Original Article

The Usefulness of Procalcitonin and C-Reactive Protein as Early Diagnostic Markers of Bacteremia in Cancer Patients with Febrile Neutropenia

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Purpose
Procalcitonin (PCT) and C-reactive protein (CRP) are well known inflammatory markers. This study was designed to determine whether PCT and CRP are useful as early diagnostic markers for bacteremia in cancer patients with febrile neutropenia (FN) in the emergency department (ED).

Materials and Methods
In this retrospective study, 286 episodes of FN in the ED were consecutively included between June 2009 and August 2010. From medical records, clinical characteristics including PCT and CRP were extracted and analyzed.

Results
Bacteremia was identified in 38 (13.3%) of the 286 episodes. The median values of PCT (2.8 ng/mL vs. 0.0 ng/mL, p=0.000) and CRP (15.9 mg/dL vs. 5.6 mg/dL, p=0.002) were significantly higher in the group with bacteremia compared to the group without bacteremia. In univariate analysis, elevated PCT ($>$0.5 ng/mL) and CRP ($>$10 mg/dL) as well as older age, hypotension, tachycardia, tachypnea, and high body temperature were significantly associated with bacteremia. On multivariate analysis, elevated PCT ($>$0.5 ng/mL) (odds ratio [OR], 3.6; 95% confidence interval [CI], 1.4 to 9.2; p$<$0.01) and tachypnea (OR, 3.4; 95% CI, 1.4 to 8.5; p$<$0.01) were independent early diagnostic markers for bacteremia in FN patients. The area under the curve of PCT was 74.8% (95% CI, 65.1 to 84.6%) and that of CRP was 65.5% (95% CI, 54.8 to 76.1%). With a PCT cut-off value of 0.5 ng/mL, sensitivity and specificity were 60.5% and 82.3%, respectively, while the sensitivity and specificity were 57.6% and 67.3%, respectively, with a CRP cutoff of 10 mg/dL.

Conclusion
These findings suggest that PCT is a useful early diagnostic marker for the detection of bacteremia in FN at the ED and has better diagnostic value than CRP.

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Introduction

Febrile neutropenia (FN) in cancer patients is a common complication related to antineoplastic therapy, such as chemotherapy and radiotherapy. It is a high risk factor for developing serious bacterial infections that can result in fatal outcomes. Mortality has been reported to be higher in FN patients with bacteremia than in those without bacteremia [1]. Recently, more cancer patients receive chemotherapy

in outpatient settings, so the number of patients that visit the emergency department (ED) with complications related to antineoplastic therapy is increasing [2]. Therefore an immediate and appropriate strategy for this population in ED is required to reduce treatment delays and improve outcomes.

The early diagnosis of bacterial infection among patients with FN is challenging. Focus of infection is uncertain, and only a few clinical signs such as fever, headache, and hypotension may indicate bacterial infections in many cases of FN [3]. Efforts to predict bacteremia have

been made, but their sensitivity and specificity have been poor [4]. Even though blood cultures are the gold standard for the diagnosis of bacteremia [5], obtaining and testing these is time-consuming and their results are not available immediately in the ED. Therefore, a predictive tool to diagnose bacterial infections in FN is crucial for early diagnosis in the ED.

Several inflammatory markers have been studied for the diagnosis of infection. Among them, C-reactive protein (CRP) is frequently used and is a good marker of infection but it rarely distinguishes between bacterial and viral infection [6]. Procalcitonin (PCT) is a prohormone of calcitonin secreted from C-cells of the thyroid gland, and has been proposed as a candidate marker for diagnosis of active bacterial infections [7]. Serum PCT concentration in healthy individuals is low, but raises during septic conditions, especially when related to bacterial infections [8].

In this study, we aimed to evaluate the usefulness of PCT and CRP as early diagnostic markers of bacteremia in cancer patients with chemotherapy-related FN in the ED.

Materials and Methods

Subjects enrolled in this study were adult cancer patients (16 years or older) with chemotherapy-associated FN who visited the ED of a university-affiliated tertiary referral medical center, between June 2009 and August 2010. Clinical data were retrospectively extracted from the electronic medical records.

