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ARTICLE

Prognostic value of procalcitonin in *Legionella* pneumonia

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Abstract The diagnostic reliability and prognostic implications of procalcitonin (PCT) (ng/ml) on admission in patients with community-acquired pneumonia (CAP) due to *Legionella pneumophila* are unknown. We retrospectively analysed PCT values in 29 patients with microbiologically proven *Legionella*-CAP admitted to the University Hospital Basel, Switzerland, between 2002 and 2007 and compared them to other markers of infection, namely, C-reactive protein (CRP) (mg/l) and leukocyte count (10^9/l), and two prognostic severity assessment scores (PSI and CURB65). Laboratory analysis demonstrated that PCT values on admission were >0.1 in over 93%, >0.25 in over 86%, and >0.5 in over 82% of patients with *Legionella*-CAP. Patients with adverse medical outcomes (59%, n=17) including need for ICU admission (55%, n=16) and/or inhospital mortality (14%, n=4) had significantly higher median PCT values on admission (4.27 [IQR 2.46–9.48] vs 0.97 [IQR 0.29–2.44], p=0.01), while the PSI (124 [IQR 81–147] vs 94 [IQR 75–116], p=0.19), the CURB65 (2 [IQR 1–2] vs 1 [1–3], p=0.47), CRP values (282 [IQR 218–343], p=0.28 vs 201 [IQR 147–279], p=0.28), and leukocyte counts (12 [IQR 10–21] vs 12 [IQR 9–15], p=0.58) were similar. In receiver operating curves, PCT concentrations on admission had a higher prognostic accuracy to predict adverse outcomes (AUC 0.78 [95%CI 0.61–96]) as compared to the PSI (0.64 [95%CI 0.43–0.86], p=0.23), the CURB65 (0.58 [95%CI 0.36–0.79], p=0.21), CRP (0.61 [95%CI 0.39–0.84], p=0.19), and leukocyte count (0.57 [95%CI 0.35–0.78], p=0.12). Kaplan-Meier curves demonstrated that patients with initial PCT values above the optimal cut-off of 1.5 had a significantly higher risk of death and/or ICU admission (log rank p=0.003) during the hospital stay. In patients with CAP due to *Legionella*, PCT levels on admission might be an interesting predictor for adverse medical outcomes.

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Introduction

In patients with clinical suspicion of community-acquired pneumonia (CAP), procalcitonin (PCT) (ng/ml) has a high diagnostic accuracy to differentiate bacterial from nonbacterial causes [1, 2]. Several intervention studies have demonstrated that PCT-guided antibiotic therapy can markedly reduce antibiotic exposure in patients presenting with CAP without compromising medical outcomes [3–6]. In addition, repeated PCT measurements have prognostic implications in critically ill patients in the ICU setting as high or increasing PCT values correlate with adverse medical outcome [7, 8]. In CAP caused by "atypical" bacteria, including *Chlamydia*

pneumoniae and *Mycoplasma pneumoniae*, lower PCT values as compared to pneumonia caused by extracellular bacteria have been reported, questioning the diagnostic reliability of PCT in atypical CAP [9, 10]. In atypical CAP caused by *Legionella*, studies using insensitive PCT assays have produced controversial results regarding the benefits and diagnostic reliability of initial PCT measurement [9, 11, 12]. Because *Legionella*-CAP has a substantial mortality and complication rate, early diagnosis and monitoring of the disease course are crucial [13]. The aim of this study was to assess the prognostic implications of initial PCT measurements in patients with microbiologically confirmed *Legionella*-CAP using a high sensitive PCT assay.

