original report

Procalcitonin and C-Reactive Protein As Markers of Bacteremia in Patients With Febrile Neutropenia Who Receive Chemotherapy for Acute Leukemia: A Prospective Study From Nepal

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abstract

PURPOSE The purpose of this study was to evaluate the clinical significance of the biomarkers procalcitonin (PCT) and C-reactive protein (CRP) in patients with febrile neutropenia (FN) undergoing chemotherapy for acute leukemia.

METHODS We conducted a prospective, observational study in patients who developed FN while undergoing chemotherapy for acute leukemia. PCT and CRP were obtained in patients who presented with FN. Blood cultures also were obtained. The primary goals were to evaluate the ability of PCT and CRP to predict bacteremia in patients with FN. The secondary goals were to assess the prognostic role of PCT and CRP and to assess the microbiologic profile and culture sensitivity patterns in the study population.

RESULTS A total of 124 episodes of FN that involved 67 patients with acute leukemia occurred in the study. PCT was superior to CRP in the prediction of bacteremia. The median PCT level in the bacteremia group was 3.25 ng/mL compared with 0.51 ng/mL in the group without bacteremia ($P < .01$). The median values of CRP in the bacteremia and without-bacteremia groups were 119.3 mg/L and 94.5 mg/L, respectively ($P = .07$). There were no differences in median PCT and CRP in patients who died and those who improved. Of the 42 positive cultures, Gram-negative bacteremia was common (86%), and *Escherichia coli* was the most frequent organism isolated. Carbapenem resistance was seen in 39% of positive cultures.

CONCLUSION PCT is an effective biomarker to predict bacteremia in patients with FN undergoing chemotherapy for acute leukemia.

INTRODUCTION

Febrile neutropenia (FN) is a common and serious complication in patients with acute leukemia who receive chemotherapy.[1] Despite advances in the prevention and treatment of FN, it remains a major cause of morbidity and mortality, uses substantial health care resources, and can compromise treatment efficacy.[2,3] Bacterial infections with both Gram-positive and Gram-negative organisms contribute to high mortality in this group of patients. Prognosis has been reported to be worse for patients with proven bacteremia; mortality rates are 18% for Gram-negative and 5% for Gram-positive bacteremia.[4] Literature from the Indian subcontinent reports mortality rates as high as 45%.[5]

In recent years, much effort has been directed toward the identification of biomarkers, such as procalcitonin (PCT) and C-reactive protein (CRP), which may help in the early clinical diagnosis of bacteremia to ensure prompt and effective management. There has been growing interest in PCT as one of these promising potential biomarkers that can distinguish infectious from noninfectious fever even in an immunocompromised state.[6,7] PCT is a hormokine composed of 116 amino acids and is the precursor of the hormone calcitonin.[8] PCT increases mostly during bacterial systemic infections, and its concentration reflects bacterial load.[9,10] Similarly, CRP is an acute-phase protein produced by the liver. Serum concentrations increase greatly during infection compared with physiologic concentrations. The serum concentration increases within few hours after the onset of bacterial infection.[11,12] CRP is an attractive biomarker because of its low cost, good reproducibility, and wide availability.[13]

Various mechanisms, including infections, drug reactions, blood products, or tumor-related events, may lead to fever in patients who have neutropenia after chemotherapy. Early identification of possible bacteremia and neutropenic sepsis is crucial in these patients to reduce morbidity and mortality.[14] Early

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TABLE 1. Baseline Characteristics

Characteristic	No. (%) of Patients
Age, years	
Median	25
Range	18-58
Sex	
Male	45 (67)
Female	22 (33)
Diagnosis	
Acute myeloid leukemia	39 (58)
Favorable risk	6 (15)
Intermediate risk	26 (67)
Poor risk	7 (18)
Acute lymphoblastic leukemia	28 (42)
B cell	27 (96)
T cell	1 (4)

prediction of an infectious cause of fever in these patients would be of great help in the context of Nepal and similar countries to optimize management and so reduce mortality as well as cost of treatment from morbidity as a result of sepsis. It is essential in a resource-scare country like Nepal, where the cost of cancer treatment, including supportive care, often is borne by the patients and their families. In addition, identification of infectious versus noninfectious causes of fever and biomarker-guided escalation or de-escalation of antibiotics might help avoid unnecessary antibiotics and the emergence of antibiotic resistance.