Fever was defined as a single oral temperature of $\geq 38.3℃$ or a temperature of $\geq 38.0℃$ for ≥ 1 hour, and neutropenia was defined as a neutrophil count of < 500 cells/mm³, or a count of $< 1,000$ cells/mm³ with a predicted decrease to < 500 cells/mm³ [9].

Laboratory data were obtained with complete blood count, serum creatinine, blood urea nitrogen, aspartate transaminase, and alanine transaminase (ALT) as well as PCT and CRP, at the time of admission to ED.

All statistical data were analyzed with SPSS ver. 12.0.1 (SPSS Inc., Chicago, IL). The Chi-square test and Student's t-test were used for univariate analysis. The Wilcoxon rank sum test for continuous data was used to screen for admission parameters potentially associated with final outcomes. Median values with interquartile range were calculated for inflammatory markers including PCT and CRP. For univariate analysis, age was categorized by the median value and clinical measurements were classified as hypotension (systolic blood pressure [SBP] < 90 mm Hg), tachycardia (pulse rate > 120 beats/min), tachypnea (respiratory rate > 24 breathes/min), and high body temperature ($> 39℃$). PCT were grouped by three cut-off values of 0.1, 0.5, and 1.0 ng/mL, and similarly CRP by cutoff values of 5, 10, and 20 mg/dL. All the categorical variables were compared using Chi-square analysis. Parameters considered significantly associated with a high risk of bacteremia were selected in univariate analysis, and the logistic regression for multivariate analysis was calculated for odds

ratio (OR) and 95% confidence interval (CI). Diagnostic values for bacteremia of PCT and CRP were calculated by analyzing the receiver operating characteristic (ROC) curves. p-values < 0.05 were considered to be statistically significant.

Results

1 Baseline characteristics of the overall population

A total of 286 patients were included as the study population, including 239 (83.6%) from solid tumors and 47 (16.4%) from hematologic malignancies. Among solid tumors, breast cancer was the most common in 94 followed by gastrointestinal cancer in 68 and lung cancer in 37 patients. Hematologic malignancies consisted of 37 lymphoma, 4 myelodysplastic syndromes, and 3 leukemia patients. The median age of patients was 54 years and females were dominant in the population (male : female=1 : 1.25).

As shown in Table 1, bacteremia was detected in 38 episodes (13.3%). In comparison between groups with and without bacteremia, the bacteremia group showed significantly higher rates of pulse (115 beats/min vs. 108 beats/min, p=0.01) and respiration (22 breaths/min vs. 20 breaths/min, p$<$ 0.01) than the non-bacteremia group whereas SBP (114 mm Hg vs. 117 mm Hg) and body temperature (38.5℃ vs. 38.4℃) were not significantly different between the two groups (p$>$ 0.05, each). The bacteremia group had poorer laboratory findings than the non-bacteremia group, although there was no significant difference in absolute neutrophil count (ANC) and ALT. In the same way, PCT and CRP showed much higher levels in the bacteremia group compared to the non-bacteremia group (the median value of PCT, 2.75 ng/mL vs. 0.00 ng/mL, p$<$ 0.01; the median value of CRP, 15.9 mg/dL vs. 5.6 mg/dL, p$<$ 0.01).

2 Comparison of early clinical features between FN groups with and without bacteremia

The majority of patients in the bacteremia group were older than those in the non-bacteremia group (68% vs. 44%, p$<$ 0.01). Two groups showed difference in gender distribution but this finding was not significant. Hypotension (24% vs. 4%), tachycardia (42% vs. 19%), tachypnea (37% vs. 9%), and high body temperature (42% vs. 21%) were reported more commonly and significantly in the bacteremia group than in the non-bacteremia group (p$<$ 0.01 for all). As shown in Table 2, in all comparisons of various cut-off values of PCT, the bacteremia group had higher PCT levels than the non-bacteremia group with statistical significance. On the other hand, in a category of CRP with the cut-off value of 5 mg/dL, there was no significant difference between bacteremia and non-bacteremia groups (68% vs. 52%, p=0.08), even though significant differences were observed in other categories of CRP with the cut-off value of 10 mg/dL