Materials and methods

Setting and study population

This study was conducted at the University Hospital Basel, Switzerland, a 700-bed primary and tertiary health care centre. It is the major provider of acute medical care for about 300,000 inhabitants. In this five-year retrospective study we included all consecutive patients admitted to our institution between September 2002 and September 2007, in whom *Legionella*-CAP was microbiologically diagnosed and a serum PCT concentration was determined on admission. In 22 patients (76%) PCT levels were also available during the course of the disease (Fig. 1) and results of PCT testing were available to the clinicians. Patient records were reviewed with a standardized data-collection form to retrieve demographic, clinical, microbiological, radiological, and laboratory data. We compared the prognostic accuracy of different laboratory and clinical data with two clinical severity prediction scores, namely, the pneumonia severity index (PSI) and the CURB65 score [14–16]. This study was approved by the local ethical committee (EKBB) and as a retrospective quality-surveillance study, the need for patient informed consent was waived.

Definitions

For this analysis, CAP was defined by the presence of one or several of the following recently acquired respiratory signs or symptoms: cough, sputum production, dyspnoea, core body temperature >38.0°C, auscultatory findings of abnormal breath sounds and rales, leukocyte count >10 or $<4\times10^9$ cells/l, and an infiltrate on chest radiograph [17]. Diagnosis of *Legionella* infection was established either by positive *Legionella* urinary antigen testing, positive *Legionella* culture, or PCR of respiratory specimen (sputum, tracheobronchial aspirate and/or bronchoalveolar lavage). Adverse medical outcome for this study was defined as inhospital death and/or need for ICU admission, respectively, up to the time of hospital discharge.

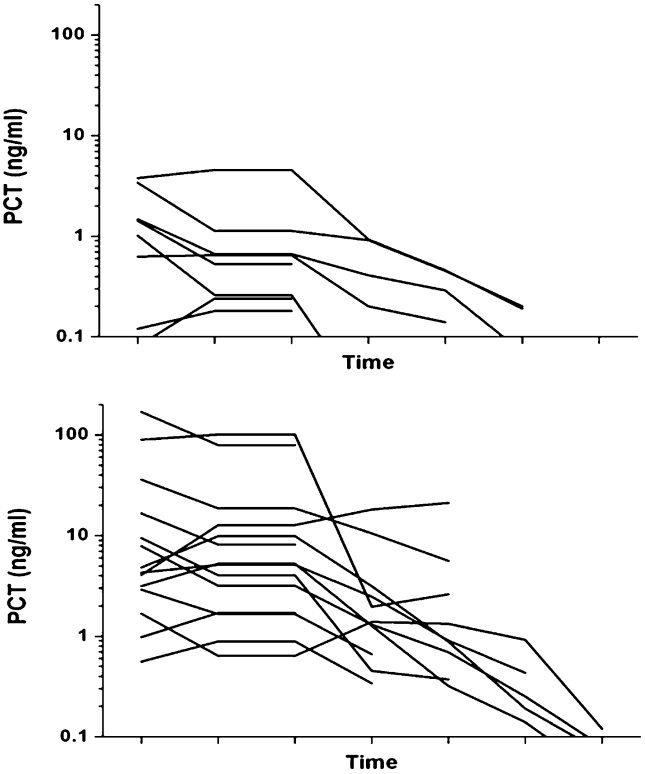

Fig. 1 Course of PCT in patients without an adverse event (**a**) and in patients with death and/or ICU admission (**b**)

Data collection

We used available laboratory results including markers of infection (PCT, C-reactive protein [CRP] (mg/l), leukocyte count [Lc] (10^9/l)), liver enzymes (ALAT, ASAT), sodium concentrations, lactate-dehydrogenase (LDH), and creatinine-kinase (CK) from the routinely collected blood analysis. CRP concentrations were determined by an enzyme immunoassay having a detection limit of <5 mg/dl (EMIT, Merck Diagnostica, Zurich, Switzerland). PCT was measured using 20–50 µl of plasma or serum by a time-resolved amplified cryptate emission (TRACE) technology assay (Kryptor PCT, Brahms AG, Hennigsdorf, Germany) as described elsewhere [3]. The assay has a functional assay sensitivity of 0.06 µg/l, which is about four-fold above mean normal levels. *Legionella* was diagnosed either by antigen in urine detection using an immunoenzymetric commercial method (*Legionella* Urinary Antigen; Binax), by PCR using an in-house PCT technique from the IMM (Institute for Medical Microbiology) in Zurich, Switzerland, or by culture [18, 19].

