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The Journal of Emergency Medicine, Vol. 60, No. 5, pp. 641–647, 2021

0736-4679/$ - see front matter

https://doi.org/10.1016/j.jemermed.2020.12.010

Clinical Communications: Adults

PROGNOSTIC VALUE OF SERUM PROCALCITONIN LEVELS IN PATIENTS WITH FEBRILE NEUTROPENIA PRESENTING TO THE EMERGENCY DEPARTMENT

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☐ **Abstract—Background: Various risk-stratification scores have been developed to identify low-risk febrile neutropenia (FN). The Multinational Association of Supportive Care in Cancer (MASCC) score is a commonly used validated scoring system, although its performance varies due to its subjectivity. Biomarkers like procalcitonin (PCT) are being used in patients with FN to detect bacteremia and additional complications. Objective: Our objective was to compare the performance of MASCC score with PCT in predicting adverse outcomes in patients with FN. Methods: This was a prospective observational study that included chemotherapy-induced FN in hematologic or solid malignancy. The MASCC score, PCT levels, and blood cultures were taken at the first point of contact, and patient treatment was managed according to routine institutional protocol. The primary outcome was mortality at 30 days. Results: A total of 100 patients were recruited, of which 92 had hematologic malignancy and 8 had solid malignancy. Forty-six patients were classified as low risk by MASCC score (≥21). The PCT threshold, 1.42 ng/mL, was taken as a cutoff value, with area under the receiver operating characteristic curve (AUROC) of 0.664 (95% confidence interval [CI] –0.55 to 0.77) for predicting mortality. AUROC for MASCC was 0.586 (95% CI 0.462 to 0.711). Conclusions: PCT is a useful marker with better prognostic efficacy than MASCC score in patients with FN and can be used as an adjunct to the score in risk-stratifying patients with FN.**

☐ **Keywords—febrile neutropenia; MASCC; procalcitonin; chemotherapy; emergency department**

INTRODUCTION

Febrile neutropenia (FN) is one of the common oncologic complications that presents to emergency department (ED). Most chemotherapy-induced neutropenic fevers have an uncomplicated course and patients can be discharged safely on oral antibiotics (1,2). Kuderer et al., in their study with approximately 42,000 patients with FN, found that the mortality associated is around 9.5% (3). FN outcome depends on patient characteristics, type of malignancy, comorbidities, and infectious complications (3). There is a need for early identification of high-risk patients who would need inpatient care with intensive antimicrobial therapy to prevent morbidity and mortality.

Various prediction rules to stratify the patients have been developed and, of them, MASCC score has been studied most frequently (4,5). MASCC score was developed based on disease burden, clinical instability, age, and comorbid conditions. It has a maximum score of 26, and scores ≤ 21 are considered high risk, that is, need inpatient management with i.v. antibiotics. However, it has limitations because of its subjective component, that is, burden of disease. Besides, in patients labeled low risk, serious complications can be seen in 9–15% of episodes (6). This led to the evaluation of acute-phase biomarkers that could identify bacteremia early in patients with FN.

RECEIVED: 10 October 2020; FINAL SUBMISSION RECEIVED: 16 November 2020;
ACCEPTED: 6 December 2020

Procalcitonin (PCT) is a useful biomarker for identifying bacteremia in patients with FN (7,8). Limited studies have compared PCT's utility with the MASCC score as a prognostic marker in predicting outcomes in patients with FN (9–11).

METHODS

Study Design and Setting

We conducted a prospective observational study to compare PCT levels with MASCC scores in risk-stratifying chemotherapy-induced FN in patients presenting to our ED during 18 months from August 2017 to April 2019.

Selection of Participants

Patients older than 12 years with hematologic and solid malignancy, meeting the criteria of chemotherapy-induced FN, were included in the study. Patients who were already on i.v. antibiotics as an outpatient for > 24 h or on i.v. antibiotics before developing FN for > 24 h were excluded. The Infectious Diseases Society of America defines fever in a neutropenic patient as a single oral temperature higher than 38°C or 100.4°F (12). We included patients with absolute neutrophil count <1000 in our study. Ethical clearance was taken by the institution's review board (IECPG/288/6/2017) and informed consent was obtained from all of the patients or their legal guardians (whichever applicable) before enrollment in the study.

Methods of Measurement

Basic demographic data, including age, sex, and primary site of cancer, were collected along with the characteristics required to calculate the MASCC score (Table 1). For calculating the MASCC score, symptoms were assessed by the emergency physician taking care of the patient, and because the grading of symptoms is subjective in MASCC, we tried to define the symptoms beforehand to maintain uniformity in the assessment.