To our knowledge, this is the first study to evaluate the clinical value of PCT and CRP as markers of bacteremia in patients who experience FN with acute leukemia in the Nepalese population. The primary objective of this study was to evaluate the role of PCT and CRP in the prediction of bacteremia in the presence of FN in patients undergoing chemotherapy for acute leukemia.

METHODS

This was a prospective, observational study conducted at the Clinical Hematology and Bone Marrow Transplant Unit, Civil Service Hospital, Nepal. The study was conducted after approval by the institutional review board, and informed written consent was obtained from each participant.

The study included adult patients age 18 years and older with a diagnosis of acute leukemia (acute myeloid leukemia [AML] and acute lymphoid leukemia [ALL]) undergoing chemotherapy who developed FN. The study period was from September 2017 to December 2018.

Blood culture was carried out aseptically; 10 mL of blood was drawn, directly added to the culture media at the onset of fever, and cultured using a Bactex-FX 200 BD instrument

TABLE 2. Demographics and Characteristics According to Disease Type

Characteristic	AML	ALL
Chemotherapy regimen		
New	7 + 3 induction + HDAC	BFM-95 protocol ± TKI (if Ph positive)
Relapse	FLAG + IDA	Hyper-CVAD
T cell		CHOEP
Nadir (range) ANC, 10^9/L	0.05 (0.002-0.3)	0.2 (0.04-0.4)
Nadir (range) hemoglobin, g/dL	7.2 (6-7.8)	7.4 (7.1-9)
Nadir (range) platelets, 10^9/L	92 (2-78)	38 (22-154)
Median (range) days since chemotherapy to onset of neutropenia	13.4 (7-18)	20.2 (6-29)
Median (range) days of neutropenia	8.1 (1-21)	14.3 (3-18)
Median (range) days of fever	3.2 (1-14)	2.4 (1-9)
No. (%) by clinical focus of infection		
Respiratory	35 (47.3)	12 (24)
Urinary tract	8 (10.8)	4 (8.0)
GI	5 (6.8)	10 (20.0)
Skin	3 (4.1)	0 (0.0)
Other	2 (2.7)	0 (0.0)
Nonlocalizing	21 (28.4)	24 (48.0)
No. (%) with possible fungal infection (by HRCT chest)	16 (21.6)	5 (10.0)

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; ANC, absolute neutrophil count; BFM, Berlin-Frankfurt-Munster; CHOEP, cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisolone; FLAG + IDA, fludarabine, cytarabine, granulocyte colony-stimulating factor, plus idarubicin; Hyper-CVAD, hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; HDAC, high-dose cytosine arabinoside; HRCT, high-resolution computed tomography; TKI, tyrosine kinase inhibitor.

TABLE 3. Median PCT and CRP in Bacteremia and Without Bacteremia

Biomarker	With Bacteremia	Without Bacteremia	*P* (Mann-Whitney *U* test)
Median (range) FN PCT value	3.25 (0.28-52.30)	0.51 (0.02-5.90)	< .01
Median (range) FN CRP value	119.3 (21-378)	94.45 (0.18-280)	.07

Abbreviations: CRP, C-reactive protein; FN, febrile neutropenia; PCT, procalcitonin.

