Serum Procalcitonin: An Independent Predictor of Clinical Outcome in Health Care-Associated Pneumonia

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Key Words

Pneumonia · Procalcitonin · Biological markers · Mortality · Prognosis

Abstract

Background: Early prediction of the clinical outcomes for health care-associated pneumonia (HCAP) patients is challenging. **Objectives:** This is the first study to evaluate procalcitonin (PCT) as a predictor of outcomes in HCAP patients. **Methods:** We conducted an observational study based on data for HCAP patients prospectively collected between 2011 and 2014. Outcome variables were intensive care unit (ICU) admission and 30-day mortality. PCT was categorized into three groups: <0.5, 0.5–2.0, and >2.0 ng/ml. We analysed multiple variables including age, sex, comorbidities, clinical findings, and PCT group to assess their association with outcomes. **Results:** Of 245 HCAP patients, 99 (40.4%) were admitted to an ICU and 44 (18.0%) died within 30 days. The median PCT level was significantly higher in the ICU admission (1.19 vs. 0.4 ng/ml; $p < 0.001$) and 30-day mortality (3.3

vs. 0.4 ng/ml; $p < 0.001$) groups. In multivariate analysis, high PCT (>2.0 ng/ml) was strongly associated with ICU admission [odds ratio 3.734, 95% confidence interval (CI) 1.753–7.951; $p = 0.001$] and 30-day mortality (hazard ratio 2.254, 95% CI 1.250–5.340; $p = 0.035$). In receiver operating characteristic analysis, PCT had a poor discrimination power regarding ICU admission [0.695 of the area under the curve (AUC)] and a fair discrimination power regarding 30-day mortality in HCAP patients (0.768 of the AUC). **Conclusions:** High PCT on admission was strongly associated with ICU admission and 30-day mortality in HCAP patients. However, application of PCT alone seems to be limited to predicting outcomes.

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Introduction

The traditional classification of pneumonia as community-acquired or nosocomial pneumonia (subcategorized as hospital-acquired and ventilator-associated pneumonia) was based on the location where infection

occurred. However, some pneumonia patients in community settings receive health care services including routine infusions, invasive therapy, and regular use of medical resources, and frequently transit from the hospital to a nursing home/care facility. Although pneumonia in these patients has been traditionally categorized as community-acquired pneumonia (CAP), their infections may have different epidemiology and characteristic pathogens from CAP, and these may resemble those observed in nosocomial pneumonia. This type of pneumonia was newly categorized as health care-associated pneumonia (HCAP) in the 2005 update of the American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) guidelines [1].

These patients have been exposed to the health care system (recent hospitalization, nursing care, and invasive regular therapy), which carries a higher risk of infections with multidrug-resistant (MDR) pathogens. Therefore, although this group of patients comes from a community-based environment, they were thought to be treated with more broad-spectrum antibiotics than CAP patients and suffered from worse clinical outcomes [1].

Data supporting the 2005 ATS/IDSA guidelines were first published in a large retrospective study in the USA [2]. Subsequent studies on HCAP were conducted in Asia and Europe for validation of HCAP in community-based pneumonia patients. These studies revealed the existence of HCAP in community-based pneumonia patients, a different distribution of pathogens from that in CAP, and a higher mortality with HCAP than with CAP [3–5].

As in CAP patients, early prediction of clinical outcomes in HCAP patients may be mandatory for physicians to make decisions on the appropriate site of care and the establishment of optimal treatment. For CAP patients, various severity scoring systems have been developed and some useful inflammatory markers have been proposed [6–8]. However, a prediction tool specifically related to clinical outcomes in HCAP patients is not well established. Some clinical studies have tried to apply severity scoring systems for CAP [such as the pneumonia severity index (PSI) and CURB-65] to HCAP patients, but these did not show the same discriminatory power for clinical outcomes as they do in CAP patients [9, 10].

Serum procalcitonin (PCT) is a useful marker for screening for bacterial infections and predicting the clinical prognosis in infectious disease [11]. In CAP patients, PCT has shown efficacy for the discrimination of bacterial infection and in the prediction of prognosis [12–14]. However, to the best of our knowledge there are no clinical data from testing the performance of PCT as a predic-

tor of clinical outcomes in HCAP. Considering the good correlation between the serum PCT level and the severity of sepsis from bacterial infection, PCT may be a good independent biomarker for predicting clinical outcomes in HCAP patients, who have a higher frequency of bacterial infection than CAP patients.

The aim of this study was to evaluate the efficacy of serum PCT in predicting clinical outcomes, including admission to an intensive care unit (ICU) and 30-day mortality, in patients with HCAP.

