The Utility of Proadrenomedullin and Procalcitonin in Comparison to C-Reactive Protein as Predictors of Sepsis and Bloodstream Infections in Critically Ill Patients With Cancer*

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Objectives: Infections in critically ill patients continue to impose diagnostic and therapeutic challenges. We seek to investigate the utility of proadrenomedullin and procalcitonin as diagnostic and prognostic biomarkers in febrile critically ill patients with cancer and compare their performance with that of C-reactive protein.

Design: Single-center prospective cohort study.

Setting: Tertiary care, academic, university hospital.

Patients: One hundred fourteen critically ill patients with cancer with fever.

Interventions: None.

Measurements and Main Results: Blood samples were withdrawn on the day of fever onset and 4 to 7 days thereafter, and the serum proadrenomedullin, procalcitonin, and C-reactive protein levels were measured using the Kryptor technology afterward. Of the 114 adult patients, 27 had bloodstream infections, 36 had localized infections, and the remaining had no infections. The area under the receiver operating characteristic curve for bloodstream infection diagnosis was significantly greater for proadrenomedullin (0.70; 95% CI, 0.59–0.82) and procalcitonin (0.71; 95% CI, 0.60–0.83) compared with C-reactive protein (0.53; 95% CI, 0.39–0.66) ($p = 0.021$ and $p = 0.003$, respectively). Receiver operating characteristic analysis also showed that proadrenomedullin ($p = 0.005$) and procalcitonin ($p = 0.009$) each had a better performance than C-reactive protein in predicting patients' mortality within 2 months after their fever onset. Regarding patients' response to antimicrobial therapy, proadrenomedullin, procalcitonin, and C-reactive protein levels all significantly decreased from baseline to follow-up in responders ($p \leq 0.002$), whereas only proadrenomedullin level significantly increased in nonresponders ($p < 0.0001$). In patients with documented infections, proadrenomedullin (0.81; 95% CI, 0.71–0.92) and procalcitonin (0.73; 95% CI, 0.60–0.85) each had a greater area under the curve compared with C-reactive protein (0.59; 95% CI, 0.45–0.73) as for as predicting response ($p = 0.004$ and $p = 0.043$, respectively). However, for all febrile patients, proadrenomedullin had a significantly greater area under the curve for predicting favorable response than procalcitonin ($p < 0.0001$).

Conclusion: In critically ill patients with cancer, proadrenomedullin and procalcitonin both have a promising role in predicting bloodstream infections in a manner more helpful than C-reactive protein. These two biomarkers were superior to C-reactive protein in the prognostic analysis of response to antimicrobial therapy for those patients with documented infections. However, proadrenomedullin was superior to procalcitonin in predicting response in all febrile patients and was unique in showing increased levels among nonresponders. (*Crit Care Med* 2014; 42:2500–2507)

Key Words: bacteremia; biomarkers; bloodstream infection; infection; proadrenomedullin; procalcitonin

Infections in critically ill immunocompromised patients with cancer are associated with various diagnostic and therapeutic challenges. They are often complex due to the inability to determine if the fever is related to an infectious

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process or merely a reflection of tumor burden ("tumor fever") or other inflammatory processes of noninfectious causes. The gold standard for infection diagnosis has been microbiological culture methods. However, the major limitation of using cultures is the length of time required to identify the pathogen and the risk of false-positive cultures associated with contamination. Cultures are also insensitive under several conditions, particularly in patients with hematologic malignancy (1). Hence, relying on fever or cultures in management of infections in this patient population may result in either inappropriately over treating or delaying of care. These patients are usually treated empirically and for long periods with multiple antimicrobials, which can result in emergence of antimicrobial resistance (2, 3).