Table 1. Baseline characteristics in the overall study population

Characteristics	All	Bacteremia (+)	Bacteremia (-)	p-value
No. of patients (%)	286	38 (13.3)	248 (86.7)	
Age (range, yr)	54 (42-64)	62 (24-91)	53 (16-82)	<0.01
Male gender	127 (44.4)	22 (57.9)	105 (42.3)	0.07
Underlying malignancy				0.24
Solid tumor	239 (84)	29/239 (12)	210/239 (88)	
Hematologic malignancy	47 (16)	9/47 (19)	38/47 (81)	
Vital signs				
SBP (mm Hg)	116 (104-128)	114 (91-126)	117 (105-128)	0.09
Pulse rate (beats/min)	108 (98-118)	115 (103-135)	108 (98-118)	0.01
Respiratory rate (breaths/min)	20 (20-22)	22 (20-24)	20 (20-20)	<0.01
Body temperature (℃)	38.4 (36.3-38.9)	38.5 (38.1-39.2)	38.4 (38.1-38.8)	0.18
Laboratory findings				
ANC (/mm^3)	130 (40-370)	90 (20-363)	140 (41-383)	0.20
Hemoglobin (g/dL)	10.6 (9.3-11.6)	9.8 (8.6-10.6)	10.7 (9.4-11.7)	<0.01
Platelet ($\times 10^3$/mm^3)	126.5 (81.5-188.0)	68.0 (28.0-126.3)	136.5 (92.0-197.3)	<0.01
AST (IU/L)	26 (20-37)	39 (24-54)	25 (20-35)	<0.01
ALT (IU/L)	23 (16-36)	28 (16-53)	23 (16-53)	0.08
BUN (mg/dL)	11 (7-16)	18 (14-31)	10 (7-15)	<0.01
Creatinine (mg/dL)	0.7 (0.6-0.9)	0.6 (0.7-1.3)	0.7 (0.6-0.8)	<0.01
CRP (mg/dL)	5.8 (2.6-14.0)	15.9 (3.6-26.0)	5.6 (2.5-12.7)	<0.01
PCT (ng/mL)	0.05 (0.00-0.36)	2.8 (0.04-20.8)	0.0 (0.00-0.18)	<0.01

Values are presented as number (%) or median (IQR). By the Shapiro-Wilk test, all variables in categories of vital signs and laboratory findings were not normally distributed. The Wilcoxon's rank-sum test was used to calculate variables in each category. SBP, systolic blood pressure; ANC, absolute neutrophil count; AST, aspartate transaminase; ALT, alanine transaminase; BUN, blood urea nitrogen; CRP, C-reactive protein; PCT, procalcitonin; IQR, interquartile range.

Table 2. Comparison of early clinical features between febrile neutropenia groups with and without bacteremia

	Bacteremia (+) (n=38)	Bacteremia (-) (n=248)	p-value
Clinical history			
Age > median age of 54 yr	26 (68)	108 (44)	<0.01
Male gender	22 (58)	105 (42)	0.08
Clinical measurements			
SBP < 90 mm Hg	9 (24)	10 (4)	<0.01
Pulse rate > 120 beats/min	16 (42)	46 (19)	<0.01
Respiratory rate > 24 breaths/min	14 (37)	21 (9)	<0.01
Body temperature > 39℃	16 (42)	53 (21)	<0.01
Inflammatory markers			
PCT (ng/mL)			
>0.1	27 (71)	84 (34)	<0.01
>0.5	23 (61)	44 (18)	<0.01
>1.0	22 (58)	28 (11)	<0.01
CRP (mg/dL)			
>5	26 (68)	130 (52)	0.08
>10	22 (58)	81 (33)	<0.01
>20	14 (37)	29 (12)	<0.01

Values are presented as number (%). SBP, systolic blood pressure; PCT, procalcitonin; CRP, C-reactive protein.