Subjects and Methods

Study Design and Clinical Setting

This observational study was conducted from October 2011 to October 2014 at the Konkuk University Medical Center, Seoul, Republic of Korea. According to the study protocol, the clinical and laboratory data for the subjects were collected prospectively and were reviewed after the study period. The overall study protocol was reviewed and approved by our hospital's Institutional Review Board (KUH-1260014). During the study period, all adult patients over 18 years old that were diagnosed in the emergency department (ED) with pneumonia (the diagnosis required new radiologic evidence of infiltration and at least 2 of the following clinical features [15]: fever or hypothermia; new cough with or without productive sputum; pleuritic chest pain; dyspnoea, and abnormal breath sound on auscultation) were enrolled and treated according to our hospital pneumonia treatment protocol, based on the ATS/IDSA pneumonia treatment guidelines. The disposition of patients was determined by emergency and respiratory physicians using our hospital pneumonia treatment protocol, which was established by referencing the 2007 ATS/IDSA guideline for pneumonia management in adults [16]. Our hospital guidance recommends that all patients requiring mechanical intubation and/or in septic shock and needing administration of a vasopressor in the ED or exhibiting at least 3 minor criteria for severe pneumonia [minor criteria included: a respiratory rate >30 breaths/min; arterial oxygen pressure/fraction of inspired oxygen ratio <250 mm Hg; multilobar infiltrates; confusion; blood urea nitrogen >20 mg/dl; white blood cell (WBC) counts <4,000 cells/mm³; platelet counts <100,000 cells/mm³; core temperature <36°C, and hypotension requiring aggressive fluid resuscitation) should be admitted to the ICU.

Study Populations

HCAP was defined according to the 2005 ATS/IDSA guidelines as a diagnosis of pneumonia in patients admitted to the hospital who met at least 1 of the following criteria: (1) hospitalization for 2 days or more in the preceding 90 days; (2) residence in a nursing home or long-term care facility; (3) intravenous antibiotics; (4) chemotherapy; (5) long-term dialysis (including haemodialysis and peritoneal dialysis), or (6) chronic home wound care. Among HCAP patients, the exclusion criteria were: (1) transfer from another hospital; (2) admission for palliative therapy only; (3) diagnosis of lung cancer with obstructive pneumonia; (4) patients with underlying immunocompromise with neutropenia or positive for human immunodeficiency virus; (5) transplant patients, and (6) patients with missing data.

Data Collection

The clinical data collected for analysis included demographics (age and sex), comorbidities (malignancy, chronic lung disease, cardiovascular disease, cerebrovascular disease, diabetes, chronic kidney disease, or chronic liver disease), clinical findings [altered mental status, systolic blood pressure (SBP), pulse rate, respiratory rate, and body temperature], systemic inflammatory response signs (SIRS), and mechanical ventilation at the ED.

We collected values for inflammatory markers on admission, including WBC, C-reactive protein (CRP), and PCT. All markers were measured in all the suspected pneumonia patients at the time of ED laboratory sampling, within 1 h of arrival.

Serum PCT levels were measured with an electrochemiluminescence immunoassay (Brahms GmbH, Henningsdorf, Germany) in the Roche Cobas e-System (Roche Diagnostics, Basel, Switzerland). The measuring range of the assay was 0.02–100 ng/ml and the functional assay sensitivity (interassay variation coefficient 20%) was 0.06 ng/ml. Total WBC counts and their differentials were measured using a Sysmex XN Automated Hematology Analyzer (Sysmex, Kobe, Japan). Serum separation tubes were used for CRP. CRP was measured using the latex immunoturbidimetric method with CRP-Latex X2 (Denka Seiken Co., Tokyo, Japan) on a Toshiba 200FR Autoanalyzer (Toshiba Medical Systems Co., Ltd., Tokyo, Japan). Microbiological specimens were obtained within 72 h of hospital admission, including sputum, tracheal aspirate, bronchoalveolar lavage fluid, and urine. Organisms isolated from positive cultures were identified using Gram's stain, and colony morphology and biochemical characteristics using the VITEK II Identification System (bioMérieux, Marcy l'Étoile, France). Susceptibility testing for oxacillin was performed on all *Staphylococcus aureus* isolates with a disk diffusion method based on the Clinical and Laboratory Standards Institute guidelines. It is defined as inappropriate antibiotics use when antibiotics on admission did not activate against the identified pathogens, based on the susceptibility test.

Based on patient demographics and baseline clinical data, the PSI and CURB-65 scores of HCAP patients on admission were assessed. PSI was calculated using the following variables: age, sex, complications, and vital sign abnormalities, together with several laboratory, blood gas analytic, and radiographic parameters [6]. The CURB-65 score is a 6-point score, with 1 point for each of the following criteria: confusion; urea >7 mmol/l or blood urea nitrogen >19 mg/dl; respiratory rate ≥30/min; SBP <90 mm Hg or diastolic blood pressure ≤60 mm Hg, and age ≥65 years [7]. By reference to the pneumonia management guideline of the IDSA, patients with PSI class IV (score 91–130) or V (score >130) were defined as the high-risk pneumonia group [17]. Patients with CURB-65 scores of 3–5 were categorized as the severe pneumonia group by reference to the British Thoracic Society pneumonia guideline [18].