Statistical analysis

Discrete variables were expressed as counts (percentage) and continuous variables as medians and interquartile ranges (IQR) unless stated otherwise. Frequency compari-

son was done by chi-square test. Two-group comparison of normally distributed data was performed by Students *t* test. For data not normally distributed, the Mann-Whitney U test was used. Receiver-operating characteristics were calculated using STATA 9.2 (Stata Corp, College Station, TX). Levels that were nondetectable were assigned a value equal to the lower limit of detection for the assay. All testing was two-tailed and *p* values less than 0.05 were considered to indicate statistical significance.

Results

Baseline parameters

From a total of 82 patients with *Legionella*-CAP admitted between September 2002 and September 2007 to our institution, 29 patients (35%) had a measurement of PCT on admission and were thus included in this analysis. The 53 patients with *Legionella*-CAP and without initial PCT measurement were similar in terms of age ($p=0.68$), gender (0.78), severity of disease as assessed by the PSI score ($p=0.13$), initial CRP concentration ($p=0.95$), initial leukocyte count ($p=0.78$), and occurrence of adverse medical outcomes ($p=0.11$).

Table 1 presents baseline characteristics including demographic, clinical, and laboratory data of the patients with *Legionella*-CAP. Patients were predominantly male (66%) with a median age of 68 years (IQR 53–77 years). Clinical examination showed a median body temperature of 39.6°C (IQR 38.8–40.3), median systolic blood pressure of 122 mmHg (IQR 113–139) and median heart rate of 105 bps (IQR 91–120). Hyponatremia (sodium concentration <131 mmol/l) was present in 41% ($n=12$), thrombocytopenia (thrombocytes $<150\times10^9$/l) in 24% ($n=7$), increased lactate dehydrogenase (LDH) (>225 U/l) and creatinine kinase (CK) (>220 U/l) in 66% ($n=19$) and 48% (n=14) of patients, respectively. Laboratory analysis demonstrated median PCT (ng/ml), C-reactive protein (CRP) (mg/l), and leukocyte count (Lc) (10^9/l) concentrations on admission of 2.9 (IQR 0.93–6.43), 240 (IQR 173–310), and 12.1 (IQR 9.4–15.9), respectively. Initial PCT values were >0.1 in over 93%, >0.25 in over 86%, and >0.5 in over 82% of patients.

The diagnostic work-up of *Legionella* infection in the 29 patients included positive urine antigen testing in 82% (23/28), positive respiratory sample culture in 32% (6/19), positive PCR in 100% (11/11), and positive serology in 50% (1/2). Because in most patients multiple diagnostic tests for *Legionella*-CAP were performed to establish the diagnosis, percentages may not sum up to 100%.

Calculation of prognostic scores demonstrated a median PSI score of 109 (range 81–140) and a median CURB65 score of 1 (IQR 1–2). The median length of hospital stay was 12 days (IQR 8–20). Adverse medical outcomes were noted in 59% of the patients ($n=17$) including 55% admissions to the ICU ($n=16$) and/or death in 14% ($n=4$).

Figure 1 illustrates PCT values on admission and during the hospital stay in patients with and in patients without adverse outcomes. PCT values on admission were significantly higher in patients with ICU admission and/or death (4.27 [IQR 2.46–9.48] vs 0.97 [IQR 0.29–2.44], $p=0.01$).

