



Procalcitonin and C-reactive protein predict infection in hematopoietic stem cell transplantation patients

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ABSTRACT

Introduction: Procalcitonin (PCT) and C-reactive protein (CRP) are known inflammatory markers of severe infection; however, their ability to differentiate between infections of different origins is not clear yet. In this study, we evaluated PCT and CRP as markers of infection in hematopoietic stem cell transplantation (HSCT) patients.

Methods: Blood samples were collected to determine serum concentrations of PCT, CRP, D-Dimer, and to perform blood culture analysis. Based on blood culture results, the patients were divided into two groups—positive blood culture (n = 271) patients and negative blood culture patients (n = 668); the negative blood culture group served as the control. The positive blood culture group was further divided into three groups based on the etiological agent of infection. PCT and CRP concentrations were compared, and ROC curve, sensitivity, specificity, and cutoff values were calculated.

Results: PCT levels in infected patients were significantly higher than those in control patients ($p < 0.001$); similarly, CRP and D-Dimer levels were also higher among infected patients when compared with those in the controls. A PCT level of 0.51 ng/mL was the best threshold for detecting the infection, with an AUC-ROC of 0.877, whereas the best threshold for CRP was 49.20 mg/L. PCT levels were the highest in patients with gram-negative bacteremia as compared to in those with gram-positive bacteremia and fungal infection. The optimal cutoff value of PCT for the detection of gram-negative and gram-positive infection was 1.63 ng/mL.

Conclusion: PCT seems to be a useful marker for the diagnosis of systemic infection in HSCT patients, probably better than CRP and D-Dimer.

1. Introduction

Advances in the study of this procedure could lead to HSC transplant-based treatments for solid tumors and other genetic diseases as well as autoimmunity [1]. Allogeneic hematopoietic stem cell transplantation is a curative treatment for many hematological diseases; however, this procedure makes the patients susceptible to infection [2]. In patients with hematologic malignancies, especially in those with neutropenia, infection remains the leading cause of premature death; therefore, the management of local or systemic infection in patients is required. In such patients, the symptoms and signs of infection are few and the infection progresses rapidly; thus, early detection and appropriate antimicrobial treatment are critical for survival [3]. Commonly used

clinical inflammatory indicators, such as IL-6 and white blood cell count, have poor specificity for the diagnosis of severe infections [4]. However; in recent years, several new markers, such as procalcitonin (PCT) and C-reactive protein (CRP), have been proposed for the diagnoses and monitoring of severe infections [5–7].

PCT, a 116-amino acid peptide with a molecular weight of 13 kDa, is a precursor of the calcitonin hormone, which does not present hormonal activity. Under physiological conditions, PCT is produced in the C cells of the thyroid gland, reaching bloodstream concentrations below ng/mL [8]; in contrast, during sepsis, PCT levels can increase to 1,100,000 times that of the baseline levels [9]. In addition, PCT can be secreted within 4 h after stimulation, and peaks at 8 h, and can increase approximately 1000-fold after highly invasive bacterial infections [10,

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Table 1
Cases Characteristics.

	Negative blood culture (n = 668)	Positive blood culture (n = 271)	<i>p</i>	Gram-positive (n = 94)	Gram-negative (n = 158)	Fungus (n = 19)	<i>P</i>
Age(years)	36(28, 50)	37(27, 49)	/	38(2650)	39(2950)	34(2637)	/
Sex(male%)	364(54.5 %)	192(70.8 %)	/	70(74.5 %)	114(72.2 %)	8(42.1 %)	/
PCT(ng/mL)	0.19 (0.12, 0.30)	2.06 (0.57, 5.72)	<0.001	0.65 (0.29, 1.32)	4.57 (1.46, 10.77)	2.10 (1.57,2.88)	<0.001
CRP(mg/L)	41.02 (143.43, 93.96)	69.56 (23.68, 121.67)	<0.001	72.92 (24.86,120.73)	56.49 (23.35,124.21)	92.45 (29.62,111.46)	0.411
D-Dimer(mg/ mL)	335.00 (183.00, 713.50)	441.00 (246.00, 873.00)	<0.001	459.50 (244.00,987.00)	427.00 (228.00,857.00)	565.0 (369.00,863.50)	0.264

CRP: C-reactive protein; PCT: procalcitonin.

11]. Its reliability and sensitivity makes it suitable for the detection of mild elevations that occur early during a bacterial infection [13]. Furthermore, PCT is stable at 4 °C for 96 h [12].