Data Analysis

Outcome variables for the study analysis were ICU admission and 30-day mortality. To verify the effectiveness of PCT as an independent marker for predicting outcomes, serum PCT was categorized into three groups of serum PCT levels based on the Food and Drug Administration approval of PCT as a marker of sepsis for clinical use in the USA: (1) <0.5 ng/ml, (2) 0.5–0.2 ng/ml, and (3) >2.0 ng/ml. Univariate and multivariate logistic regression testing and a Cox hazard regression model were used to determine the

Table 1. Baseline characteristics of the enrolled patients

Criteria for HCAP ^a	
Previous hospitalization for 2 days or more in the preceding 90 days	100 (40.8)
Nursing home residency	134 (54.7)
Intravenous antibiotics within 30 days	11 (4.5)
Chemotherapy within 30 days	5 (2.0)
Haemodialysis	12 (4.9)
Wound care within 30 days	0 (0)
Age, years	76.5 ± 10.3
Male	143 (58.4)
Comorbidities ^a	
Malignancy	67 (27.3)
Chronic lung disease	43 (17.6)
Cardiovascular disease	34 (13.9)
Cerebrovascular disease	100 (40.8)
Diabetes	57 (23.3)
Chronic kidney disease	17 (6.9)
Chronic liver disease	11 (4.5)
Initial findings	
Altered mental status	57 (23.3)
SBP <90 mm Hg	24 (9.8)
Pulse rate >125/min	33 (13.5)
Respiratory rate ≥30/min	46 (18.8)
Temperature <35 or ≥40° C	26 (10.6)
SIRS at ED	206 (84.1)
MDR pathogens	55 (22.4)
Inappropriate antibiotics use	31 (12.7)
Mechanical ventilation at ED	57 (23.3)
ICU admission at ED	99 (40.4)
30-day mortality	44 (18.0)

Values are presented as n (%) or mean ± SD.

^a Cases are duplicated.

factors associated with outcome variables. In addition, we constructed receiver operating characteristic (ROC) curves, and the areas under the curves (AUCs) and confidence intervals (CIs) were calculated to compare the discriminatory power for outcomes among the inflammatory markers (WBC, CRP, and PCT) and pneumonia scoring systems (PSI and CURB-65). All data were processed and all statistical analyses were performed with SPSS Statistics 17.0 (SPSS Inc., Chicago, Ill., USA). A two-sided *p* value of <0.05 was considered significant.

Results

Baseline Data of the Study

During the study period (from October 2011 to October 2014), 318 adult patients with suspected HCAP were admitted. Of these, 73 patients were excluded because they had been transferred from another hospital (*n* = 35) or because they were admitted only for palliative care

Table 2. Comparisons of baseline characteristics and clinical features between the three PCT groups

	<0.5 ng/ml (n = 115)	0.5–2.0 ng/ml (n = 64)	>2.0 ng/ml (n = 66)	p value
Age, years	76.4±10.4	76.7±11.4	76.3±8.9	0.964
Male	61 (53.0)	36 (56.3)	46 (69.7)	0.084
Comorbidities				
Malignancy	24 (20.9)	24 (37.5)	19 (28.8)	0.065
Chronic lung disease	31 (27.0)	7 (10.9)	5 (7.6)	0.001
Cardiovascular disease	19 (16.5)	6 (9.4)	9 (13.6)	0.414
Cerebrovascular disease	45 (39.1)	24 (37.5)	31 (47.0)	0.482
Diabetes	20 (17.4)	15 (23.4)	22 (33.3)	0.051
Chronic kidney disease	5 (4.3)	8 (12.5)	4 (6.1)	0.114
Chronic liver disease	2 (1.7)	4 (6.3)	5 (7.6)	0.138
Initial findings				
Altered mental status	14 (12.2)	14 (21.9)	29 (43.9)	<0.001
SBP <90 mm Hg	3 (2.6)	4 (6.3)	17 (25.8)	<0.001
Pulse rate >125/min	10 (8.7)	10 (15.6)	13 (19.7)	0.095
Respiratory rate ≥30/min	17 (14.8)	13 (20.3)	16 (24.2)	0.273
Temperature <35 or ≥40° C	7 (6.1)	12 (18.8)	7 (10.6)	0.031
SIRS at ED	90 (78.3)	61 (95.3)	55 (83.3)	0.011
MDR pathogens	24 (20.9)	12 (18.8)	19 (28.8)	0.334
Inappropriate antibiotics use	11 (9.6)	9 (14.1)	11 (16.7)	0.355
Mechanical ventilation at ED	17 (14.8)	9 (14.1)	31 (47.0)	<0.001
ICU admission at ED	32 (27.8)	23 (35.9)	44 (66.7)	<0.001
30-day mortality	9 (7.8)	8 (12.5)	27 (40.9)	<0.001

Values are presented as n (%) or mean ± SD. Italics denote significance.