Mild symptoms were generally considered events that did not interfere with performance or functioning (e.g., myalgias, chills, and nausea). Moderate symptoms were those that made the patient uncomfortable and negatively affected their daily activities. Severe symptoms were those that caused severe discomfort or severely limited functioning and the performance of daily activities.

For all of the patients with FN, serum PCT levels were done in the ED's point of care laboratory using QDx Instacheck PCT kits (DiaSys India, Maharashtra, India). QDx Instacheck PCT in conjunction with QDx Instacheck Reader is a fluorescence immunoassay for quantitative measurement of PCT concentration in human whole blood, serum, and plasma. The test uses a sandwich immunodetection method. PCT levels were available between 3 and 15 min. It measures the PCT value lying in the range of 0.25 to 100 ng/mL. Blood cultures and samples for PCT were taken before the start of antibiotics.

Table 1. Multinational Association of Supportive Care in Cancer Score

Characteristics	Weight
Burden of febrile neutropenia with no or mild symptoms	5
No hypotension (SBP > 90 mm Hg)	5
No chronic obstructive pulmonary disease	4
Solid tumor or hematological malignancy with no previous fungal infection	4
No dehydration requiring parenteral fluid	3
Burden of febrile neutropenia with moderate symptoms	3
Outpatient status	3
Younger than 60 years	2

SBP = systolic blood pressure.

The primary outcome measure was 30-day mortality. The patients were followed up at 1 month to note the outcomes. For those admitted, data were taken from their admission file, and for those transferred to other hospitals, the condition of the patient was requested via telephone.

Statistical Methods

A sample size of 85 was determined as adequate, assuming a confidence level of 95%, power of 80%, and anticipating 20% mortality in our study group. A total of 129 patients were screened, of which 100 were included in the study (Figure 1). Baseline characteristics and outcomes were summarized by frequency tabulation or mean values and χ^2 test was used for univariate analysis. Continuous variables were categorized based on results from the receiver operating characteristic (ROC) curve analysis. For the PCT threshold, ROC analysis

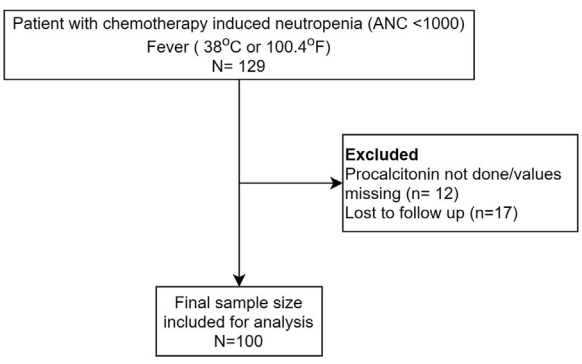


Figure 1. Plot for patient enrollment. ANC = absolute neutrophil count.

Table 2. Basic Characteristics (100 Patients)

Characteristics	Data
Age (years), mean ± SD	30.22 ± 14.72
Male patients, n (%)	70 (70)
Underlying malignancies, n (%)	
Solid	92 (92)
Hematologic	8 (8)
Vital signs, mean ± SD	
Systolic blood pressure (mm Hg)	108.1 ± 38.03
Pulse rate (beats/min)	115 ± 19.39
Respiratory rate (breaths/min)	20.0 ± 3.39
Body temperature (°C)	101.5 ± 1.18
Laboratory findings, mean ± SD	
ANC (cells/mm^3)	219.52 ± 334
Hemoglobin (g/dL)	6.61 ± 2.09
PCT (ng/mL)	9.76 ± 20.54
Creatinine (mg/dL)	0.72 ± 0.49
Positive blood culture, n (%)	7 (7)
MASCC ≥ 21	54 (54)
Death	34 (34)