In light of these disadvantages, intensivists have been striving to identify biomarkers not only to stratify the degrees of illness but also to predict the course of illness and thus patients' prognosis. Researchers have become interested in developing adjunct diagnostic methods using molecular tests, with a recent focus on proadrenomedullin (proADM) and procalcitonin (PCT), two peptides derived from the calcitonin gene family with distinct functions and properties (4, 5). Also C-reactive protein (CRP) is a positive acute phase protein produced by the liver in response to stimulation by several cytokines, which is widely available (6, 7). Few studies have explored the roles of proADM and PCT in critically ill patients with cancer (8). Various studies have evaluated the role of PCT as a marker of bloodstream infection (BSI) (9) and as a guide to antibiotic therapy in critically ill patients (10–15). proADM has been suggested to be a useful tool for the risk assessment in patients with sepsis and patients with community-acquired pneumonia (4, 16).

Our research group has investigated the role of proADM in comparison to PCT for prediction and diagnosis of infections in febrile patients with hematological malignancies outside the critical care setting. Thereby, we found that proADM was a good predictor of localized infections (17). We also found that both proADM and PCT were useful in differentiating BSI from no infection in neutropenic noncritically ill patients and were good indicators of response to therapy (17). The purpose of the present study is to expand these previous findings to the more challenging setting of the febrile, critically ill patients with cancer to investigate the role and utility of proADM and PCT in comparison with the widely available CRP as biomarkers for the diagnosis, prognosis, and therapy response in this more complicated critical care setting.

MATERIALS AND METHODS

Design

In this prospective laboratory observational study, we evaluated 114 critically ill patients with cancer between June 2009 and December 2010 at University of Texas MD Anderson Cancer Center in Houston, Texas. All patients 18 years or older who were febrile at admission to the ICU or became febrile during the course of their stay in the ICU were enrolled in this study. Patients with medullary thyroid carcinoma and patients with small cell carcinoma were excluded to reduce false positives, as PCT can be produced by medullary thyroid cells (18). Approval from the MD Anderson Cancer Center Institutional Review Board and waiver of informed consent were obtained.

We collected data pertaining to demographic characteristics of patients, admission date and diagnosis, medical history including underlying cancer and stage, comorbidities, defervescence date, neutropenia presence and duration, and radiological studies. Furthermore, patients were identified microbiologically as to whether they had a documented bacterial, fungal, or viral infection. Antimicrobial therapy data included the type and number of antimicrobials used, initiation date, and therapy duration. Patients' responses to antimicrobial therapy were defined as defervescence or microbiological eradication within 96 hours of therapy initiation. All patients were evaluated for overall diagnosis and outcome, including clinical and microbiologic response to antimicrobial therapy and the outcome's correlation with the biomarkers tested.

Laboratory Methods

proADM, PCT, and CRP levels were tested on plasma collected no more than 24 hours from the onset of fever and repeated 4–7 days thereafter. At least two residual samples were obtained from all patients. The first sample was a baseline residual sample obtained within 24 hours of the onset of fever or other documented clinical manifestations of infection. The subsequent residual plasma was obtained within 4–7 days after the onset of fever or the documented clinical manifestations of infection (follow-up sample). All plasma proADM and PCT levels were measured using the high-sensitive Kryptor assay (Brahms Thermo-Fisher, Middletown, VA). The plasma Kryptor compact analyzer automatically dispensed conjugate plasma sample into each well and continuously measured the signal emitted. Approximately 50 μL of plasma was automatically pipetted into the test tube. Samples were incubated for 10 minutes with continuous measurement. In cases of high concentration values, automatic dilution occurred after a few minutes. The system then automatically calculated the result. The assay used two polyclonal antibodies to proADM (amino acid 45–92) and had an analytical detection limit of 0.08 nmol/L and functional assay sensitivity of 0.12 nmol/L. CRP biomarker was quantitated in human plasma following the package insert for the human CRP DuoSet ELISA (1) (R&D Systems, Minneapolis, MN). Human plasma was diluted 50,000 to 200,000 times in order to be in the detectable range of CRP standards provided in the kit. A standard curve was generated, and final CRP concentration in human plasma was calculated in μg/mL.