(n = 38); 245 patients with a definite diagnosis of HCAP were included in the study. Nursing home residency (n = 134; 54.7%) and previous hospitalization (n = 100; 40.8%) were the most common criteria for defining HCAP (table 1).

Pathogens and Laboratory Results

A bacterial cause of HCAP was clearly identified in 115 patients (46.9%). In 55 (47.8%) of these, the bacteria were MDR pathogens including *Pseudomonas aeruginosa* (n = 25; 21.7%), methicillin-resistant *S. aureus* (n = 22; 19.1%), *Acinetobacter baumannii* (n = 5; 4.3%), and extended-spectrum β -lactamase-producing Enterobacteriaceae species (n = 3; 2.6%). *Streptococcus pneumoniae* (n = 24; 20.9%), methicillin-susceptible *S. aureus* (n = 13; 11.3%), *Klebsiella* species (n = 6; 5.2%), *Haemophilus influenzae* (n = 4; 3.5%), and others (n = 13; 11.3%) were also identified.

PCT was checked in all 245 patients. Table 2 shows the comparison of baseline characteristics and clinical features for the three PCT groups. Compared with the low PCT (<0.5 ng/ml) and moderate PCT (0.5–2.0 ng/ml) groups, the high PCT group (>2.0 ng/ml) showed a high-

er incidence of altered mental status and low SBP (<90 mm Hg). More patients with high PCT (>2.0 ng/ml) were treated with mechanical ventilation and admitted to the ICU from the ED. A higher rate of 30-day mortality (40.9%) was also observed in this group.

Factors for an Association with ICU Admission and 30-Day Mortality from the ED

Of the 245 patients, 99 (40.4%) were initially admitted to the ICU directly from the ED. Compared with the patients not admitted to the ICU, the patients admitted to the ICU had an altered mental status, lower SBP, and higher pulse and respiratory rates at the vital sign examination. The patients admitted to the ICU had a high risk of being in the severe pneumonia group according to both PSI and CURB-65 scores.

Among the inflammatory markers, PCT and CRP levels in patients admitted to the ICU were higher than those in patients not admitted to the ICU. There were no differences between the two groups in other factors (table 3).

In multivariate logistic regression analysis, low SBP and increased respiratory rate had shown significantly high odds ratios (ORs) for predicting ICU admission.

Table 3. Comparisons of baseline characteristics and clinical features for ICU admission and 30-day mortality

	ICU admission			30-day mortality		
	yes (n = 99)	no (n = 146)	p value	yes (n = 44)	no (n = 201)	p value
Age, years	76.9±8.2	76.1±11.4	0.527	79.8±7.6	75.7±10.6	0.003
Male	58 (58.6)	85 (58.2)	1.000	26 (59.1)	117 (58.2)	1.000
Comorbidities ^a						
Malignancy	23 (23.2)	44 (30.1)	0.247	14 (31.8)	53 (26.4)	0.460
Chronic lung disease	22 (22.2)	21 (14.4)	0.126	4 (9.1)	39 (19.4)	0.127
Cardiovascular disease	16 (16.2)	18 (12.3)	0.453	6 (13.6)	28 (13.9)	1.000
Cerebrovascular disease	43 (43.4)	57 (39.0)	0.510	16 (36.4)	84 (41.8)	0.612
Diabetes	23 (23.2)	34 (23.3)	1.000	9 (20.5)	48 (23.9)	0.698
Chronic kidney disease	6 (6.1)	11 (7.5)	0.800	5 (11.4)	12 (6.0)	0.199
Chronic liver disease	7 (7.1)	4 (2.7)	0.125	2 (4.5)	9 (4.5)	1.000
Initial vital signs						
Altered mental status	34 (34.3)	23 (15.8)	0.001	22 (50.0)	35 (17.4)	<0.0001
SBP <90 mm Hg	19 (19.2)	5 (3.4)	<0.001	14 (31.8)	10 (5.0)	<0.001
Pulse rate >125/min	23 (23.2)	10 (6.8)	<0.001	8 (18.2)	25 (12.4)	0.331
Respiratory rate ≥30/min	31 (31.3)	15 (10.3)	<0.001	14 (31.8)	32 (15.9)	0.019
Temperature <35 or ≥40°C	10 (10.1)	16 (11.0)	1.000	5 (11.4)	21 (10.4)	0.792
SIRS at ED	87 (87.9)	119 (81.5)	0.215	36 (81.8)	170 (84.6)	0.652
Inflammatory markers						
WBC, ×10 ³ /μl	1.27 (0.78–1.95)	1.14 (0.81–1.54)	0.073	1.14 (0.51–2.48)	1.22 (0.52–1.63)	0.538
CRP, mg/dl	13.91 (6.28–23.48)	11.3 (5.40–19.14)	0.034	16.54 (9.72–27.91)	11.00 (4.32–19.28)	<0.001
PCT, ng/dl	1.19 (0.3–8.4)	0.4 (0.1–1.0)	<0.001	3.3 (0.8–14.8)	0.4 (0.1–1.3)	<0.001
PSI						
High risk (class IV–V)	64 (64.69)	57 (39.0)	<0.001	39 (88.6)	82 (40.8)	<0.001
CURB-65						
Severe (score 3–5)	57 (59.6)	52 (35.6)	0.001	33 (75.0)	76 (37.8)	<0.001
MDR pathogens	25 (20.5)	30 (25.3)	0.436	11 (25.0)	44 (21.9)	0.394
Inappropriate antibiotics use	12 (12.1)	19 (13.0)	1.000	5 (11.4)	26 (12.9)	1.000
Mechanical ventilation at ED	58 (58.6)	0 (0.0)	<0.001	27 (67.6)	31 (13.9)	<0.001