CRP is an acute-phase reactant secreted by the liver in response to bacterial infections. It is synthesized 4–6 hours after the occurrence of tissue injury or inflammation. Moreover, its levels doubles every 8 h and peaks at approximately 36 h [14,15]. Recently, certain infection markers, including PCT and CRP, that easily distinguish bacterial infections from viral infections have been identified [16–18]. Some studies have found that PCT and CRP have very high sensitivity and specificity, with PCT performing better than CRP at different cutoff levels [19].

Although many studies have suggested that PCT and CRP seem to be markers for bacterial infection, there is still uncertainty and controversy about whether PCT and CRP are able to distinguish between bacterial and non-bacterial infections, between gram-positive and gram-negative bacterial infection, and also on the cutoff level in patients infected after HSCT. The aim of this study was to clarify these uncertainties by analyzing the detection and monitoring potential of PCT and CRP, in a large number of HSCT patients.

2. Materials and methods

2.1. Patients

A total of 939 patients (male 556, female 383) from Peking University People's Hospital participated in the study, from October 2016 to October 2019. All participants were 18–78 years old and had undergone allogeneic HSCT because of various hemopathies. The study protocol was approved by the Hospital Research Ethics Committee, and written consent of patients was obtained in all cases.

2.2. Methods

Before HSCT, all patients receive prophylactic antibiotics. All the blood samples were collected within the first 12 h of the patient presenting a fever, and before adjusting any antibiotics. The “criteria of fever” was that the patients must present an axillary temperature above 38.0°C or an axillary temperature above 37.7°C for 1 h. Blood samples were cultured using the American BD FX400 automatic blood culture system (Becton, Dickinson and Company). Blood culture results were considered negative if there was no growth after 5 days. PCT levels were detected using the Roche E411 autoimmune analyzer (Roche Diagnostics, Germany), D-Dimer levels were assayed using the ACL TOP700 analyzer (WerfenInc, Spain), and serum CRP levels were measured using the AU5832 automatic biochemical analyzer (Beckman Coulter Inc.).

2.3. Statistical analyses

Qualitative variables (e.g., gender) were described as counts, and quantitative variables (e.g., years, PCT, CRP, D-Dimer) were described using medians and interquartile ranges (IQR). Comparisons between negative blood culture groups and positive blood culture groups were

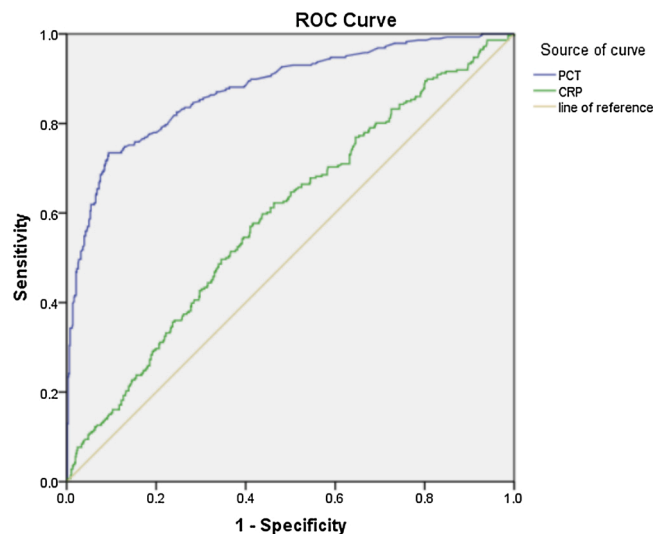


Fig. 1. Receiver Operating Characteristic Curve for PCT and CRP Accuracy in the Distinction between positive blood culture and negative blood culture in HSCT patients (PCT cutoff = 0.51 ng/mL, CRP cutoff = 49.20 mg/L).

performed using one-sample T-test and one-way analysis of variance for three groups. Receiver operating characteristic (ROC) curves and comparative analysis of the area under the curve (AUC) were performed to evaluate the discriminatory power of PCT and CRP, to differentiate between negative blood culture groups and positive blood culture groups, and between gram-negative and gram-positive infections. All data were analyzed using SPSS version 22.0., and $p < 0.05$ was considered significant.