(Becton and Dickinson, Franklin Lakes, NJ). Antibiotic sensitivity testing was performed by the Kirby-Bauer disc diffusion method. Anaerobic, fungal, and viral cultures were not done because of the lack of laboratory facilities and economic constraints. Comprehensive metabolic parameters, including complete hemogram, renal function tests, liver function tests, and urinalysis, were obtained in each patient. Cultures from other sites, including sputum, urine, or throat swab, were sent as clinically indicated. After collection of samples for culture, piperacillin plus tazobactam was initiated after development of FN. Antibiotics were changed on the basis of the report of culture sensitivity. Patients with negative culture reports who experienced clinical improvement continued taking the same antibiotics, but treatment changed to second-line meropenem and amikacin if clinical deterioration occurred. Ciprofloxacin was used as prophylaxis in both groups beginning with the induction therapy. Fluconazole and voriconazole were used for patients with ALL and AML, respectively, as antifungal prophylaxis. Amphotericin B was initiated if a clinical suspicion of fungal infection was noted on high-resolution computed tomography of chest.

Blood samples for PCT and CRP were sent within 24 hours of onset of FN. Serum CRP was measured using the nephelometric method (Genrui-PA 54/Vitrus 4600; Genrui, Shenzhen, China). Serum PCT was measured using a fluorescent immunoassay technique (Getien Biotech, Nanjing, China). Normal PCT values were 0.0 to 0.1 ng/mL; normal CRP values were less than 10 mg/L. Values were obtained within 2 hours of test request.

FN was defined according to Infectious Diseases Society of America guidelines[15]: Fever was defined as a single oral temperature measurement of more than 38.3°C (101°F) or a temperature of more than 38.0°C (100.4°F) sustained over a 1-hour period. Neutropenia was defined as an absolute neutrophil count of fewer than 500 cells/mm^3 or an a count that is expected to decrease to fewer than 500 cells/mm^3 during the next 48 hours.

Systemic bacteremia was documented by positive blood culture. Subsequent episodes of FN in the same patient were included in the study and were considered as separate episodes. Outcome was defined as expired if the patient died without resolution of neutropenic fever, and it was defined as improved if the patient recovered after the episode of FN.

TABLE 4. Median PCT and CRP in Patients Who Died and Those Who Improved

Biomarker	Patients Who Died	Patients Who Improved	*P* (Mann-Whitney *U* test)
Median (range) FN PCT value	2.62 (0.28-19.92)	1.44 (0.02-52.30)	.14
Median (range) FN CRP value	115.6 (28-224.32)	97.94 (0.18-378)	.61

Abbreviations: CRP, C-reactive protein; FN, febrile neutropenia; PCT, procalcitonin.

Study Objectives

The primary goal was to evaluate the role of PCT and CRP in prediction of bacteremia in patients with FN undergoing chemotherapy for acute leukemia. The secondary goals were to assess prognostic role of PCT and CRP and to assess the microbiologic profile and culture sensitivity patterns in the study population.

Data Collection and Statistical Analysis

Data were recorded on a standardized data collection sheet. Frequencies and percentages were obtained for each categoric variable. The mean and median were estimated for continuous variables. Data were analyzed with SPSS software, version 25 (SPSS, Chicago, IL). The nonparametric Mann-Whitney *U* test was used to compare the results of PCT and CRP between the two groups. A two-tailed level of significance at a *P* value of less than .05 was considered significant and was applied to all statistical tests. Receiver operating characteristic (ROC) curves were constructed with 95% CIs. The area under the curve (AUC) was used to evaluate the predictive power of PCT and CRP for bacteremia. Using the coordinates of the curve, the cutoff value was determined for the value with best predictive ability.

RESULTS

Patient demographics are listed in Table 1. The median age of the study population was 25 years; 58% of cancers were AML, and 42% were ALL. A total of 124 episodes of FN were observed in 67 patients (men, n = 45; women, n = 22). Clinical foci of infection were present in 79 patients (63.7%; Table 2).

Prediction of Bacteremia

The median values of PCT and CRP after FN in the entire cohort were 1.58 ng/mL and 97.94 mg/L, respectively. The median PCT level in the bacteremia group was 3.25 ng/mL and was 0.51 ng/mL in the group without bacteremia ($P < .01$; Table 3). The median values of CRP in the bacteremia and without-bacteremia groups were 119.30 mg/L and 94.45 mg/L, respectively ($P = .07$).