**Table 3.** Multivariate analysis for bacteremia in febrile neutropenia patients

	Odds ratio (95% CI)	p-value
Age > median age of 54 yr	1.7 (0.8-3.9)	0.19
SBP < 90 mm Hg	2.4 (0.8-7.7)	0.14
Pulse rate > 120 beats/min	1.8 (0.8-4.0)	0.18
Respiratory rate > 24 breaths/min	3.4 (1.4-8.5)	<0.01
Body temperature > 39℃	1.6 (0.7-3.5)	0.31
PCT > 0.5 ng/mL	3.6 (1.4-9.2)	<0.01
CRP > 10 mg/dL	0.8 (0.34-2.1)	0.71

CI, confidence interval; SBP, systolic blood pressure; PCT, procalcitonin; CRP, C-reactive protein.

(58% vs. 33%, p < 0.01) and 20 mg/dL (37% vs. 12%, p < 0.01) (Table 2). On multivariate analysis, PCT with a cutoff value of 0.5 ng/mL (OR, 3.6; 95% CI, 1.4 to 9.2; p < 0.01) and tachypnea (OR, 3.4; 95% CI, 1.4 to 8.5; p < 0.01) were independent early diagnostic markers for bacteremia in FN patients at ED (Table 3).

3 Diagnostic accuracy of PCT and CRP for bacteremia in FN

The ROC curves of PCT and CRP are shown in Fig. 1. The area under the curve (AUC) of PCT was 74.8% (95% CI, 65.1 to 84.6%)
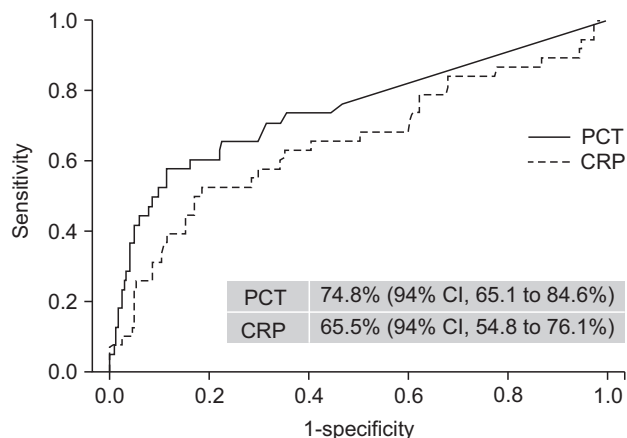
Fig. 1. Receiver operating characteristic (ROC) curves of procalcitonin (PCT) and C-reactive protein (CRP). The areas under the ROC curves of PCT and CRP were 74.8% and 65.5%, respectively. CI, confidence interval.

Table 4. Diagnostic accuracy of PCT and CRP for bacteremia in febrile neutropenia

Parameters	Sensitivity (%)	Specificity (%)	LR +	LR-
PCT (ng/mL)				
>0.1	71.1	66.1	2.1	0.4
>0.5	60.5	82.3	3.4	0.5
>1.0	57.9	88.7	3.8	0.7
CRP (mg/dL)				
>5	68.4	47.6	1.3	0.7
>10	57.6	67.3	1.8	0.6
>20	36.8	88.3	3.1	0.7

PCT, procalcitonin; CRP, C-reactive protein; LR, likelihood ratio.

while the AUC of CRP was 65.5% (95% CI, 54.8 to 76.1%), representing higher diagnostic accuracy of PCT to predict bacteremia than the accuracy of CRP ($p < 0.05$). With a PCT cutoff of 0.5 ng/mL, sensitivity and specificity of PCT were 60.5% and 82.3%, respectively. CRP with a cutoff of 10 mg/dL showed sensitivity and specificity of CRP as 57.6% and 67.3%, respectively. Table 4 shows sensitivity and specificity, as well as positive and negative likelihood ratios for PCT and CRP.

Discussion

FN with infection is a medical emergency that requires rapid diagnosis and intervention as soon as possible. Localizing signs and symptoms of infection are minimal or often absent and the progression of infection can be rapid in FN patients [9]. Therefore, an early diagnostic test to predict bacteremia in FN would be of great value by providing physicians with more definite evidence of the etiology of fever; especially in the ED where the first point of care has to be done.