3. Results

3.1. PCT and CRP levels for detecting infection and non-infection

Of the 939 patients enrolled in this study, the number of ALL in the patients was 310(33 %); the number of AML was 385(41 %); the number of CML was 47(5%); the number of MDS was 122(13 %); the number of AA was 47(5%); the number of Lymphoma was 310(33 %). 668 patients were allocated to the control group, which presented a negative blood culture at the time of fever. Blood cultures of 271 patients who had infection followed by sepsis were positive (Table 1). The median age of the control patients was 36 (28, 50) years, and among them 364 (54.5 %) were males. The median age was 37 (27, 49) years for the infected patients; 192 (70.8 %) of these were males. The PCT levels in infected patients [2.06 (0.57, 5.72)ng/mL] were significantly higher than those in the controls [0.19 (0.12,0.30) ng/mL] ($p < 0.001$). The CRP levels and D-Dimer levels among infected patients were also significantly higher than those in the control patients.

The AUC-ROC of PCT for detecting the infection was 0.877 (95 % confidence interval 0.851–0.902; $p < 0.001$) (Fig. 1). The optimal cutoff

Table 2

Sensitivity, Specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV) of Procalcitonin and CRP Cutoff for the Distinction between positive blood culture and negative blood culture in HSCT patients.

		Sensitivity (95 % CI)	Specificity (95 % CI)	PPV (95 % CI)	NPV (95 % CI)	Youden
Procalcitonin (ng/mL)	0.10	98.98 (97.0–99.8)	16.59 (13.8–19.6)	34.40 (31.2–37.7)	97.30 (92.4–99.4)	0.16
	0.20	91.13 (87.3–94.1)	53.39 (49.5–57.2)	46.40 (42.2–50.5)	93.20 (90.1–95.5)	0.45
	0.50	73.72 (68.3–78.7)	90.20 (87.7–92.4)	76.90 (71.5–81.7)	88.60 (85.9–90.9)	0.64
	0.51	73.72 (68.3–78.7)	90.65 (88.2–92.8)	77.70 (72.3–82.5)	88.60 (86.0–90.9)	0.64
	1.00	62.46 (56.6–68.0)	94.57 (92.6–96.2)	83.60 (78.0–88.2)	85.10 (82.3–87.6)	0.57
CRP (mg/L)	10.00	86.01 (81.4–89.8)	21.11 (18.1–24.4)	31.80 (28.6–35.2)	77.90 (71.7–84.3)	0.07
	30.00	68.53 (62.8–73.9)	42.37 (38.6–46.4)	33.80 (29.9–37.7)	75.90 (71.3–80.2)	0.11
	49.20	59.79 (53.9–65.5)	56.29 (52.4–60.1)	36.90 (32.5–41.5)	76.60 (72.6–80.3)	0.16
	50.00	58.39 (52.4–64.2)	56.74 (52.9–60.5)	36.60 (32.2–41.2)	76.10 (72.1–79.8)	0.15
	100.00	33.22 (27.8–39.0)	77.69 (74.3–80.8)	38.90 (32.8–45.4)	73.10 (69.6–76.3)	0.10

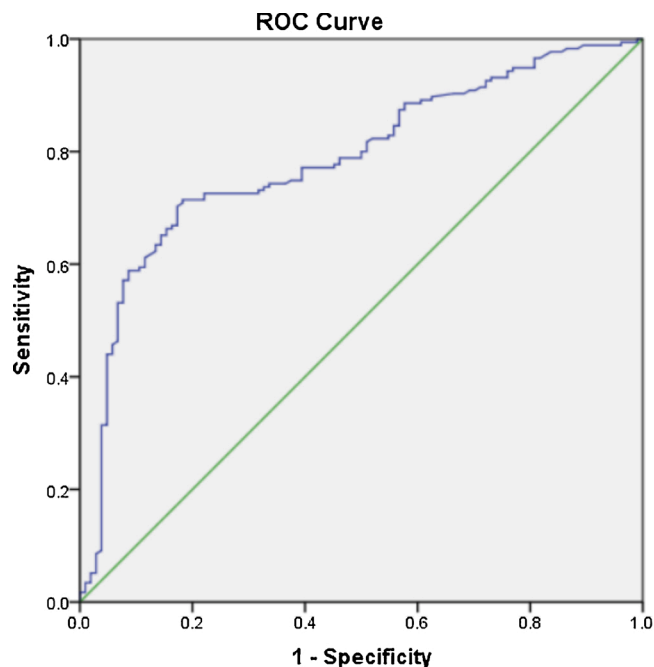


Fig. 2. Receiver Operating Characteristic Curve for PCT Accuracy in the Distinction between Gram-positive and Gram-negative blood bacterial infection in HSCT patients (PCT cutoff = 1.63 ng/mL).

value of PCT level, as determined by AUC-ROC analysis, was 0.51 ng/mL. Using published threshold values (0.10 ng/mL, 0.20 ng/mL, 0.50 ng/mL, 1.00 ng/ml) and the determined cutoff value of 0.51 ng/mL, we described the characteristics for the clinical use of PCT level (Table 2). Of the five analyzed values, the PCT level of 0.51 ng/mL was the best threshold for detecting infection and non-infection conditions, with a sensitivity of 73.72 % (68.3–73.7 %), a specificity of 90.65 % (88.2–92.8 %), a positive predictive value of 77.70 % (72.3–82.5 %), and a negative predictive value of 88.60 % (86.0–90.9 %).

