Renal dysfunction	206 (22.3)	177 (20.2)	29 (58.0)	<0.0001
Neoplastic disease	118 (12.8)	107 (12.2)	11 (22.0)	<0.05
Diabetes	162 (17.5)	152 (17.4)	10 (20.0)	0.63
Complains, n (%)				
Cough	762 (82.4)	721 (82.4)	41 (82.0)	0.14
Sputum production	437 (47.2)	409 (46.7)	28 (56.0)	0.08
Dyspnea	696 (75.2)	654 (74.7)	42 (84.0)	0.0006
Fever	618 (66.8)	595 (68.0)	23 (46.0)	0.001
Chills	301 (32.5)	291 (33.3)	10 (20.0)	0.079
Clinical findings				
Confusion, n (%)	74 (8.0)	64 (7.3)	10 (20.0)	0.003
Respiratory rate, breaths/min	20 (16–25)	20 (16–25)	24 (19–30)	0.02
Systolic blood pressure, mmHg	132 (119–148)	132 (120–149)	120 (100–140)	<0.01
Heart rate, beats/min	95 (82–108)	95 (82–108)	98 (75–108)	0.35
Body temperature, °C	38.1 (37.2–38.9)	38.1 (37.3–38.9)	37.4 (36.7–38.6)	<0.01
Rales, n (%)	894 (96.6)	599 (68.5)	37 (74.0)	0.24
Laboratory findings				
Procalcitonin (PCT), ng/L	0.46 (0.15–2.66)	0.46 (0.15–2.61)	0.83 (0.30–5.66)	0.023
C-reactive protein, mg/dL	155 (75–252)	155.5 (74.4–252)	153 (75–258)	1.0
White blood cells, WBC	12 (9–16.4)	12 (9–16.4)	12.2 (9.5–16.9)	0.72
CURB-65 scores				
0–1	459 (49.6)	450 (51.4)	9 (18.0)	<0.001
2	306 (33.1)	284 (32.5)	22 (44.0)	0.092
3–4	160 (17.3)	141 (16.1)	19 (38.0)	<0.001

CURB-65, confusion, urea, respiratory, blood pressure, age 65 years or older.

Table 2 Association of biomarker levels and survival.

					Mortality
	Unadjusted OR (95%)	p-Value[a]	AUC	Adjusted OR (95% CI)[b]	p-Value[a]
Laboratory findings					
PCT (per 10-fold increase)					
Day 1	1.19 (1.03–1.38)	0.019	0.595	1.06 (0.90–1.25)	0.439
Day 3	1.26 (1.03–1.54)	0.023	0.609	1.14 (0.92–1.41)	0.222
Day 5	1.40 (1.08–1.80)	0.009	0.680	1.30 (0.99–1.71)	0.056
Day 7	1.69 (1.27–2.24)	<0.001	0.733	1.67 (1.25–2.23)	0.001
Difference in PCT level from admission					
Day 3	1.35 (1.06–1.71)	0.013	0.688	1.31 (1.03–1.67)	0.030
Day 5	1.23 (0.91–1.66)	0.178	0.649	1.22 (0.90–1.66)	0.204
Day 7	1.43 (1.02–2.00)	0.038	0.707	1.42 (1.00–2.00)	0.044
CRP					
Day 1	1.01 (0.77–1.33)	0.933	0.450	0.99 (0.75–1.30)	0.933
Day 3	1.51 (0.94–2.43)	0.090	0.621	1.40 (0.86–2.27)	0.171
Day 5	1.95 (1.20–3.15)	0.007	0.680	1.92 (1.15–3.19)	0.013
Day 7	3.31 (1.79–6.12)	<0.001	0.780	3.46 (1.82–6.56)	<0.001
Difference in CRP level from admission					
Day 3	1.00 (0.67–1.49)	0.995	0.503	1.02 (0.68–1.52)	0.939
Day 5	0.84 (0.48–1.46)	0.530	0.438	0.85 (0.48–1.52)	0.585
Day 7	1.61 (0.66–3.94)	0.297	0.622	1.38 (0.52–3.65)	0.513
WBC					
Day 1	1.01 (0.56–1.86)	0.954	0.515	0.98 (0.54–1.80)	0.971
Day 3	2.80 (1.56–5.05)	0.001	0.665	2.65 (1.14–2.82)	0.002
Day 5	3.17 (1.51–6.67)	0.002	0.653	2.89 (1.29–6.48)	0.010
Day 7	8.43 (2.50–28.37)	0.001	0.773	8.12 (2.42–27.25)	0.001
Difference in WBC level from admission					
Day 3	1.56 (0.94–2.58)	0.083	0.672	1.73 (0.98–3.04)	0.059
Day 5	1.28 (0.75–2.19)	0.371	0.579	1.27 (0.73–2.19)	0.397
Day 7	3.88 (1.23–12.23)	0.020	0.794	3.74 (1.21–11.61)	0.022