Definitions

Fever was defined as central body temperature of greater than or equal to 38.3°C or two consecutive readings of greater than 38°C. A definite infection was defined as documented clinical and microbiological evidence of an infection according to the definition set by the Centers for Disease Control and Prevention and the International Conference on Definitions of Infections in the Intensive Care Unit (19). Patients with fevers of unknown

origin who did not experience a response to antimicrobial therapy and in whom all diagnostic tests were negative for bacterial, viral, and fungal infections were considered to have no evidence of infection and were categorized as having no infection.

We defined systemic inflammatory response syndrome (SIRS) and sepsis on the basis of the consensus panel of the American College of Chest Physicians (ACCP) and Society of Critical Care Medicine and the published modifications by Annane et al (20–23). SIRS was defined by the presence of two or more of the following: temperature > 38.5°C or < 35°C, heart rate > 90 beats/min, respiratory rate > 20 breaths/min, or $Paco_2$ < 32 mm Hg, WBC count > 12,000 cells/mm^3, < 4,000 cells/mm^3, or > 10% immature (band) forms. Sepsis was defined by the presence of both a culture-proven infection and SIRS.

Statistical Methods

BSI and sepsis were the primary outcomes of this study. We aimed at investigating the relationship between each outcome and the proADM and PCT levels measured at patients' fever onset and seeing how well the biomarkers predict infection and sepsis. Patients' response to their microbial therapies was the secondary outcome. We studied the relationship between response and the changes of proADM and PCT levels within 4–7 days after fever onset and evaluated whether percentage of these changes was a good predictor of favorable response. We compared the two biomarkers in their diagnostic performance as well as each with another biomarker CRP. Wilcoxon rank-sum tests were used to compare proADM, PCT, or CRP values between two groups of patients. Kruskal-Wallis tests were used to compare values of the biomarkers among three groups of patients. If a significant result ($p < 0.05$) was found in a Kruskal-Wallis test, Wilcoxon rank-sum tests were used for the pairwise comparisons. The α levels of the post hoc pairwise comparisons were adjusted using a sequential Bonferroni adjustment. Patients' baseline and follow-up proADM, PCT, or CRP values were compared using signed rank tests. The diagnostic performance of the biomarkers was assessed as following: First, the receiver operating characteristic (ROC) curve was constructed for each test and the area under the curve (AUC) was estimated. Then the AUCs of different tests were compared using a nonparametric method developed by De Long et al (24) based on Mann-Whitney *U* statistics. The ROC-CONTRAST statement in SAS program PROC LOGISTIC is available for such comparison. Besides, the optimal cutoff value for some tests was determined on the basis of its ROC curve and the Youden index, a function of sensitivity and specificity, which is commonly used to measure overall performance of a diagnostic test (23). Then, sensitivity, specificity, and positive and negative predictive values were estimated. All tests except those pairwise comparisons were two-sided at a significance level of 0.05. The statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC).

RESULTS

One hundred fourteen critically ill adult patients with cancer (≥18 yr) with fever were enrolled in the study (**Table 1**). Patients' ages ranged from 19 to 84 years with a median of 57 years.

