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ORIGINAL ARTICLE

Adding procalcitonin to the MASCC risk-index score could improve risk stratification of patients with febrile neutropenia

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Abstract
Purpose Infectious complication could be life-threatening in patients with chemotherapy-induced febrile neutropenia (FN). The Multinational Association of Supportive Care in Cancer (MASCC) risk-index score is used to predict the complications of these patients, and it has been focused on identifying low-risk patients who may be candidates for outpatient management. In this study, we evaluated procalcitonin (PCT) and the MASCC score in predicting bacteremia and septic shock in patients with FN.
Methods From November 2010 to October 2011, 355 patients with FN were prospectively enrolled. Clinical and laboratory findings, including procalcitonin, and the MASCC score were analyzed and correlated with the infectious complications of FN.
Results Of the 355 patients, 35 (9.9 %) had bacteremia, and 25 (7.0 %) developed septic shock. PCT ≥0.5 ng/mL (OR 3.96, 95 % CI 1.51–10.40), platelet count $<100\times10^3/mm^3$ (OR 2.50, 95 % CI 1.10–5.66), and MASCC score <21 (OR 2.45, 95 % CI 1.03–5.85) were independently predictive of bacteremia, and PCT ≥1.5 ng/mL (OR 29.78, 95 % CI 9.10–97.39) and MASCC score <21 (OR 9.46, 95 % CI 3.23–27.72) were independent factors of septic shock. In 306 patients with low-risk FN classified by the MASCC score, 52 had PCT ≥0.5 ng/mL and 31 had PCT ≥1.5 ng/mL. Of the 52 patients with PCT ≥0.5 ng/mL, 12 (23.1 %) had bacteremia, and of the 31 patients with PCT ≥1.5 ng/mL, 7 (22.6 %) developed septic shock.
Conclusion Implicating PCT as a routine use in clinical practice along with the MASCC score could improve risk stratification of patients with FN.

Keywords Procalcitonin · Febrile neutropenia · Bacteremia · Septic shock

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Introduction

Chemotherapy-induced febrile neutropenia (FN) is a common complication in cancer patients. Despite the availability of more effective and less toxic antibiotics, FN still remains a difficult therapeutic problem with a significant mortality rate. Among the risk stratification models developed for the prediction of complications in FN, the Multinational Association of Supportive Care in Cancer (MASCC) risk-index score is widely used and internationally validated, indicating MASCC score of ≥21, a low-risk episode for serious complications (Table 1) [1–4]. Bacteremia, the bacterial infection in the blood stream, could be life-threatening for patients with neutropenia; therefore, its early diagnosis is crucial in the management of FN [5]. Inflammatory markers including procalcitonin (PCT) are widely investigated as a tool for this purpose [6–8]. In this study, we analyzed serum PCT concentrations as an early marker of bacteremia and septic shock, and they were compared with the MASCC score in identifying these outcomes among the patients with FN. We also tried to find out if adding PCT to the MASCC score could improve risk stratification in FN.

Table 1 MASCC risk-index score

Factors	Score
Burden of illness	
No or mild symptoms	5
Moderate symptoms	3
Severe symptoms	0
No hypotension	5
No chronic obstructive pulmonary disease	4
Solid tumor or hematologic malignancy without previous fungal infection	4
No dehydration	3
Outpatient status at onset of fever	3
Age <60 years	2

A total score of ≥21 means that the patient is considered as low-risk for complication