AUC, area under the curve; CRP, C-reactive protein; OR, odds ratio; PCT, procalcitonin; WBC, white blood cells. [a]p-Values are derived from the χ^2-test; [b]Adjusted for CURB-65.

Finally, we also investigated the potential of the different markers assayed on admission and during follow-up to improve prognostication performed using the clinical CURB-65 score alone. This was done by using multivariate logistic regression models to compare the AUC of the CURB-65 score alone with the AUC of the CURB-65 score in combination with levels of each biomarker individually and all together (Table 4). When looking at levels of these biomarkers at admission, PCT, CRP, and the combination of all biomarkers together improved the AUC of the CURB-65 score for prediction of adverse clinical outcome (from AUC 0.68 to 0.74). The same was not applicable for mortality prediction, where no significant improvements in AUC based on admission biomarker levels could be observed. Examination of improvements in AUC based on follow-up biomarker levels revealed the most significant improvements to have occurred on days 5 and 7 for both survival prediction and adverse clinical outcome.

Discussion

The added value of prognostic information derived from inflammatory biomarkers in addition to established clinical scores remains a topic of debate, with multiple smaller studies providing somewhat heterogeneous results. Viewed in this context, the findings of our study conducted in a large and well-characterized CAP cohort are important and provide information on the value not only of initial but also of follow-up biomarker levels. The main findings of this study are three-fold. First, initial biomarker levels provide only limited information to assist with mortality prediction and do not improve prognostic capacity of the CURB-65 score. Second, considering the kinetics of the markers, PCT, CRP and to a lesser degree WBC provide additional prognostic information for mortality risk prediction. Third, all biomarkers combined and added to the CURB-65 score improve the ability to identify patients at risk for adverse clinical outcomes when

Table 3 Association of biomarker levels and adverse clinical outcomes.

				Death and ICU admission	
	Odds ratio (95%)	p-Value[a]	AUC	Adjusted OR	Adjusted p-Value
Laboratory findings					
PCT					
Day 1	1.34 (1.21–1.49)	<0.001	0.655	1.25 (1.12–1.40)	<0.001
Day 3	1.44 (1.27–1.64)	<0.001	0.674	1.37 (1.20–1.57)	<0.001
Day 5	1.64 (1.41–1.92)	<0.001	0.711	1.57 (1.34–1.84)	<0.001
Day 7	1.72 (1.44–2.05)	<0.001	0.695	1.67 (1.40–2.00)	<0.001
Difference in PCT level from admission					
Day 3	1.37 (1.16–1.62)	<0.001	0.693	1.34 (1.13–1.59)	0.001
Day 5	1.60 (1.25–2.06)	<0.001	0.782	1.59 (1.24–2.05)	<0.001
Day 7	1.56 (1.21–2.03)	0.001	0.764	1.56 (1.20–2.03)	0.001
CRP					
Day 1	1.61 (1.27–2.04)	<0.001	0.638	1.59 (1.26–2.02)	<0.001
Day 3	1.97 (1.44–2.70)	<0.001	0.663	1.90 (1.39–2.62)	<0.001
Day 5	2.05 (1.53–2.74)	<0.001	0.679	2.03 (1.50–2.75)	<0.001
Day 7	1.76 (1.36–2.28)	<0.001	0.661	1.75 (1.35–2.28)	<0.001
Difference in CRP level from admission					
Day 3	1.14 (0.83–1.57)	0.423	0.544	1.16 (0.83–1.60)	0.385
Day 5	1.19 (0.74–1.91)	0.467	0.561	1.22 (0.75–1.97)	0.420
Day 7	1.30 (0.65–2.61)	0.463	0.557	1.21 (0.59–2.49)	0.606
WBC					
Day 1	0.86 (0.57–1.29)	0.461	0.494	0.83 (0.55–1.25)	0.376
Day 3	2.27 (1.48–3.49)	<0.001	0.630	2.19 (1.40–3.41)	0.001
Day 5	4.18 (2.35–7.39)	<0.001	0.709	4.21 (2.32–7.65)	<0.001
Day 7	5.49 (2.72–11.10)	<0.001	0.701	5.42 (2.66–11.03)	<0.001
Difference in WBC level from admission					
Day 3	1.28 (0.90–1.82)	0.164	0.590	1.38 (0.93–2.03)	0.106
Day 5	1.39 (1.00–1.94)	0.049	0.623	1.42 (1.01–2.00)	0.047
Day 7	1.51 (0.99–2.31)	0.054	0.633	1.50 (0.98–2.29)	0.064