TABLE 1. Demographic and Clinical Characteristics of Patients

Characteristic	Patients (*n* = 114)
Male gender, *n* (%)	67 (58.8)
Age, median in years (range)	57 (19–84)
Sepsis, *n* (%)	51 (44.7)
SIRS, *n* (%)	41 (36.0)
Nonsepsis/SIRS, *n* (%)	22 (19.3)
Acute Physiology and Chronic Health Evaluation score (range), *n* (%)	
0–9	15 (13.2)
10–19	68 (59.6)
20–29	27 (23.7)
≥ 30	4 (3.5)
Intubation, *n* (%)	73 (64.0)
Underlying cancer diagnosis, *n* (%)	
Hematologic malignancy	55 (48.2)
Solid tumor	59 (51.8)
Bone marrow transplant, *n* (%)	12 (10.5)
Graft-versus-host disease, *n* (%)	2 (1.8)
Neutropenia (absolute neutrophil count < 500), *n* (%)	
At onset	20 (17.5)
During study period	24 (21.1)
Comorbidities, *n* (%)	
Diabetes	26 (22.8)
Chronic kidney disease	9 (7.9)
Chronic obstructive pulmonary, *n* (%) disease/asthma	15 (13.2)
Coronary artery disease/congestive heart failure, *n* (%)	14 (12.3)
Documented bloodstream infection, *n* (%)	27 (23.7)
Bacteremia	22 (19.3)
Fungemia	1 (0.9)
Viremia	4 (3.5)
Localized infections, *n* (%)	36 (31.6)
Pneumonia	25 (21.9)
Other localized infections	11 (9.6)
Upper respiratory tract	2 (1.8)
Soft tissue	3 (2.6)
Genitourinary tract	6 (5.3)
Death within 2 mo after fever onset, *n* (%)	26/110 (23.6)

SIRS = systemic inflammatory response syndrome.

TABLE 2. Comparison of Proadrenomedullin, Procalcitonin, and C-Reactive Protein Levels in Patients With Bloodstream Infections, Localized Bacterial Infections, and Those Without Infection

Biomarker Levels	Bloodstream Infection ($n = 27$)	Localized Bacterial Infection ($n = 29$)	Noninfection ($n = 51$)	p
Median proadrenomedullin (range), nmol/L	2.92 (0.05–12.97)	1.57 (0.34–9.52)	1.45 (0.26–16.33)	0.006
Median procalcitonin (range), ng/mL	5.04 (0.075–235.0)	0.47 (0.075–154.7)	0.80 (0.075–24.67)	0.003
Median C-reactive protein (range), μg/mL	122.1 (16.9–273.5)	103.9 (8.4–245.5)	104.1 (5.2–285.2)	0.78

Pairwise comparisons (proadrenomedullin): bloodstream infection (BSI) versus localized bacterial infection: $p = 0.007$; BSI versus noninfection: $p = 0.003$; localized bacterial infection versus noninfection: $p = 0.97$.

Pairwise comparisons (procalcitonin): BSI versus localized bacterial infection: $p = 0.003$; BSI versus noninfection: $p = 0.003$; localized bacterial infection versus noninfection: $p = 0.23$.

The criteria for sepsis were met in 44.7% of the patients, 36.0% had SIRS but no sepsis, and 19.3% had fever but did not meet either SIRS or sepsis criteria. There were 63 patients (55.3%) with documented infections including 27 BSIs (22 bacteremia, one fungemia, and four viremia) and 36 (31.6%) localized infections that consisted of 25 patients with pneumonia and 11 patients with other localized infections. Almost half (48.2%) of the patients had hematologic malignancies and the remainder (51.8%) had solid tumors. About 17.5% had neutropenia at baseline, and 21.1% had persistent neutropenia during the study period measured between day 4 and 7. Ninety-eight percent of the 114 patients were receiving antimicrobial therapy at their fever onset. The rate of all-cause mortality within 2 months of follow-up was 23.6%. Patients' comorbidities and other characteristics are detailed in Table 1.

The proADM level at baseline in patients with BSI (median, 2.92 nmol/L) was significantly higher than in those with localized bacterial infection (median, 1.57 nmol/L; $p = 0.007$) and no infection (median, 1.45 nmol/L; $p = 0.003$), while no significant difference was found between the latter two groups ($p = 0.97$) (**Table 2**). Among patients with localized infections, no proADM difference was found in patients with pneumonia versus other localized infections ($p = 0.37$). Similarly, the PCT level at baseline was significantly higher in patients with BSIs (median, 5.04 ng/mL) than in those with no documented infections (median, 0.80 ng/mL; $p = 0.003$) and those with localized bacterial infections (median, 0.47 ng/mL, $p = 0.003$), whereas no significant difference was found between the latter two groups ($p = 0.23$). In addition, no significant PCT difference was found between patients with pneumonia versus those with other localized infections ($p = 0.24$). In contrast to proADM and PCT, CRP level at baseline showed no significant difference ($p = 0.78$) among patients with BSI (median, 122.1 μg/mL) when compared with localized bacterial infections (median, 103.9 μg/mL) or those with no infection (median, 104.1 μg/mL).