MASCC Multinational Association of Supportive Care in Cancer

Methods

A prospective observational study was performed on all adult cancer patients who presented to the Asan Medical Center Emergency Department (ED) with complaints of fever and chemotherapy-induced neutropenia between November 2010 and October 2011. At the time of the ED visit, demographic characteristics including underlying malignancies, Eastern Cooperative Oncology Group Performance Status (PS), and laboratory data were collected. FN was defined as a temperature of ≥38 °C with a neutrophil count of <500 cells/mm^3, or a count of <1,000 cells/mm^3 with a predicted decrease to <500 cells/mm^3 [9]. After the diagnoses of FN were made, all patients were administered with empirical broad-spectrum parenteral antibiotics including piperacillin/tazobactam as monotherapy, or ceftazidime and cefazolin in combination. Further antibiotic treatments were adjusted according to the guidelines of the Infectious Diseases Society of America [9]. The patients were admitted, and antibiotics were maintained until their neutrophil counts had recovered to >500 cells/mm^3 and the patients became afebrile. Bacteremia was defined as positive blood cultures for pathogenic organism from peripheral blood or from central venous indwelling catheter if present. Septic shock was defined by hypotension (i.e., systolic arterial blood pressure of <90 mmHg or a reduction of ≥40 mmHg from baseline) despite fluid resuscitation, or by the need for administration of vasoactive drugs.

Baseline characteristics and outcomes were summarized by frequency tabulation or mean values. Continuous variables were categorized on the basis of previously published reports or the results from the receiver operating characteristic (ROC) curve analysis. For the threshold of PCT, the tradeoff between sensitivity and specificity was based on our purpose to gain high specificities rather than high sensitivities in order to rule out bacteremia and septic shock with the test. The relationship between each clinical factor and outcome was analyzed by univariate logistic regression analysis. Variables that achieved statistical significance ($P<0.05$) were selected for multivariate stepwise logistic regression analysis, and estimated odd ratios with confidence intervals were calculated for all significant variables. All statistical analyses were performed with SPSS ver. 12.0.1 (SPSS Inc, Chicago, IL, USA). This study was approved by the hospital's institutional review board.

Results

A total of 400 separate events of FN were recorded in 355 patients during the study period, and only the first episode for each patient was analyzed in the study. The mean (±SD) age was 54.0 (±14.2), with a range of 17 to 86 years. Of

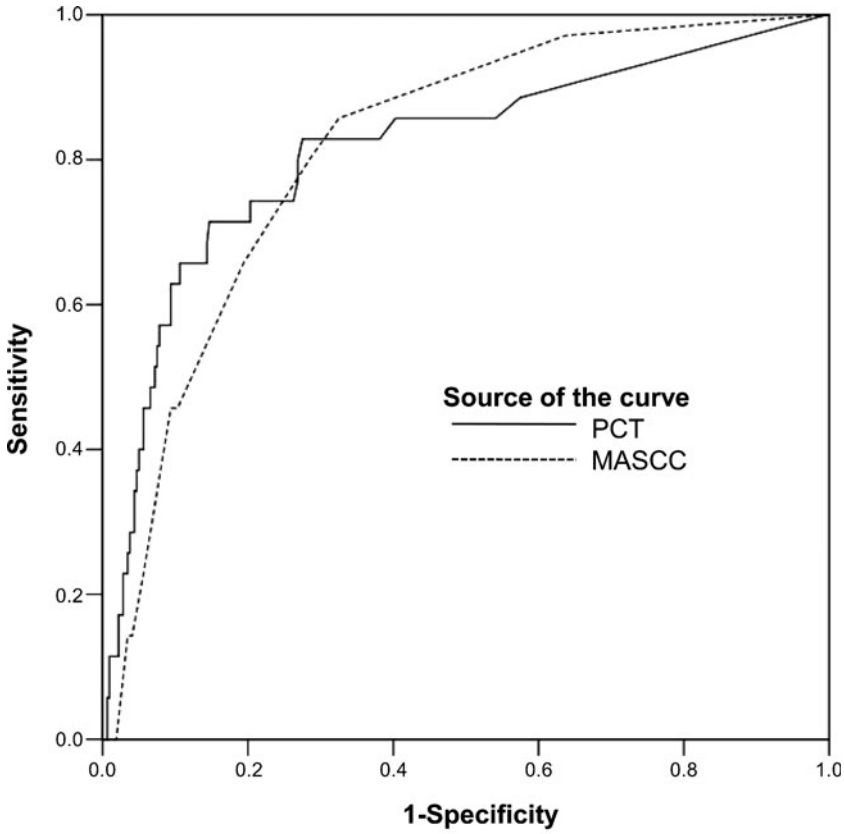
Table 2 Characteristics of patient episodes