The AUC-ROC of CRP for detecting an infection was 0.591 (95 % CI 0.552–0.630; $p < 0.001$) (Fig. 1), and the optimal cutoff value of CRP level, as determined by the AUC-ROC analysis, was 49.20 mg/L. Using

Table 3

Sensitivity, Specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV) of PCT cutoff for the Distinction between Gram-positive and Gram-negative blood bacterial infection in HSCT patients.

Procalcitonin (ng/mL)	Sensitivity (95 % CI)	Specificity (95 % CI)	PPV (95 % CI)	NPV (95 % CI)	Youden
0.50	82.86 (96.4–88.1)	45.19 (35.4–55.3)	71.80 (65.0–77.9)	61.00 (49.2–72.0)	0.28
1.00	74.29 (67.8–81.1)	63.46 (53.4–72.7)	77.40 (70.3–83.5)	59.50 (49.7–68.7)	0.38
1.63	71.43 (64.1–78.0)	81.73 (72.9–88.6)	86.80 (80.2–91.9)	63.00 (54.2–71.7)	0.53
2.00	65.71 (58.2–72.7)	84.62 (76.2–90.9)	87.70 (80.8–92.8)	59.50 (50.7–67.1)	0.50
10.00	25.14 (18.9–32.2)	96.15 (90.4–98.9)	91.70 (80.0–97.7)	43.30 (36.8–49.9)	0.21

this value and the previously published threshold values of CRP (10.00 mg/L, 30.00 mg/L, 50.00 mg/L, 100.00 mg/L), we described the characteristics for the clinical use of CRP level (Table 2). Of the five values assessed, the CRP level of 49.20 mg/L was the best threshold for detecting infection and non-infection, with a sensitivity of 59.79 % (53.9–65.5 %), a specificity of 56.29 % (52.4–60.1 %), a positive predictive value of 36.90 % (32.5–41.5 %), and a negative predictive value of 76.06 % (72.6–80.3 %).

3.2. PCT level for detecting gram-negative and gram-positive bacteremia

Among the infected patients, 94 were infected with gram-positive bacteria, while 158 were infected with gram-negative bacteria; in 19 blood cultures revealed fungal infection. On the first identification of microbiological growth in blood cultures, PCT levels were the highest in patients with gram-negative bacteremia [4.57 (1.46, 10.77) ng/mL] compared to those in patients with gram-positive bacteremia [0.65 (0.29, 1.32) ng/mL] and to those with fungal infection [2.10 (1.57, 2.88) ng/mL] ($p < 0.001$). On the contrary, CRP levels were statistically insignificant (Table 1).

The AUC showed a significant level of accuracy for discriminating gram-negative bacteremia from gram-positive bacteremia (AUC, 0.786; 95 % CI, 0.731–0.841, $p < 0.001$) (Fig. 2). The optimal cutoff value of PCT level as determined by the AUC-ROC analysis was 1.63 ng/mL for detecting infection (Table 3), with a sensitivity of 71.43 % (64.1–78.0 %), specificity of 81.73 % (72.9–88.6 %), positive predictive value of 86.80 % (80.2–91.9 %), and negative predictive value of 63.00 % (54.2–71.7 %). However, the area under the ROC curve of CRP was close to 0.5, which was low in authenticity and had no application value.

4. Discussion

Infections and infection-related complications are the major causes of morbidity and mortality in febrile neutropenic patients after HSCT. Laboratory biomarkers have been helpful for early identification of critically ill patients and optimal therapy management [20]. In patients with hematologic disorders after HSCT, it is difficult to distinguish bloodstream infections from aseptic causes of febrile episodes. The objective of this study was to investigate the diagnostic value of PCT and CRP in predicting systemic infections in patients with HSCT.