Values are presented as n (%), median (IQR), or mean ± SD. Italics denote significance. IQR = Interquartile range 25–75%. ^a Cases are duplicated.

Fig. 1. Survival plot using a multivariate Cox hazard regression model after adjustment for other risk factors for cumulative survival at 30 days. There were significant differences between the group with PCT levels >2.0 ng/ml versus the group with PCT levels of 0.5–2.0 ng/ml or the group with PCT levels <0.5 ng/ml ($p < 0.05$).

Table 4. Univariate and multivariate logistic regression analyses of factors for ICU admission at the ED

	Univariate			Multivariate		
	OR	95% CI	p value	OR	95% CI	p value
Age	1.008	0.983–1.033	0.550			
Male	0.985	0.587–1.653	0.954			
Comorbidities						
Malignancy	0.702	0.391–1.260	0.235			
Chronic lung disease	0.588	0.303–1.140	0.116			
Cardiovascular disease	0.729	0.352–1.511	0.396			
Cerebrovascular disease	0.834	0.497–1.400	0.493			
Diabetes	1.003	0.548–1.835	0.992			
Chronic kidney disease	1.263	0.451–3.535	0.657			
Chronic liver disease	0.370	0.105–1.300	0.121			
Initial findings						
Altered mental status	2.797	1.522–5.141	0.001	1.336	0.528–3.069	0.494
SBP <90 mm Hg	6.697	2.409–18.622	<0.001	4.383	1.258–15.277	0.020
Pulse rate >125/min	4.116	1.861–9.102	<0.001	2.406	0.936–6.184	0.068
Respiratory rate ≥30/min	3.981	2.012–7.879	<0.001	3.086	1.365–6.977	0.007
Temperature <35 or ≥40° C	0.831	0.396–2.104	0.831			
WBC count >10.0 or <4.0 × 10 ³ /μl ^a	2.565	1.391–4.730	0.003	2.846	1.408–5.756	0.004
CRP >3.0 mg/dl ^a	1.356	0.640–2.870	0.426			
PCT						
<0.5 ng/ml	1.000	Reference				
0.5–2.0 ng/ml	1.455	0.757–2.797	0.261	1.172	0.574–2.393	0.662
>2.0 ng/ml	5.188	2.696–9.981	<0.001	3.734	1.753–7.951	0.001
PSI						
High risk (class IV–V)	2.855	1.681–4.848	<0.001	1.414	0.696–2.874	0.338
CURB-65						
Severe (score 3–5)	1.566	1.206–2.034	0.001	0.734	0.347–1.551	0.417
MDR pathogens	0.748	0.713–2.394	0.387			
Inappropriate antibiotics use	1.085	0.501–2.348	0.837			
SIRS at ED	0.608	0.292–1.267	0.184			

Italics denote significance. ^a These values, indicating inflammation, were defined as guiding values for the laboratory department in the hospital.

Among the inflammatory markers, a high PCT (>2.0 ng/ml), leukocytosis, or leukopenia (WBC count >10.0 or <4.0 × 10³/μl) were significantly associated with ICU admission (OR 3.734 and 2.846, respectively) (table 4).