Characteristics	Number
Total number of episodes/patients	400/355
Age (years)	
Mean ± SD	54.0±14.2
Male sex, *n* (%)	131 (36.9)
Underlying malignancies, *n* (%)	
Solid	287 (80.8)
Hematologic	68 (19.2)
Vital signs, mean ± SD	
Systolic blood pressure (mmHg)	120.4±19.8
Pulse rate (beats/min)	108.8±17.3
Respiratory rate (breaths/min)	20.0±2.0
Body temperature (°C)	38.5±0.6
Laboratory findings, mean ± SD	
ANC (cells/mm^3)	236.0±283.2
Hemoglobin (g/dL)	10.5±2.0
Platelet (×10^3/mm^3)	143.0±79.0
CRP (mg/dL)	8.5±8.4
PCT (ng/mL)	2.5±9.3
Aspartate aminotransferase (IU/L)	34.0±40.4
Alanine aminotransferase (IU/L)	31.8±36.4
Creatinine (mg/dL)	0.8±0.5
Albumin (g/dL)	3.4±0.6
Outcomes, *n* (%)	
Bacteremia	35 (9.9)
Septic shock	25 (7.0)
Death	11 (3.1)
MASCC score ≥21, *n* (%)	306 (86.2)

ANC absolute neutrophil count, *CRP* C-reactive protein, *PCT* procalcitonin, *MASCC* Multinational Association of Supportive Care in Cancer