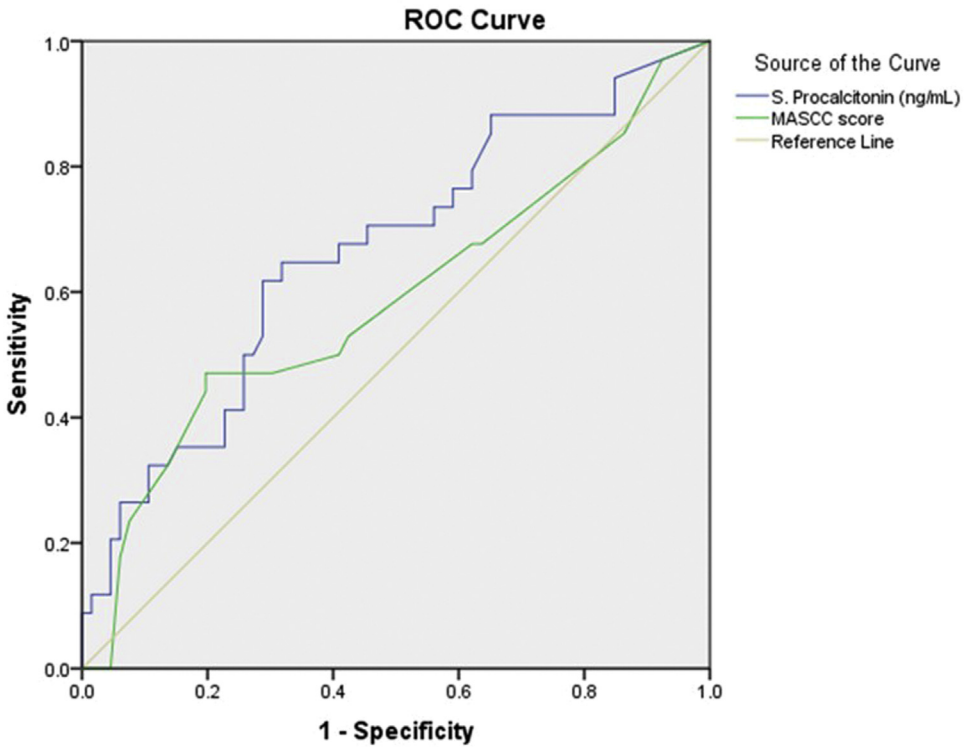
ANC = absolute neutrophil count; MASCC = Multinational Association of Supportive Care in Cancer; PCT = procalcitonin.

was done and the cutoff was decided using Youden's J statistics. The tradeoff between sensitivity and specificity was based on our purpose to gain fair diagnostic accuracy in predicting outcomes and bacteremia in patients. Data were collected in a predesigned proforma and entered into a Microsoft Excel (Microsoft, Redmond, WA) spreadsheet on the computer. The analysis was carried out in SPSS (version 23; IBM Corp., Armonk, NY).