Table 1 Baseline characteristics in patients with community-acquired pneumonia due to *Legionella* ($n=29$)

Baseline characteristics	Value
Demographic characteristics	
- Age (y)	68 (53–77)[a]
- Gender (male), *n* (%)	19 (66)
Coexisting illnesses, *n* (%)	
- Congestive heart disease	5 (17)
- Cerebrovascular disease	3 (10)
- Renal dysfunction	3 (10)
- COPD	3 (10)
- Neoplastic disease	2 (7)
- Liver disease	5 (17)
Clinical and laboratory findings	
- Confusion, *n* (%)	5 (18)
- Respiratory rate (breaths/min)	18 (16–29)[a]
- Systolic blood pressure (mmHg)	122 (113–139)[a]
- Heart rate (beats/min)	105 (91–120)[a]
- Body temperature (°C)	39.6 (38.8–40.3)[a]
- Pleural effusion, *n* (%)	11 (38)
Laboratory findings	
- C-reactive protein (mg/l)	240 (173–310)[a]
- Procalcitonin (μg/l)	2.90 (0.93–6.43)[a]
- Hematocrit (%)	37 (35–41)[a]
- Leukocyte count ($\times10^9$/l)	12.1 (9.4–15.9)[a]
- Platelets count ($\times10^9$/l)	200 (153–257)[a]
- Sodium (mmol/l)	132 (129–134)[a]
- Creatinine (umol/l)	100 (69–130)[a]
- Urea (mmol/l)	7.6 (5.2–12.8)[a]
- Elevated liver enzymes[b], *n* (%)	21 (72)
- CK (U/l)	175 (48–742)[a]
- LDH (U/l)	253 (186–354)[a]
- Glucose (mmol/l)	7.1 (6.2–10.7)[a]
- Oxygen saturation (%)	95 (90–96)[a]
- PaO_2 (kPa)	7.6 (7.2–10.6)[a]
- pH	7.45 (7.42–7.49)[a]
Risk assessment	
- PSI points	109 (81–140)[a]
- CURB65	1 (1–2)[a]
Outcome	
- Death, *n* (%)	4 (14)
- Admission to ICU, *n* (%)	16 (55)

COPD chronic obstructive pulmonary disease, *CK* creatinine-kinase, *LDH* lactate-dehydrogenase, *PSI* pneumonia severity index
CURB65 Confusion, Urea, Respiratory Rate, Blood Pressure, Age >65
[a] Denotes median (interquartile range)
[b] Denotes ASAT and/or ALAT

Patients with adverse medical outcomes had similar PSI scores (124 [IQR 81–147] vs 94 [IQR 75–116], p=0.19), similar CURB65 scores (2 [IQR 1–2] vs 1 [IQR1–3], p=0.47), similar CRP values (282 [IQR 218–343] vs 201 [IQR 147–279], p=0.28), and similar leukocyte count (12 [IQR 10–21] vs 12 [IQR 9–15], p=0.58) as compared to those without adverse outcome (Fig. 2). In addition, initial clinical parameters including total body temperature, diastolic and systolic blood pressure and pulse frequency, and other laboratory analysis including thrombocyte levels, sodium concentrations, liver enzyme concentrations, LDH and CK levels in patients with and without adverse outcomes were similar.

To assess the prognostic usefulness of the different parameters, we calculated receiver operating curves (ROC) with the area under the curve (AUC) as an overall prognostic measure of the parameter. PCT concentrations on admission had the highest prognostic accuracy to predict adverse medical outcome (AUC 0.78 [95%CI 0.61–0.96]), as compared to CRP (0.61 [95%CI 0.39–0.84], p=0.19) and leukocyte count (0.57 [95%CI 0.35–0.78], p=0.12), and compared to the PSI (0.64 [95%CI 0.43–0.86], p=0.23) and the CURB65 score (0.58 [95%CI 0.36–0.79], p=0.21). At an optimal PCT cut-off of 1.5 the sensitivity and specificity to predict adverse outcome was 82% (95%CI 57–96%) and 75% (95%CI 43–94%) with corresponding positive and negative likelihood ratios of 3.3 and 0.24. Likewise, at a PCT cut-off of 0.5, sensitivities and specificities to predict adverse outcome were 94% (95%CI 71–99%) and 33% (95%CI 10–65%), respectively, with corresponding positive and negative likelihood ratios of 1.41 and 0.18, respectively.