Prognostic Significance

To explore the prognostic significance of serum PCT and CRP levels, we also analyzed data on serum PCT and CRP levels in patients who died and those who improved. Six

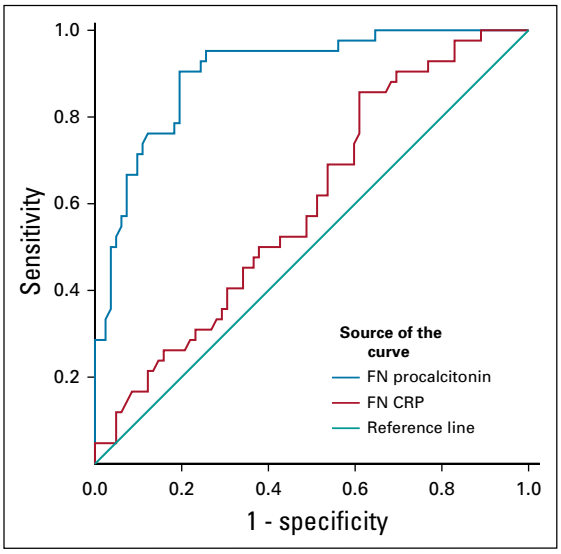

FIG 1. Receiver operating characteristic curve of procalcitonin and CRP for prediction of bacteremia. Diagonal segments are produced by ties. CRP, C-reactive protein; FN, febrile neutropenia.

patients died in the study group. The median PCT in those who died was 2.62 ng/mL, whereas it was 1.44 ng/mL in the improved group ($P = .14$). The median CRP values in those who died and in the improved group were 115.60 mg/L and 97.94 mg/L, respectively ($P = .61$; Table 4).

Using the ROC curve with 95% CIs, the optimal AUC was constructed for the predictive ability of PCT and CRP (Fig 1). The AUC for PCT was 0.90, and that for CRP was 0.59, which indicated a better predictive power for PCT to diagnose bacteremia in the study population. Using coordinates of the curve to determine the cutoff value with the best specificity and sensitivity, a value of 2.5 ng/mL for PCT had a specificity of 91% and a sensitivity of 69%. At the cutoff value of 3.25 ng/mL, the sensitivity for PCT was 82.1%, and the specificity was 80.2%. ROC curves also were generated to assess the prognostic value for PCT and CRP and revealed AUC values of 0.68 and 0.56, respectively. This result implies that neither PCT nor CRP has a good ability to prognosticate in this study population.

TABLE 5. Culture Report in Study Population

Culture Result	Total No. (%)
Negative culture	242 (85.2)
Positive culture	42 (14.8)
Gram-negative organism	36 (85.7)
Escherichia coli	15 (41.7)
Klebsiella	8 (22.2)
Pseudomonas	9 (25)
Acinetobacter	3 (8.3)
Citrobacter	1 (2.9)
Gram-positive organism	
Staphylococcus aureus	6 (14.3)

A total of 284 blood cultures were sent during the FN episodes, of which 42 (15%) were positive (Table 5). Gram-negative bacteremia was common in our study population, as listed in Table 4 and shown in Figure 2. Of the 42 positive cultures, 36 (86%) were Gram negative and six were Gram positive. *Escherichia coli* was the most common Gram-negative organism (Table 4), and *Staphylococcus aureus* was the most common Gram-positive organism. Only 61% of Gram-negative organisms were carbapenem sensitive. *E. coli* was the organism most resistant to carbapenem (70%). The median duration of antibiotics in the bacteremia group was 11.4 days (range, 5 to 21 days); in the no-bacteremia group, it was 10.8 days (range, 3 to 18 days).