On account of difficulties in diagnosis of bacterial infection in the FN, attempts to improve accuracy and rapidity of diagnosis of infection have been made through efforts on biomarkers [10]. Among various biomarkers, PCT and CRP have been considered useful [11]. In previous reports on PCT and CRP, PCT was shown to be more strongly associated with documented bacterial infection in FN patients [12]. PCT increased earlier in bacterial infection and returned to the normal range more quickly than CRP. In healthy individuals, PCT concentrations were below the detection limit but levels increased with increasing severity of the inflammatory response to bacterial infection [13]. In comparison with PCT, there was a wider overlap of CRP levels between groups with and without bacteremia. On multivariate

analysis, PCT was an independent, useful marker whereas CRP was not significant in predicting bacteremia. Similarly, the ROC curve showed superior sensitivity and specificity of PCT over CRP. A cut-off value of serum PCT to discriminate bacteremia from non-bacterial infection was adopted in this study as proposed previously [14,15]. PCT ≥ 0.5 ng/mL showed statistical significance in predicting bacteremia in FN patients. On the basis of the reported PCT values in FN, PCT values < 0.5 ng/mL were less likely to occur in patients with bacteremia. For a cut-off value of CRP, 10 mg/dL was used as proposed in the previous study [16].

In this study, the incidence of bacteremia was 13.3% and variables including age, initial vital signs, laboratory data except ANC and ALT, PCT and CRP, were significantly different between groups with and without bacteremia. However, to discover factors related with unrevealed bacteremia in early phase and to evaluate the usefulness of inflammatory markers, vital signs recorded initially at the ED and inflammatory markers, including PCT and CRP, at the time of admission were analyzed. As the result, tachypnea as well as PCT was significant as an early diagnostic marker for bacteremia. In the study by Bossink et al. [17], among the Systemic Inflammatory Response Syndrme (SIRS) criteria, tachypnea was the only factor that significantly predicted shock development in febrile patients using multivariate analysis. Considering that rapid respiratory rate and elevated PCT were independently and strongly associated with bacteremia, physicians should pay more attention to FN patients who present these characteristics.

Origins of inflammatory PCT are controversial since the production of PCT in the infection phase is not related to thyroid tissues [18]. The exact site of production during sepsis has not been identified, but it has been demonstrated that immunoreactive cells including neutrophils were possible sources of PCT production [19]. Therefore, concerns have been raised about possible impairment of PCT production in patients with neutropenia. However, other studies have demonstrated higher PCT levels in FN patients with documented bacterial infections [20], and our study also supported the plausibility of PCT as a reliable marker for bacterial infection in FN.

This study has several limitations. Some recent studies suggested

that PCT kinetics were more valuable to assess prognosis in infectious diseases [21]. In this study, however, the levels of PCT were evaluated only once at the time of admission at the ED. Another limitation is the heterogeneity of the cancer population. Cancer patients have great variation in the degree of immunosuppression and long-term survival. The majority of patients enrolled in this study were with solid tumors. Patients with hematologic malignancies are more likely to be immunocompromised than patients with solid organ malignancy and are at high risk of sepsis and have worse prognosis compared to solid tumors [22].

Limitation of PCT is that PCT only reflects systemic manifestation of bacterial infection. PCT may not or may only slightly increase when infection remains in a localized tissue with no systemic manifestations [23]. In patients with localized infections without signs of systemic manifestation, therapeutic measures such as antibiotics or surgical intervention may be necessary despite of normal PCT levels. Although elevated PCT values during severe infections may decrease to very low levels with appropriate therapy, this does not always indicate complete eradication of the infection but merely that generalization of the infection or the septic response is under control. Continuation of antibiotic therapy or surgical measures may be necessary until all clinical signs of infection have disappeared [13].

Conclusion

Bacteremia were detected in 13.3% of enrolled episodes of FN. Serum PCT concentration were significantly higher in patients with bacteremia. In a multivariate analysis, tachypnea and elevated PCT were independently and significantly associated with bacteremia.

These findings suggest that PCT is a useful early diagnostic marker to detect bacteremia in cancer patients with FN and has better diagnostic value than CRP. It is recommended to establish an early treatment strategy to prevent complications of bacterial infection in FN patients with high serum PCT concentration in the ED.

Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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