Forty-four patients (18.0%) died within 30 days of being admitted to the hospital from the ED. With regard to their vital signs on admission taken in the ED, the non-survivors showed a significantly lower SBP and a higher pulse rate than those who survived. The patients who died were older and had a higher rate of mechanical ventilation. Among the inflammatory markers, PCT and CRP levels in the patients who died were higher than the levels in those who survived. However, there were no significant differences between the two groups in other factors (table 3). In the analysis of 30-day mortality using a multivariate Cox hazard regression model after adjustment

for other significant factors, a high PCT (>2.0 ng/ml) showed a significant association with risk of mortality compared with the low PCT range [hazard ratio (HR) 2.254, 95% CI 1.250–5.340; *p* = 0.045], as did being at high risk according to the PSI (HR 3.417, 95% CI 1.168–9.999; *p* = 0.025), mechanical ventilation (HR 2.562, 95% CI 1.246–5.266; *p* = 0.011), and age (table 5). The plots for cumulative survival at 30 days showed a significant increase in 30-day mortality in patients with a high PCT (>2.0 ng/ml) compared with those with moderate and low PCT (fig. 1).

Discrimination of ICU Admission and 30-Day Mortality

In the ROC curve analysis for the prediction of ICU admission from the ED, the AUCs were higher for PSI

Table 5. Univariate and multivariate logistic regression analyses of factors for 30-day mortality at the ED

	Univariate			Multivariate		
	HR	95% CI	p value	HR	95% CI	p value
Age	<i>1.040</i>	<i>1.007–1.075</i>	<i>0.018</i>	1.038	0.999–1.078	0.056
Male	1.034	0.567–1.886	0.913			
Comorbidities						
Malignancy	0.816	0.433–1.540	0.531			
Chronic lung disease	2.291	0.820–6.403	0.114			
Cardiovascular disease	1.207	0.434–2.429	0.952			
Cerebrovascular disease	1.240	0.671–2.292	0.492			
Diabetes	1.194	0.574–2.483	0.636			
Chronic kidney disease	0.500	0.197–1.270	0.145			
Chronic liver disease	1.005	0.243–4.153	0.994			
Initial findings						
Altered mental status	<i>3.767</i>	<i>2.085–6.807</i>	<i><0.001</i>	1.202	0.569–2.542	0.630
SBP <90 mm Hg	<i>5.347</i>	<i>2.830–10.103</i>	<i><0.001</i>	1.788	0.805–3.970	0.153
Pulse rate >125/min	1.537	0.714–3.306	0.272			
Respiratory rate ≥30/min	<i>2.319</i>	<i>1.229–4.377</i>	<i>0.009</i>	1.512	0.740–3.093	0.257
Temperature <35 or ≥40° C	1.049	0.413–2.661	0.920			
WBC count >10.0 or <4.0 ×10 ³ /μl ^a	<i>2.285</i>	<i>1.019–5.127</i>	<i>0.045</i>	1.748	0.749–4.083	0.197
CRP >3.0 mg/dl ^a	<i>3.652</i>	<i>0.884–15.090</i>	<i>0.074</i>	1.344	0.288–6.268	0.707
PCT						
<0.5 ng/ml	1.000	Reference				
0.5–2.0 ng/ml	1.624	0.627–4.209	0.318	1.279	0.484–3.379	0.620
>2.0 ng/ml	<i>6.155</i>	<i>2.893–13.098</i>	<i><0.001</i>	<i>2.254</i>	<i>1.250–5.340</i>	<i>0.045</i>
PSI						
High risk (class IV–V)	<i>9.260</i>	<i>3.648–23.504</i>	<i><0.001</i>	<i>3.417</i>	<i>1.168–9.999</i>	<i>0.025</i>
CURB-65						
Severe (score 3–5)	<i>4.218</i>	<i>2.131–8.349</i>	<i><0.001</i>	0.938	0.392–2.244	0.886
SIRS at ED	1.093	0.746–1.604	0.647			
MDR pathogens	0.864	0.437–1.709	0.674			
Inappropriate antibiotics use	1.178	0.464–2.988	0.731			
Mechanical ventilation at ED	<i>6.363</i>	<i>3.462–11.693</i>	<i><0.001</i>	<i>2.562</i>	<i>1.246–5.266</i>	<i>0.011</i>

Italics denote significance. ^a These values, indicating inflammation, were defined as guiding values for the laboratory department in the hospital.

(0.705, 95% CI 0.640–0.770) and PCT (0.695, 95% CI 0.627–0.763) than for the other factors (fig. 2). The optimal PCT cut-off value for predicting ICU admission was 0.44 ng/ml, with a sensitivity of 70.7%, a specificity of 53.8%, a positive predictive value of 52.6%, and a negative predictive value of 74.1%.