The ROC curve analysis for BSI diagnosis was performed and compared among the biomarkers (**Fig. 1**). The AUC was 0.70 (95% CI, 0.59–0.82) for proADM test and 0.71 (95% CI, 0.60–0.83) for PCT test, each significantly greater than the AUC for CRP test (0.53; 95% CI, 0.39–0.66) ($p = 0.021$ and $p = 0.003$, respectively). The AUC was comparable between proADM and PCT tests ($p = 0.84$). With the optimal cutoff value of 2.2 nmol/L, the sensitivity of proADM test for BSI diagnosis was 67% (95% CI, 49–84%), with a specificity of 68% (95% CI, 58–78%), a positive predictive value (PPV) of 39% (95% CI, 25–52%), and a negative predictive value (NPV) of 87% (95% CI, 80–96%). The proADM test had the highest PPV of 56% (95% CI, 23–88%) with a cutoff value of 6.0 nmol/L and the highest NPV of 92% (95% CI, 81–100%) with a cutoff value of 1.0 nmol/L. Regarding PCT test for BSI diagnosis, with the optimal cutoff value of 1.9 ng/mL, it had a sensitivity of 67%

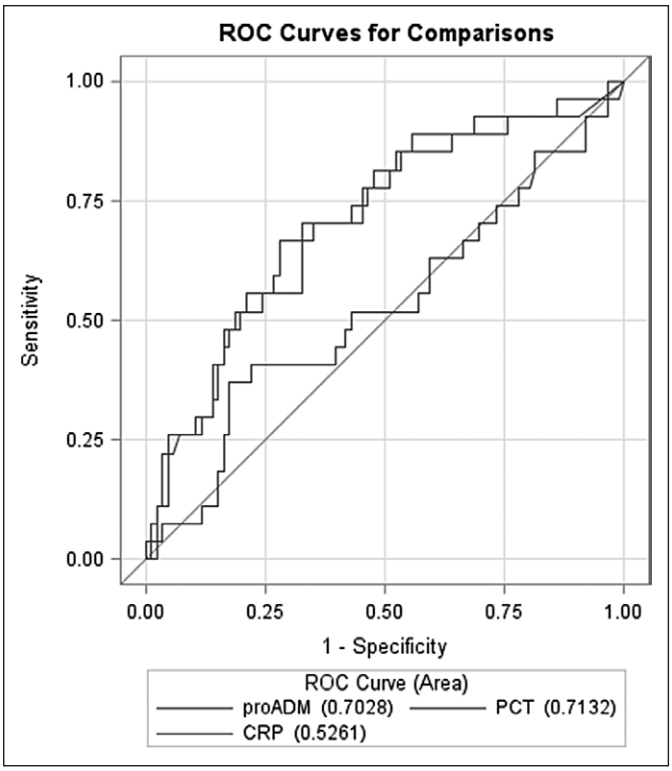

Figure 1. Receiver operating characteristic (ROC) curves for proadrenomedullin (ProADM), procalcitonin (PCT), and C-reactive protein (CRP) tests for bloodstream infection diagnosis.