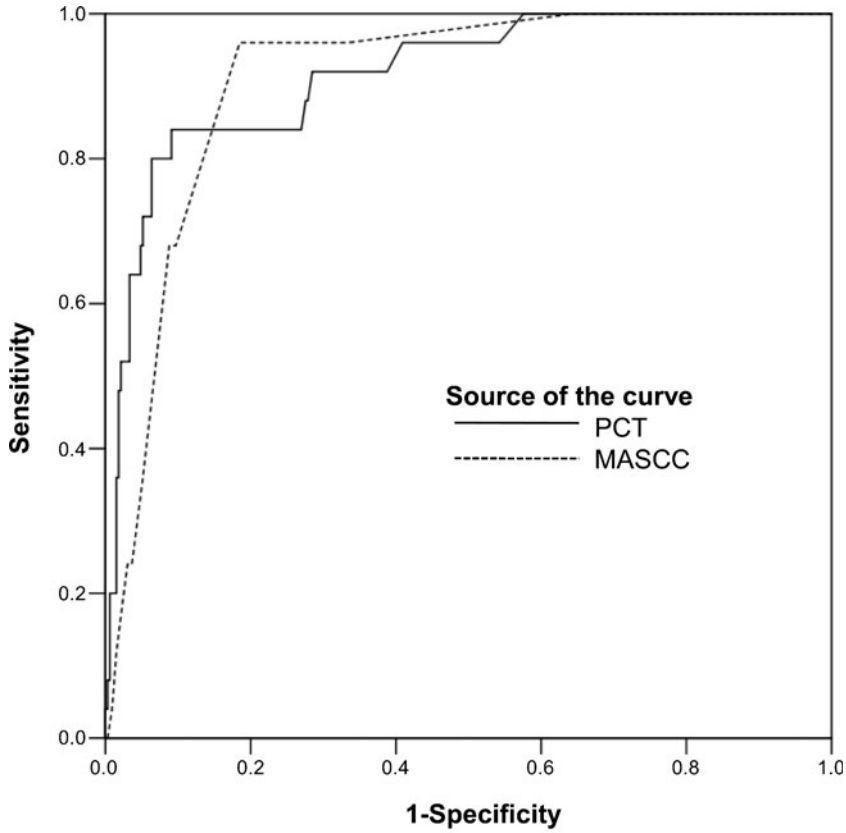
these 355 patients, 306 (86.2 %) were considered as low-risk FN with a MASCC score ≥21. Thirty-five (9.9 %) patients had bacteremia, and 25 (7.0 %) developed septic shock (Table 2). The ROC curve for PCT and the MASCC score proved to be highly accurate in predicting bacteremia and septic shock. In bacteremia, the area under the ROC curve for PCT was 0.815 (95 % CI 0.730–0.900), and the MASCC score was 0.815 (95 % CI 0.753–0.881). In septic shock, the area under the ROC curve for PCT was 0.916 (95 % CI 0.860–0.973), and the MASCC score was 0.909 (95 % CI 0.866–0.953) (Figs. 1 and 2). The thresholds for PCT were chosen through the ROC curve analyses, a cutoff of ≥0.5 ng/mL for bacteremia and ≥1.5 ng/mL for septic shock. The data were dichotomized, and the serum PCT ≥0.5 ng/mL, MASCC score <21, platelet count $<100\times10^3/mm^3$, CRP ≥10 mg/dL, PS ≥2, and age ≥60 were significant in univariate analysis for both bacteremia and septic shock. In multivariate analysis, serum PCT ≥0.5 ng/mL (OR 3.96, 95 % CI 1.51–10.40), platelet count $<100\times10^3/mm^3$ (OR 2.50, 95 % CI 1.10–5.66), and MASCC score <21 (OR 2.45, 95 % CI 1.03–5.85) were independently predictive of bacteremia. Serum PCT ≥1.5 ng/mL (OR 29.78, 95 % CI 9.10–97.39), and MASCC score <21 (OR 9.46, 95 % CI 3.23–27.72) were independent factors of septic shock (Tables 3 and 4). PCT ≥0.5 ng/mL was predictive of bacteremia with sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of 71, 82, 30, and 97 %. PCT ≥1.5 ng/mL was predictive of septic shock with sensitivity, specificity, PPV, and NPV of 84.0, 90.7, 40, and 99 %. The sensitivity and specificity of the MASCC score <21 were 46 and 90 % in predicting bacteremia, and 68 and 90 % in predicting septic shock, respectively (Table 5).

PCT was sequentially added to the MASCC risk-index score for risk stratification of the patients. In 306 patients with low-risk FN defined by the MASCC score of ≥21, 52 had PCT ≥0.5 ng/mL, and 31 had PCT ≥1.5 ng/mL. Of the 52 patients with PCT ≥0.5 ng/mL, 12 (23.1 %) had bacteremia, compared to 2.8 % in PCT <0.5 ng/mL. Of the 31 patients with PCT ≥1.5 ng/mL, 7 (22.6 %) developed septic shock, compared to 0.4 % in PCT <1.5 ng/mL (Fig. 3).



Area Under the Curve	
PCT	0.815 (95% CI 0.730 – 0.900)
MASCC	0.815 (95% CI 0.753 – 0.881)

Fig. 1 Receiver operating characteristic curves for predicting bacteremia. *PCT* procalcitonin, *MASCC* Multinational Association of Supportive Care in Cancer



Area Under the Curve	
PCT	0.916 (95% CI 0.860 – 0.973)
MASCC	0.909 (95% CI 0.866 – 0.953)

Fig. 2 Receiver operating characteristic curves for predicting septic shock. *PCT* procalcitonin, *MASCC* Multinational Association of Supportive Care in Cancer