For the prediction of 30-day mortality, the AUCs were higher for PSI (0.799, 95% CI 0.737–0.860), PCT (0.768, 95% CI 0.692–0.844), and CURB-65 (0.767, 95% CI 0.693–0.841) than for the other factors (fig. 2). The optimal PCT cut-off value for 30-day mortality was 0.81 ng/ml, with a sensitivity of 77.3%, a specificity of 67.7%, a positive predictive value of 34.3%, and a negative predictive value of 93.2%.

Discussion

In the current clinical study, we found out that, after adjustment for various baseline characteristics of the patients and clinical factors, a high PCT (>2.0 ng/ml) on admission is an independent predictor of ICU admission and 30-day mortality in HCAP patients. For the prediction of outcomes, PCT levels on admission had a poor discriminative power for ICU admission (0.695 of the AUC) and a fair discriminative power for 30-day mortality in HCAP patients (0.768 of the AUC). In particular, PCT levels <0.81 ng/ml were highly useful for predicting a very low risk of 30-day mortality for HCAP patients.

Fig. 2. ROC curves of the predictive value of inflammatory markers (WBC, CRP, and PCT) and severity scoring systems (PSI and CURB-65) for ICU admission (**a**) and 30-day mortality (**b**).

PCT is a prohormone of calcitonin, which is produced from thyroid C cells and neuroendocrine cells of the lung and intestine [19]. PCT may be the biomarker of inflammation that has been most widely researched in recent years. Serum levels of PCT seldom increase in healthy humans or during inflammation caused by viral infections or autoimmune illness. In pneumonia patients, application of PCT is attractive for diagnosis of a bacterial cause and for prediction of patient outcomes because of its easy application and simplicity. Many studies dealing with the clinical efficacy of PCT in CAP have been published, and PCT has been shown to have greater efficacy as a predictive marker than as a diagnostic tool for bacterial infection [13, 14, 20–23].

Based on the above, we hypothesized that the PCT level on admission may be a useful predictive marker for clinical outcomes in HCAP patients. MDR pathogens are more frequently identified in HCAP patients than in CAP patients, and HCAP patients also have a relatively higher incidence of ICU admission and a higher mortality rate than CAP patients [24–26]. The higher incidence of ICU admission and higher mortality rate in HCAP patients are explained by the following characteristics of HCAP patients. These patients are generally older than CAP patients and have a higher incidence of combined comor-

bidity and immunocompromising conditions [5]. They are more susceptible to progression to severe infection. In most cases of severe infection or septic conditions, the level of PCT increases. In addition, inappropriate initial antibiotic treatment is given to HCAP patients more frequently than to CAP patients. Some doctors who initially examined HCAP patients who had MDR pathogens first used the recommended empirical antibiotic treatment for CAP patients because the patients were from an out-of-hospital environment [3, 4, 24–26].

In our study, 40% of the patients were initially admitted to the ICU and 18% died within 30 days. Various factors were related to ICU admission, and high PCT (>2.0 ng/ml) showed a high OR for ICU admission compared with low PCT (<0.5 ng/ml). The vital signs of a lower SBP and a higher respiratory rate, which are closely related to shock or lung dysfunction, showed a significantly high OR as well. For the patients who died, plasma PCT was demonstrated to be a better predictive factor than any other variable. Among the other variables, only age and mechanical ventilation on admission showed HRs of 1.050 and 2.940, respectively. For 30-day mortality, a high PCT (>2.0 ng/ml) on admission compared with a low PCT showed a high HR for 30-day mortality.

PCT is a well-known inflammatory marker of the presence of bacterial infection, and its concentration correlates with severity of sepsis as well. Various cut-off values have been suggested in previous studies, and 0.1, 0.25, 0.5, and 2.0 ng/ml are often used. A PCT concentration <0.1 ng/ml is an indicator of absence of bacterial infection, and >0.5 ng/ml strongly indicates the presence of bacterial infection. A PCT concentration of 0.1–0.25 ng/ml suggests a possible bacterial infection, and 0.25–0.5 ng/ml indicates that a bacterial infection is less likely. The PCT concentrations of 0.1, 0.25, and 0.5 ng/ml are used for guiding the prescription of antibiotics to patients with lower respiratory tract infections [27, 28]. Otherwise, a PCT concentration >0.5 ng/ml is used mainly as an indicator of severity of infection and infectious disease prognosis [29, 30].

Our study shows a good correlation between PCT level and clinical outcomes in HCAP patients. Compared with CAP patients, those with HCAP have a higher occurrence of bacterial infections, including with MDR pathogens, which may be life-threatening because of a failure of antibiotic treatment on admission [1, 24, 25, 31]. Notably, most patients display sepsis (bacterial infection with SIRS) or severe sepsis (defined as sepsis-induced tissue dysfunction or organ dysfunction) [32]. An interesting point in our study was that ICU admission and mortality rates were significantly lower among HCAP patients with a PCT concentration of 0.5–2.0 ng/ml than among those with a PCT concentration >2.0 ng/ml. A PCT concentration in the range of 0.5–2.0 ng/ml was not a significant predictor of ICU admission and mortality for HCAP patients in our multivariate regression analysis model. Otherwise, a PCT concentration >2.0 ng/ml had the strongest predictive power for early mortality. When patients come to the ED, their pulmonary function and severity of sepsis critically affect their outcomes. Therefore, a high PCT (>2.0 ng/ml) can be a useful threshold for predicting clinical outcomes because of its strong association with sepsis progression.