Adjusted OR, odds ratio adjusted for CURB-65; Adjusted p-Value, p-Value adjusted for CURB-65; AUC, area under the curve; CRP, C-reactive protein; ICU, intensive care unit; PCT, procalcitonin; WBC, white blood cells. [a]p-Values are derived from the χ^2-test.

compared with the CURB-65 score alone, both on admission and to a greater extent if the kinetics of these biomarkers over time are also considered.

Respiratory infection management guidelines recommend stratifying patients with CAP based on the predicted risk of mortality using risk scores, such as the CURB-65 [13, 15, 16]. However, clinical risk scores are somewhat limited in their practicality in routine clinical practice and carry the risk of miscalibration due to different patient populations and therefore have only moderate operational utility [17]. As a consequence, there is heightened interest in the development of additional prognostication parameters based on newly identified biomarkers that are objectively and rapidly measurable, responsive to clinical recovery, and add relevant, reliable, and real-time information [18–20]. Different studies have evaluated the prognostic potential of PCT in patients with CAP [20–25]. Some of these studies have found that PCT levels only have moderate prognostic accuracy with regard to prediction

of mortality. In a large study from the US, most of the benefit of adding PCT levels to existing prediction rules was found in patients with high risk as assessed using a clinical severity score (the PSI) [23]. A low PCT level (<0.1 mg/L) almost always excluded mortality in high-risk patients. A previous Swiss study using the ProHOSP patient cohort showed that simply measuring the initial PCT level did not improve clinical score for mortality but that following the kinetics of PCT did so, with falling levels demonstrating improved clinical outcomes during follow-up [26]. The same study found that PCT can better predict serious events, such as ICU admission and complications of CAP (e.g., empyema). As a predictor of these outcomes, PCT could significantly improve clinical risk scores such as the PSI and CURB-65, a finding that was confirmed by our results. A study of low-risk CAP patients showed PCT to be a good predictor of mortality and to also significantly improve clinical risk scores [21]. The current report further extends the findings of these studies by also comparing

Table 4 Prognostic value of the CURB-65 score alone and in combination with biomarker levels.

Biomarkers		Mortality	Adverse clinical outcomes
	n total	AUC (95% CI)	AUC (95% CI)
Day 1			
CURB-65	917	0.72 (0.66–0.78)	0.68 (0.64–0.73)
CURB-65+PCT	917	0.73 (0.67–0.79)	0.71 (0.66–0.76)
CURB-65+CRP	917	0.72 (0.66–0.78)	0.73 (0.68–0.78)
CURB-65+WBC	917	0.73 (0.67–0.79)	0.68 (0.63–0.73)
All	917	0.73 (0.67–0.79)	0.74 (0.69–0.78)
Day 3			
CURB-65+PCT	644	0.74 (0.66–0.83)	0.71 (0.65–0.77)
CURB-65+CRP	644	0.74 (0.65–0.83)	0.73 (0.67–0.80)
CURB-65+WBC	644	0.76 (0.69–0.84)	0.68 (0.62–0.74)
All	644	0.76 (0.68–0.84)	0.75 (0.69–0.81)
Day 5			
CURB-65+PCT	464	0.71 (0.62–0.81)	0.75 (0.70–0.81)
CURB-65+CRP	464	0.71 (0.60–0.83)	0.76 (0.69–0.82)
CURB-65+WBC	464	0.69 (0.58–0.80)	0.74 (0.68–0.80)
All	464	0.73 (0.63–0.83)	0.79 (0.74–0.84)
Day 7			
CURB-65+PCT	371	0.77 (0.65–0.89)	0.71 (0.64–0.78)
CURB-65+CRP	371	0.82 (0.72–0.92)	0.68 (0.61–0.76)
CURB-65+WBC	371	0.74 (0.62–0.86)	0.72 (0.66–0.79)
All	371	0.85 (0.80–0.93)	0.75 (0.68–0.81)
Difference day 1–3			
CURB-65+PCT	640	0.68 (0.58–0.78)	0.54 (0.47–0.62)
CURB-65+CRP	640	0.63 (0.53–0.72)	0.52 (0.46–0.59)
CURB-65+WBC	640	0.70 (0.59–0.81)	0.69 (0.62–0.75)
All	640	0.78 (0.71–0.85)	0.70 (0.63–0.76)
Difference day 1–5			
CURB-65+PCT	461	0.65 (0.50–0.79)	0.55 (0.47–0.64)
CURB-65+CRP	461	0.72 (0.60–0.85)	0.60 (0.53–0.68)
CURB-65+WBC	461	0.61 (0.49–0.74)	0.71 (0.64–0.77)
All	461	0.70 (0.59–0.80)	0.74 (0.68–0.80)
Difference day 1–7			
CURB-65+PCT	369	0.62 (0.45–0.79)	0.50 (0.41–0.59)
CURB-65+CRP	369	0.79 (0.66–0.92)	0.54 (0.46–0.62)
CURB-65+WBC	369	0.62 (0.43–0.81)	0.69 (0.62–0.76)
All	369	0.76 (0.67–0.86)	0.71 (0.64–0.79)