RESULTS

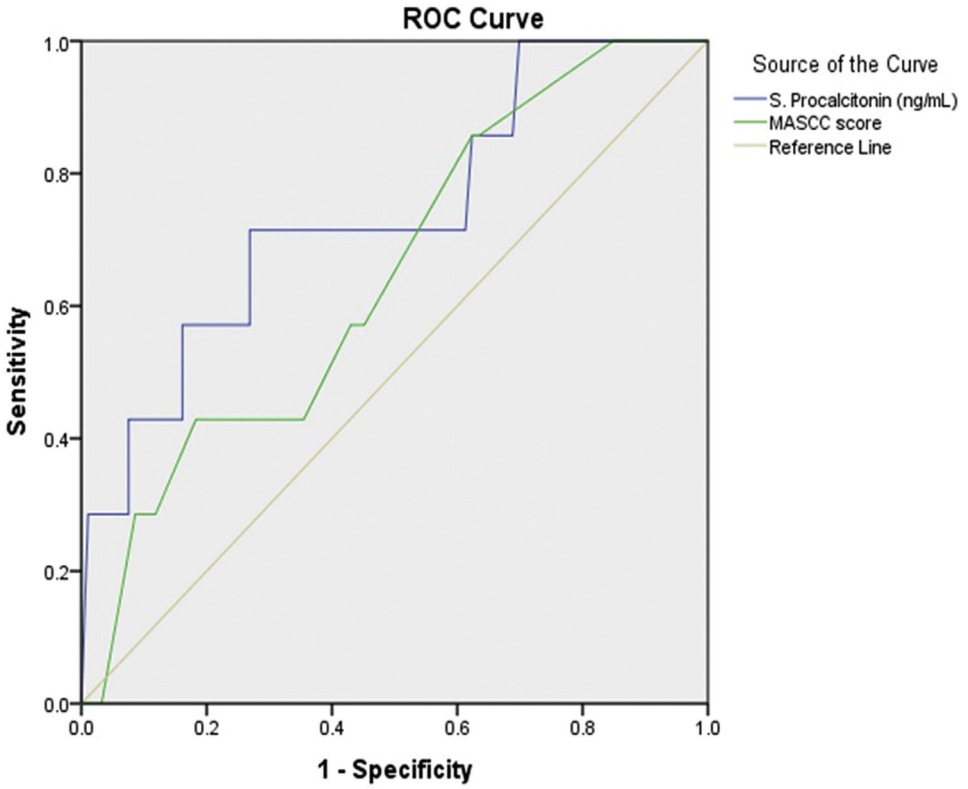
Characteristics of Study Subjects

A total of 100 patients were recruited for the study, of which 70% were male. Among them, 92% had hematologic malignancies and 8% had solid malignancies. Mean age was 30.2 years (range 13–61 years). Of the 100 patients, 46 were classified as low risk by the MASCC score (≥21). Only 7 patients had positive blood culture reports (Table 2).



Area Under Curve		
PCT	0.664 (95%CI 0.550-0.778)	*P*= 0.007
MASCC	0.586 (95% CI 0.462-0.711)	*P*= 0.158

Figure 2. Receiver operating characteristic (ROC) for predicting mortality. MASCC = Multinational Association of Supportive Care in Cancer; PCT = procalcitonin.



Area Under Curve		
PCT	0.739 (95%CI 0.537-0.941)	*P*= 0.036
MASCC	0.646 (95% CI 0.449-0.843)	*P*= 0.199

Figure 3. Receiver operating characteristic (ROC) for predicting bacteremia. MASCC = Multinational Association of Supportive Care in Cancer; PCT = procalcitonin.

Compared with PCT, the ROC curve for MASCC for predicting adverse outcomes performed poorly, and PCT performed fairly well in predicting bacteremia compared with MASCC (Figures 2 and 3).

The PCT threshold, 1.42 ng/mL, was taken as a cutoff value with area under the receiver operating characteristic curve (AUROC) of 0.664 (95% confidence interval [CI] –0.55 to 0.77) for predicting mortality. A PCT of > 1.42 ng/mL was predictive of mortality with sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) 65%, 65%, 49%, and 78%, respectively, and for predicting bacteremia, the sensitivity, specificity, PPV, NPV was 71%, 57,% 11%, and 96%, respectively (Table 3).

Table 3. Test Accuracy (95% Confidence Interval) of the MASCC Risk-Index Score and Serum Procalcitonin Concentration in Identifying Bacteremia and Septic Shock in Patients With Febrile Neutropenia

Variable	Sensitivity, %	Specificity, %	PPV, %	NPV, %
Mortality				
PCT	64.7 (46.5–79.6)	65.1 (52.3–76.1)	48.8 (33.9–64.0)	78.1 (64.6–87.7)
MASCC	52.9 (35.3–69.8)	57.5 (44.8–69.4)	39.1 (25.4–54.6)	70.3 (56.2–81.6)
Bacteremia				
PCT	71.4 (30.2–94.8)	56.9 (46.3–67.0)	11.1 (4.1–24.8)	96.2 (86.3–99.3)
MASCC	57.1 (20.2–88.1)	54.8 (44.2–65.1)	8.6 (2.8–21.6)	94.4 (83.6–98.5)

MASCC = Multinational Association of Supportive Care in Cancer; NPV = negative predictive value; PCT = procalcitonin; PPV = positive predictive value.
Values in parentheses are 95% confidence intervals.

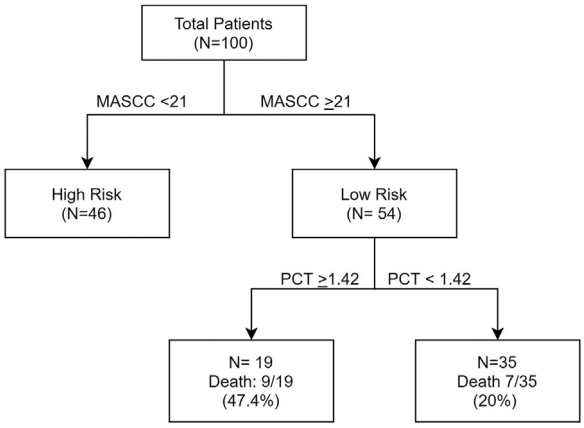


Figure 4. Incorporation of procalcitonin to the Multinational Association of Supportive Care in Cancer (MASCC) risk-index score in the risk stratification of febrile neutropenia. Procalcitonin (PCT) was added to the low-risk febrile neutropenic patients with MASCC score of ≥21, and the incidence of death was calculated according to each PCT cutoff. MASCC = Multinational Association of Supportive Care in Cancer.