Discussion

Since infection is the major cause of morbidity and mortality in neutropenic patients, considerable attention has been focused on early identification of infection with the acute-phase reactants [10–12]. Although previous study results were found to be inconsistent with controversial consequences, most recent trials confirmed the validity of PCT as a marker of bacterial infection in FN [13]. In our study, PCT was the independent risk factor predicting both bacteremia and septic shock in FN with the highest adjusted odd ratios. The MASCC scoring system has been focused on identifying low-risk patients who may be candidates for outpatient therapy in FN [1–4]. The system was designed to predict complications during the episodes, which did not include bacteremia as one of the serious outcomes in its

Table 3 Analysis of predictive factors for bacteremia in patients with febrile neutropenia

	Univariate analysis			Multivariate analysis		
	OR	95 % CI	*p* value	OR	95 % CI	*p* value
PCT ≥0.5 ng/mL	11.06	5.04–24.27	<0.001	3.96	1.51–10.40	0.005
MASCC score <21	7.32	3.44–15.60	<0.001	2.45	1.03–5.85	0.044
Platelet count $<100\times10^3/mm^3$	4.75	2.27–9.94	<0.001	2.50	1.10–5.66	0.028
CRP ≥10 mg/dL	8.25	3.71–18.33	<0.001			0.058
PS ≥2	3.13	1.54–6.36	0.002			0.837
Age ≥60 years	4.11	1.94–8.70	<0.001			0.209

PCT procalcitonin, *CRP* C-reactive protein, *MASCC* Multinational Association of Supportive Care in Cancer, *PS* Eastern Cooperative Oncology Group Performance Status

Table 4 Analysis of predictive factors for septic shock in patients with febrile neutropenia

	Univariate analysis			Multivariate analysis		
	OR	95 % CI	*p* value	OR	95 % CI	*p* value
PCT ≥1.5 ng/mL	48.89	15.80–151.30	<0.001	29.78	9.10–97.39	<0.001
MASCC score <21	19.79	7.92–49.46	<0.001	9.46	3.23–27.72	<0.001
Platelet count $<100\times10^3/mm^3$	3.45	1.50–7.94	0.004			0.997
CRP ≥10 mg/dL	14.44	4.82–43.23	<0.001			0.092
PS ≥2	5.67	2.36–13.59	<0.001			0.668
Age ≥60 years	2.63	1.14–6.03	0.023			0.101

PCT procalcitonin, *MASCC* Multinational Association of Supportive Care in Cancer, *CRP* C-reactive protein, *PS* performance status

derivation study. However, some studies have shown that bacteremia was less often reported in patients classified as low-risk based on MASCC score [5, 14, 15], indicating that this scoring system could help risk stratification of patients with FN in terms of predicting infection. We found a significant association between infection and the MASCC score: patients considered as high-risk group for complication (MASCC score <21) were independently predictive of bacteremia, and this trend was also shown in patients with septic shock. These results supported previous studies that the MASCC score could help in predicting the infectious complications in FN. The ROC curve analysis showed good performance of the PCT and MASCC score in predicting bacteremia, and excellent performance in predicting septic shock. Platelet count $<100\times10^3/mm^3$ was also associated with bacteremia in multivariate analysis. However, it was not predictive in septic shock. In patients with FN, along with MASCC score of <21, PCT ≥0.5 ng/mL was a significant predictor of bacteremia, and PCT ≥1.5 ng/mL was in septic shock. When adding the MASCC score and PCT together, specificities and test accuracies were improved. However, sensitivities were decreased. This tradeoff between sensitivity and specificity was based on our purpose to gain high specificities and high NPVs rather than high sensitivities in setting the cutoff values of PCT, in order to rule out bacteremia and septic shock with the test.