Our study assessed serum PCT, CRP, and D-Dimer levels of 939

patients with HSCT. The results showed that serum PCT levels of HSCT patients with infection [2.06 (0.57, 5.72) n g/mL] were significantly higher than those of uninfected patients [0.19 (0.12, 0.30) n g/mL]. The levels of CRP and D-Dimer in infected patients were also higher than those in uninfected patients. Our study also showed that PCT was more valuable than CRP and D-Dimer for discriminating between bacteremia and non-bacteremia, independent of HSCT. C S Michel et al. [20] showed that PCT or IL-8, in combination with clinical parameters, should be considered as a routine measurement to identify critically ill patients as early as possible, compared to CRP and sTREM-1, in febrile neutropenia. The study by Yasuhiro Ebihara [21] indicated that the levels of PCT, but not CRP or presepsin, were significantly higher in the infected group than in the uninfected group ($P < 0.03$), indicating that PCT might be a more sensitive biomarker of infections; the performance results of PCT obtained in our study were consistent with these results. However, the results reported by Ahmad Baraka [22] supported that presepsin is superior to PCT and CRP for identifying bacterial infection in febrile neutropenia, which is not consistent with our findings.

Our research showed that PCT levels were the highest in patients with gram-negative bacteremia [4.57(1.46, 10.77) ng/mL] compared to in patients with gram-positive bacteremia [0.65(0.29, 1.32) ng/mL] and fungal infection [2.10 (1.57, 2.88) ng/mL] ($p < 0.001$). The optimal cutoff value of PCT level as determined by the AUC-ROC analysis was 1.63 ng/mL for detecting infection, with a sensitivity of 71.43 % (64.1–78.0 %) and specificity of 81.73 % (72.9–88.6 %). Thomas-Ruddel DO et al., who conducted a secondary analysis of a prospectively collected data set that included a very large sample of 4858 septicemic patients from 40 hospitals, showed that serum PCT concentrations are higher in patients with gram-negative bacteremia than in those with gram-positive bacteremia, or candidemia. The area under the curve was 0.72 (95 % confidence interval 0.71–0.74) for the prediction of gram-negative bacteremia as compared to all other blood culture results, including the negative blood cultures. The optimized cutoff value was 10 ng/mL (sensitivity 69 %, specificity 35 %) [23]. H H Liu et al. showed that serum PCT levels were higher in gram-negative sepsis than in gram-positive sepsis after 72 h; however, no differences were observed in CRP levels. The area under the ROC curve of PCT was 0.73 (95 % confidence interval 0.65–0.81), with a PCT cutoff value of 2.1 ng/mL [24]. Shuhua Li et al. showed that serum PCT levels were significantly higher in patients with gram-negative sepsis than in those with gram-positive or fungal sepsis. ROC analysis revealed an optimal cutoff value of 2.44 n g/mL for PCT, in discriminating gram-negative sepsis from gram-positive sepsis [25]. Several studies have shown that serum PCT levels are significantly higher in patients with gram-negative sepsis than in those with gram-positive or fungal sepsis; nevertheless, the PCT cutoff was different and very few study groups included patients with HSCT. However, the discriminatory power of this difference was too low to guide therapeutic decisions. Variations in PCT serum concentrations are not determined solely by gram-negative or gram-positive bacteria but are also affected by distinct groups of pathogens and different foci of infection.

In our study, CRP levels were found to be higher in patients with positive blood cultures compared to those that did not present bacteremia; however, CRP did not distinguish between gram-negative and gram-positive infections; this was consistent with the results of María Varela-Patiño et al. [26]. The study by Yang M [27] revealed that bacterial infection episodes show higher PCT and CRP levels than non-bacterial events, independent of neutropenia or HSCT.

Therefore, in our experiment, we studied the ability of PCT to predict early infection in patients with fever after HSCT, and calculated its cutoff value, sensitivity, specificity, positive predictive value, and negative predictive value.

Nevertheless, our study has certain limitations. First, it was a single-center study with a small number of patients; second, the patients may have complex clinical complications, such as high fever and hematocytosis; and last, the cutoff value of this study is not applicable in other

studies. We expect that future studies will contribute to validate our experimental results, so as to provide a basis for early clinical medication, and guide clinical medication.

Author contributions

Shanshan Li, Junxu Gu, and Ming Su: conception and design of the study; Wenhui Nan, Na Zhang, and Li Qin: acquisition of data, analysis, and interpretation of data; Shanshan Li, Junxu Gu, and Mei Jia: drafting of the article and critical revision for important intellectual content; Ming Su and Mei Jia: final approval of the version to be submitted.

Declaration of Competing Interest

The authors report no declarations of interest.

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