Median (interquartile range [IQR]) values of PCT in patients with MASCC score ≥ 21 was 0.735 ng/mL (IQR 0.36–2.39 ng/mL), and in patients with MASCC score < 21, it was 1.48 ng/mL (IQR 0.61–18.03 ng/mL). The *p* value was 0.0062, which is statistically significant. On adding PCT values sequentially to MASCC score, in patients with low-risk scores (≥21), 19 had PCT ≥ 1.42 ng/mL, of which 9 (47.4%) died (Figure 4).

DISCUSSION

Our study revealed that although MASCC did not perform optimally in correctly identifying low-risk cases, the addition of PCT values can help in further risk-stratifying the patient. The MASCC score has been widely validated as a bedside screening to identify low-risk FN patients (13). The subjective component in the MASCC score has led to lesser reliability and missing serious complications in around 10% of the patients (14). In our study, the MASCC score showed a poor discriminating power with an AUROC of 0.586 in predicting adverse outcomes in patients with FN. Of 54 patients identified as low risk, 16 (29.6%) died at the end of 30 days. Therefore, discharging patients based on the MASCC score only can be unreliable.

Because infection is the most common cause of adverse outcomes in patients with FN, biomarkers like PCT have a crucial clinical role in FN (15). Our study compared PCT accuracy with MASCC score in predicting mortality and bacteremia in patients with FN and found that PCT performed better both in predicting adverse outcomes and identifying bacteremia in FN. In similar studies by García de Guadiana-Romualdo et al. and Ahn et al., they found PCT performed better than MASCC in predicting severe complications (e.g., septic shock, respiratory failure, and disseminated intravascular coagulation) and bacteremia (9,11).

In the study by Ahn et al., a cutoff for 0.5 ng/mL was used to detect bacteremia with sensitivity and specificity of 71% and 82%, respectively (11). We used a cutoff of 1.42 ng/mL, which showed a similar sensitivity of 71% but a low specificity of 57%. This low specificity could be due to the low number of positive blood cultures in our study.

When categorized as high risk by the MASCC score, the patients are monitored more closely and managed aggressively with intravenous antibiotics. However, there are still chances of bacteremia and adverse outcomes in the low-risk category, as demonstrated in our study. The addition of a biomarker in risk stratification has been shown to improve decision-making in patients with FN (9,11,16). We sequentially added PCT levels (cutoff 1.42 ng/mL) to the low-risk MASCC score, and on reclassifying them, found that patients with higher PCT 48% died. This highlights the role of adding PCT as an adjunct to the routine MASCC score in risk-stratifying the patients. These patients who otherwise looked well at the time of presentation would have deteriorated later. The addition of PCT will identify these subsets of patients who would need either admission or a prolonged observation in the ED and i.v. antibiotics.

Limitations

Our study has several limitations. This is a single-center study with a small sample size that included a high percentage of hematologic malignancy, limiting the generalization of the result. For a test to be of good predictive value, the sensitivity and specificity should be high. The limited number of patients and lower blood culture positivity rate led to the low sensitivity and specificity in our study. This prevents us from reaching a strong conclusion about the utility of PCT. A larger study to validate the findings would be needed. Adding the newer Clinical Index of Stable Febrile Neutropenia score in this study would have improved the utility of the study.

CONCLUSIONS

Our results suggest PCT's role as a useful marker with better prognostic efficacy than MASCC score in patients with FN and can be used as an adjunct to the score in risk-stratifying patients with FN.

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ARTICLE SUMMARY

1. Why is this topic important?

Febrile neutropenia (FN) is a frequent complication of chemotherapy. Risk-stratifying these patients is essential in deciding the management strategy. The Multinational Association of Supportive Care in Cancer (MASCC) score and different biomarkers are essential tools for the emergency physician for decision making.

2. What does this study attempt to show?

This study compares the performance of point of care procalcitonin with MASCC score in identifying adverse outcomes in patients with FN.

3. What are the key findings?

PCT performs better than the MASCC score in predicting mortality in FN patients and identifying bacteremia. On adding PCT as an adjunct to the MASCC score, it helps in identifying high-risk cases.

4. How is patient care impacted?

Adding a biomarker like PCT, which can be performed rapidly at bedside, to the existing MASCC score, will help improve the emergency department's decision-making.