The rules for predicting the outcome for HCAP patients are not well established. A severity scoring system such as the PSI or CURB-65 – both of which have been widely used for patients with CAP – could be expected to be a tool for the prediction of HCAP outcomes and severity. However, there are considerable limitations to the use of these scoring systems. First, they do not show a consistently high discriminatory power for predicting outcomes in HCAP patients compared with CAP patients. The discriminatory power varies according to the diverse distribution of patient populations in hospitals. In a clinical

study by Jeong et al. [10] comparing HCAP and CAP, the discriminatory power for predicting 30-day mortality in HCAP (0.679 of the AUC for PSI and 0.599 of the AUC for CURB-65) was relatively lower than that seen in our study (0.799 of the AUC for PSI and 0.767 of the AUC for CURB-65). Their study included a larger proportion of patients with advanced cancer who had been treated with chemotherapy (30%), whereas our study had only few patients on chemotherapy and mainly included previously hospitalized patients or nursing home care patients. Second, many emergency or respiratory physicians who are responsible for the emergency care of pneumonia patients infrequently use the PSI and are scarcely able to apply the PSI calculation system to patients, because it is too difficult and time-consuming to measure the necessary parameters and calculate the PSI score in a busy ED [33]. The CURB-65 may be more easily applicable for use by these physicians, because it is relatively simple; however, its discriminatory power for predicting outcome is low compared with the PSI scoring system or the PCT level [10].

Inflammatory markers, which are thought to be well correlated with the severity of infection and sepsis, have the advantage of early prediction of the clinical prognosis of various infectious diseases. Checking the results of tests of inflammatory markers is not complex, and is easily applicable to the busy situation in the ED. Many inflammatory markers such as WBC, CRP, and PCT have been suggested to be useful candidates for predicting outcomes in pneumonia patients. Numerous studies have shown PCT as the most useful predictor of outcomes in CAP patients [20, 21, 23], with a good discriminatory power (over 0.8 of the AUC) for predicting outcomes [34]. Our study demonstrated that in HCAP patients PCT has a higher AUC value for clinical outcomes than WBC and CRP.

PCT on admission may have some attractive features for predicting outcome in HCAP patients. First, its discriminatory power for predicting ICU admission and 30-day mortality is not significantly inferior to that of the conventional scoring systems PSI and CURB-65. In particular, a high PCT concentration (>2 ng/ml) was a significant independent predictor of ICU admission and 30-day mortality after adjusting for other factors that might have affected the clinical outcomes, such as altered mentality, unstable vital signs, leukocytosis, elevated CRP concentration, high pneumonia severity score, mechanical ventilation at the ED, the presence of an MDR pathogen, and initially inappropriate use of antibiotics. This strong predictive power may be very helpful when designing new prediction tools in the future. Second, PCT

is more easily checkable and is highly applicable for use in a busy ED compared with the complex scoring systems. PCT may be a good candidate marker for predicting outcomes in HCAP patients considering its good ability to predict outcomes and the practical advantages in the interpretation of these outcomes.

There are several limitations to our study. First, the data were collected from patients hospitalized in the ED of a single tertiary hospital. Some HCAP patients who suffered milder symptoms may have visited the outpatient department, and our results do not reflect these HCAP patients. Second, we did not control for a possible measurement bias given the retrospective study design. There may have been considerable differences between patients in the time of PCT sampling or injection of intravenous antibiotics, and these may have affected our study results. Third, our study population consisted mainly of patients in nursing home care and recently hospitalized patients, and only small numbers of patients receiving chemotherapy, haemodialysis, and wound care

were included. This selection bias may be an obstacle to generalization of the results of the study. Therefore, our study may be more appropriately representative not of a tertiary hospital that has large numbers of cancer patients, but of a community-based hospital responsible mainly for acute or nursing home care patients. HCAP affects diverse patient populations, and further, detailed approaches may be required to correctly assess the prognosis of the disease.

In conclusion, high PCT (>2 ng/ml) on admission was strongly associated with ICU admission and 30-day mortality in HCAP patients. However, application of PCT alone seems to be limited to predicting ICU admission and 30-day mortality. A prediction model combined with high PCT may be more useful in HCAP patients.

Financial Disclosure and Conflicts of Interest

None of the authors have any conflicts of interest to declare.

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