All, CURB-65+PCT+CRP+WBC; AUC, area under the curve; 95% CI, 95% confidence intervals; CRP, C-reactive protein; ICU, intensive care unit; PCT, procalcitonin; WBC, white blood cells.

PCT to other inflammatory markers and their combination with clinical CAP risk scores.

Similar to our findings but with more statistical power, a large study from Germany including 1671 CAP patients found that PCT levels at admission predict the outcome of CAP with a similar prognostic accuracy as the CRB-65 score and with a higher prognostic accuracy compared with CRP and WBC [27]. The AUC for mortality for PCT was 0.80 (95% CI 0.75–0.84), as compared to an AUC of 0.79 (0.74–0.84) for CRB-65, 0.62 (0.54–0.68) for CRP, and 0.61 (0.54–0.68) for WBC. This study also documented the added utility of PCT in the identification of patients at very low risk of death despite increased CRB-65 scores. Another study from France that included 100 patients admitted to the ICU with CAP reported that increased PCT from day 1 to day 3 in patients with severe CAP is suggestive of a poor prognosis and a PCT level <0.95 ng/mL on day 3 in intubated patients is associated with a better outcome [28]. The kinetics of biomarkers on follow-up also has additional prognostic accuracy in our study. The CRP value for mortality was not informative, contrary to the findings of a previous study [7].

Improved prediction of 30-day mortality in CAP patients by using a combination of CRP in conjunction with the PSI, CURB-65, and CRB65 clinical severity indices has also been described [7]. We did not find a significant correlation of CRP levels at admission with outcome and can confirm the results of other studies documenting the poor prognosis value of CRP levels [29, 30]. Kruger et al. found PCT, CRP, and WBC to be predictive of 28-day mortality exclusively in patients without antimicrobial pre-treatment [21].

Our study had limitations. This cohort included mainly inpatients. Therefore it is not possible to determine whether the results would also be applicable to lower risk outpatients with CAP. Quantification of PCT levels on days 3, 5, and 7 was based on patient availability and contributed to information not being complete in the case of a few patients. The potential impact of antimicrobial pre-treatment on marker levels was not considered in this analysis. Moreover, this was a secondary analysis of a previously published randomized study, and exclusion criteria and the resulting non-participation of some patients may limit the external validity of our findings. Specifically, patients with immunosuppression and chronic infection were not included, which limits the generalizability of our results in regard to this important patient population. Finally, our study was an observational, exploratory study and, thus, hypothesis generating. Future interventional studies should ultimately test the potential of a biomarker-enhanced clinical risk score strategy on patient outcomes. As good examples in this regard, two recently published trials found improved outcomes following use of the inflammatory biomarker ProADM (ProAdrenomedullin) in addition to CURB-65 to facilitate site-of-care decisions in CAP [31, 32].

Conclusions

This study demonstrated that PCT, and to a lesser degree CRP, provide prognostic information on CAP outcomes,

particularly when their kinetics are taken into consideration and when adverse clinical outcomes are also considered instead of mortality alone. The most important improvements were found on days 5 and 7 for prediction of both survival and adverse clinical outcomes. Future randomized trials should assess whether integration of initial and follow-up biomarker levels results in improved decision making by physicians regarding initial site of care and early discharge from the hospital.

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