The fact that high-risk patients with a MASCC score of <21 should be managed more carefully and aggressively is beyond dispute, and even the low-risk patients still have the risk of bacteremia and even septic shock [8, 16]. So, we thought that adding PCT to the low-risk patients should be more practical than routinely adding PCT to MASCC score

Table 5 Test accuracy of the MASCC risk-index score and serum procalcitonin concentration in identifying bacteremia and septic shock in patients with febrile neutropenia

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Bacteremia					
MASCC <21	46	90	33	94	85
PCT >0.5 ng/mL	71	82	30	96	81
MASCC <21 and PCT >0.5 ng/mL	37	94	41	93	88
Septic shock					
MASCC <21	68	90	35	97	89
PCT >1.5 ng/mL	84	90	40	99	90
MASCC <21 and PCT >1.5 ng/mL	56	98	64	97	95

MASCC Multinational Association of Supportive Care in Cancer, *PCT* procalcitonin, *PPV* positive predictive value, *NPV* negative predictive value

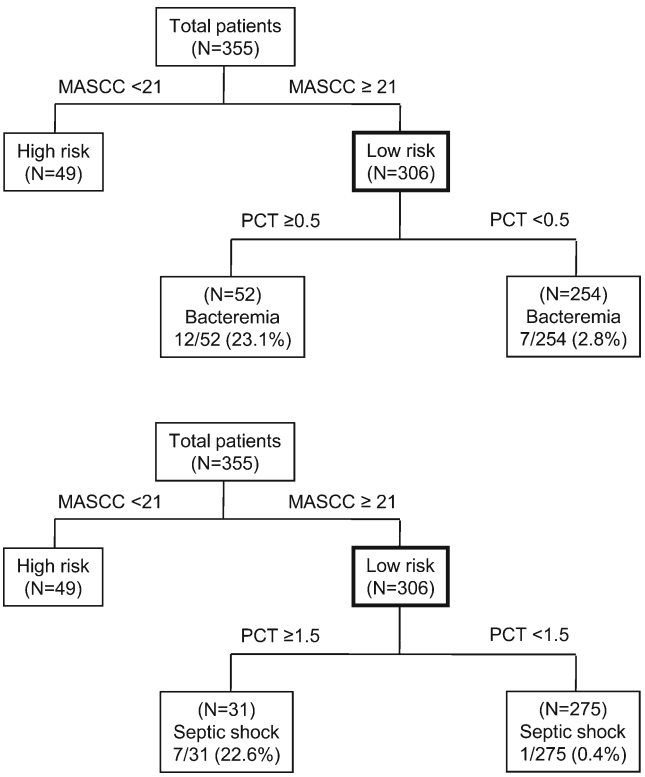


Fig. 3 Incorporation of procalcitonin to the MASCC risk-index score in the risk stratification of febrile neutropenia. PCT was added to the low-risk febrile neutropenic patients with MASCC score of ≥21, and the incidence of bacteremia and septic shock was calculated according to each PCT cutoff. *PCT* procalcitonin, *MASCC* Multinational Association of Supportive Care in Cancer

in all patients. Even in the 306 patients with low-risk FN, 19 had bacteremia and 8 developed septic shock. Of the 19 patients with bacteremia, 12 (63 %) had PCT ≥0.5 ng/mL; of the 8 patients with septic shock, 7 (87.5 %) had PCT ≥1. 5 ng/mL. In contrary, in patients with PCT <0.5 ng/mL, bacteremia was present in 2.8 %; in PCT <1.5 ng/mL, septic shock was developed in 0.4 %. Adding PCT to identify patients with bacteremia or septic shock in the low-risk patients could improve the performance of the MASCC risk-index score.

Our study has some limitations beyond the requirement of validation. This was a single center study, which could limit the generalizability of the results. To be a good predictive test, the sensitivity and specificity need to be high enough to make it useful. However, the selection of the threshold for PCT was based on our limited number of patients, and their sensitivities were relatively lower than the specificities in identifying bacteremia and septic shock.

This study showed that implicating PCT as an adjunctive biomarker along with the MASCC score could improve the risk stratification of patients with chemotherapy-induced FN. As infections including bacteremia and septic shock are the most life-threatening complications in FN, the results of this study are encouraging. However, additional studies are required to confirm these results and to refine their threshold before using PCT with the MASCC index in the routine management of FN in cancer patients.

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Conflict of interest None

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