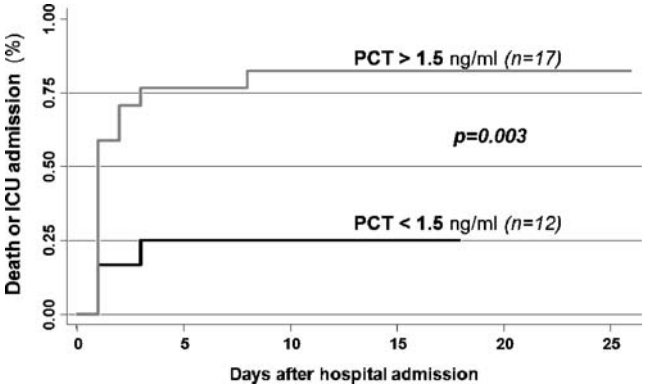

Fig. 3 Kaplan Meier curves depicting time to adverse medical outcome stratified by initial PCT value (optimal PCT cut-off value of 1.5 ng/ml)

To illustrate the capacity of initial PCT for risk assessment in patients with *Legionella*-CAP admitted to the emergency departement, we performed a comparison of adverse medical outcome in patients with PCT below and above the optimal cut-off of 1.5 by Kaplan-Meier curves (Fig. 3). Patients with PCT levels above this cut-off had a significantly higher risk for adverse medical outcome during the hospital stay as compared to patients below the cut-off (log-rank test p=0.003).

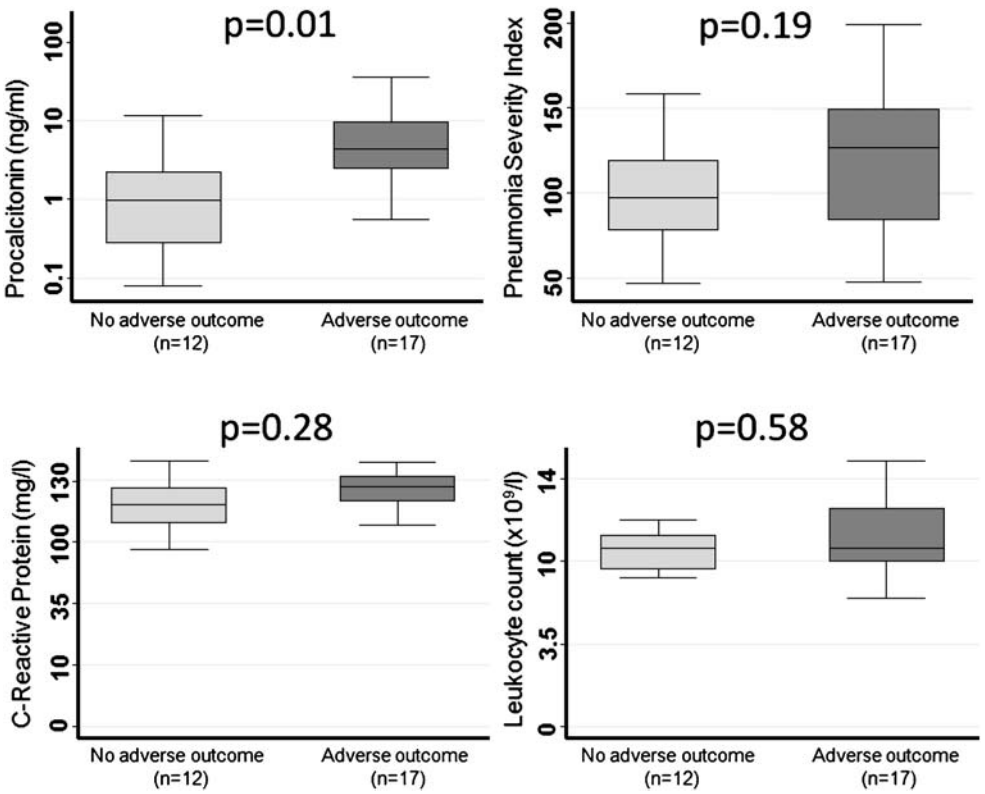

Fig. 2 Prognostic assessment in patients with community-acquired pneumonia due to *Legionella*

Discussion

In this study we found increased PCT values in the large majority of patients, namely, PCT concentrations >0.1 in over 93% and >0.25 in over 86% of patients using a high sensitive PCT assay. Importantly, the initial PCT concentrations had a high prognostic accuracy to predict adverse medical outcomes including inhospital mortality and/or need for ICU admission.