DISCUSSION

FN during chemotherapy in patients with acute leukemia is the leading cause of morbidity and mortality. Thus, early diagnosis and prompt treatment of infection are important to improve outcomes. The use of biomarkers like PCT and CRP for early prediction of bacteremia or sepsis might provide a reasonable basis for appropriate treatment, pending culture reports.[16-18]

In the meta-analysis by Wu et al,[19] PCT had the best performance in patients with hematologic malignancy. In this study, PCT served as a predictive diagnostic marker of bacteremia in the patients with FN. As presented, PCT with an ROC AUC of 0.90 was more predictive than CRP in this setting and is what we would recommend as a diagnostic aid to predict bacteremia in our patients with FN. These findings are similar to those reported in other literature.[20,21] Although higher specificity and sensitivity values would be ideal, our results showed a specificity of 91% and sensitivity of 69% at a cutoff value of 2.5 ng/mL; at a value of 3.25 ng/mL, the sensitivity for PCT was 82.1% and the specificity was 80.2%, which both are still practically acceptable. In this study, neither PCT nor CRP was helpful as a prognostic marker in terms of the outcome of mortality, which is inconsistent with other literature.[22] However, only six patients (10%) died, and a larger sample size may provide different results.

Although culture of the pathogenic organism remains the gold standard for investigation and identification of bacterial infections, delay in obtaining the results might adversely affect the outcome of patients in the setting of neutropenia after chemotherapy for acute leukemia. Therefore, the evaluation of biomarkers like PCT might serve as a quick and indirect evidence of bacteremia and help optimize antibiotics in this high-risk population. On the basis of these study results, it seems reasonable to use PCT to assess risk of bacteremia.

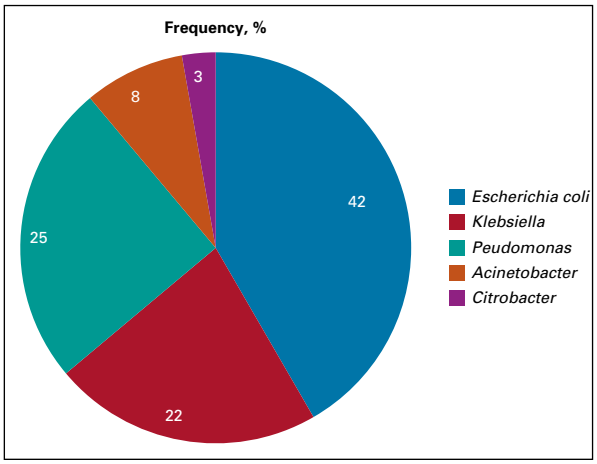

FIG 2. Gram-negative organisms isolated in culture.

This study revealed a high prevalence of Gram-negative bacteremia, as in other studies.[23] There was also a high incidence of carbapenem-resistant organisms in this study. Mortality in patients with FN and bacteremia is high, so this study provides a basis for additional, larger studies with PCT as a biomarker to determine whether evidence can be obtained to justify escalation of antibiotics in clinically ill patients, pending blood culture reports, who have high PCT levels. This approach could help reduce mortality from sepsis in resource-limited settings.

We acknowledge the limitations of this study. It was a single-institution study, and only one measurement each of PCT and CRP was obtained. Serial measures of PCT and CRP might have provided a better adjunctive guide for antibiotic management, yet these are less practical and more costly. This study raises the possibility that, in a prospective, appropriately controlled and powered study, early discontinuation of antibiotics in patients with a low probability of sepsis on the basis of PCT measurements could reduce cost and reduce the increasing prevalence of antibiotic resistance. In a resource-limited environment like Nepal, these considerations are of paramount importance.

In conclusion, PCT is an effective biomarker to predict bacteremia in patients with FN undergoing chemotherapy for acute leukemia. Additional larger, appropriately designed, randomized, controlled studies must be done to determine the practical clinical implications of PCT measurement before a clinical conclusion is reached. Its use as a standard-of-care biomarker might improve outcomes in neutropenic sepsis and help avoid unnecessary antibiotics use.

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