In bacterial infection, microbial antigens stimulate different pro- and antiinflammatory mediators, which eventually penetrate into the blood circulation where they can be measured. In recent years, PCT has emerged as a surrogate biomarker for bacterial infections, because PCT concentrations correlate with the likelihood and the severity of bacterial infections [1, 2]. Based on these considerations, a new strategy to reduce antibiotic exposure in patients with lower respiratory tract infections is guidance of antibiotic therapy based on PCT cut-off ranges [3–6]. Because different microbes might induce a distinct response in different organs resulting in a variable increase of PCT blood concentrations, reassurance of the diagnostic reliability of PCT to detect relevant infections caused by distinct pathogens is of relevance. This study confirms that unlike in mild atypical CAP caused by *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*, PCT levels increase to a higher extent in severe atypical CAP caused by *Legionella* species [9, 10]. Importantly, the increase of PCT had a higher prognostic accuracy as compared to the PSI to predict unfavourable outcomes, thus confirming prior studies in *Legionella*-CAP and in critically ill patients in the ICU setting [7, 11]. The finding of initially high PCT values in patients with adverse outcome is of particular importance with regard to PCT-guided antibiotic therapy in CAP and the possibility of initially withholding antibiotic therapy and reassessing PCT values after 6–24 hours in patients with low PCT values [20, 21].

A previous study has focussed on PCT in *Legionella*-CAP patients using a semiquantitative PCT assay. They reported high frequencies of "negative" PCT results when a cut-off value of 0.5 was applied [11]. High sensitive PCT measurements, as used in this study, provide an increase in diagnostic reliability, especially in sensitivity, and thus in the safety of patients. Our findings underline the importance of the use of more sensitive PCT assays to appreciate its full diagnostic potential [22]. In addition, using PCT cut-off ranges instead of a single cut-off value reflects more physiologically the interindividual variability of the increase of PCT upon bacterial infections.

With a retrospective design, this study has limitations and the results need prospective confirmation. The fact that physicians were not blinded and thus aware of PCT results may have influenced their decision to transfer patients to the ICU. In addition, in a prospective study, without the results of *Legionella* testing in real-time, the prognostic information of PCT may be difficult. Observational studies have produced contradictory results regarding the diagnostic reliability of PCT in CAP, mainly because the causative microorganisms in presumed bacterial CAP cannot be detected in most patients [2, 23, 24]. This study circumvents this "gold standard dilemma" because it only includes patients with microbiologically proven *Legionella*-CAP. Because testing for *Legionella* using urine antigen testing is mandatory in our institution, in the initial work-up of all patients with CAP, it is reasonable to believe that we included the majority of *Legionella*-CAP patients. Another important limitation of this study is the small sample size restricting the statistical power, particularly of the ROC statistics. Thus, despite numerical differences in the AUCs, statistical differences were not detected. The high number of adverse medical outcomes found in this study may be particular for a referred *Legionella*-CAP population from a University Hospital, thus limiting the generalisability of this study.

In conclusion, increased PCT concentrations were found in the large majority of patients with *Legionella*-CAP, predicting worse outcome. If confirmed in future studies, PCT could be an interesting prognostic tool complementing clinical severity prediction scores.

Competing interests Authors PS, MCC and BM received support from BRAHMS to attend meetings and fulfilled speaking engagements. BM has served as a consultant and received research support to attend meetings and for travel expenses. All other co-authors declare that they have no competing interests.

Authors' contributions Authors PS, JH, RZ, RF, MCC, and BM had the idea for the study and directed the study design, data collection, and analysis and writing of the report. Authors RF, IS, and AT each had substantial contributions in planning of the study, data collection, interpretation of data, and/or writing of the manuscript.

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