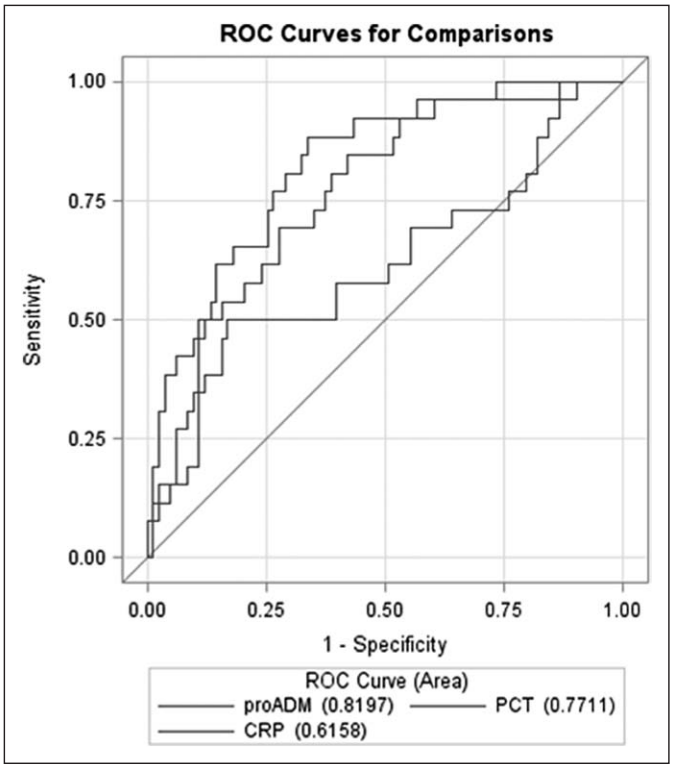

Figure 2. Receiver operating characteristic (ROC) curves for proadrenomedullin (ProADM), procalcitonin (PCT), and C-reactive protein (CRP) tests for death prediction.

(95% CI, 49–84%), a specificity of 72% (95% CI, 63–82%), a PPV of 43% (95% CI, 28–58%), and an NPV of 88% (95% CI, 80–95%). The PCT test had the highest PPV of 48% (95% CI, 29–67%) with a cutoff value of 6.0 ng/mL and the highest NPV of 93% (95% CI, 85–100%) with a cutoff value of 0.5 ng/mL.

proADM and PCT tests also had good performance in predicting patients' mortality within 2 months after their fever onset. We found that proADM and PCT levels at follow-up (4–7 d after fever onset) were both significantly higher in patients who died during that time period than those who did not, whereas CRP level at follow-up showed no statistical difference, which was consistent with our ROC curve analysis (**Fig. 2**). The AUC for mortality prediction was 0.82 (95% CI, 0.73–0.91) for proADM test and 0.77 (95% CI, 0.67–0.87) for PCT test, each significantly greater than the AUC for CRP test (0.62; 95% CI, 0.48–0.75) ($p = 0.005$ and $p = 0.009$, respectively).

When evaluating patients' response to antimicrobial therapy, we found that proADM level significantly decreased from baseline to follow-up in responders (median, 1.63 nmol/L vs 1.29 nmol/L; $p = 0.002$) and increased in nonresponders (median, 2.19 nmol/L vs 4.16 nmol/L; $p < 0.0001$) (**Table 3**). PCT level also significantly decreased in responders (median, 0.77 ng/mL vs 0.44 ng/mL; $p = 0.002$) but did not change significantly in nonresponders ($p = 0.32$). Similarly, we found a significant decrease in CRP in responders (median, 117.3 μg/mL vs 53.3 μg/mL; $p < 0.0001$) but a nonsignificant change in nonresponders ($p = 0.38$). For each biomarker, similar results were also found in patients with documented infections and those with bacterial infections.

ROC curve analysis was performed to study the association between patients' response and the percentage of change of their biomarker levels from baseline to follow-up. The AUC for such change to predict a favorable response among all febrile patients was 0.79 (95% CI, 0.70–0.87) for proADM test and 0.32 (95% CI, 0.22–0.42) for PCT test. proADM test and CRP test both had a significantly greater AUC than PCT test ($p < 0.0001$). However, the performance of PCT test in response

TABLE 3. Comparing Initial and Follow-Up Proadrenomedullin, Procalcitonin, and C-Reactive Protein in Responders and Nonresponders to Antimicrobial Therapies

Group	Patients	Time	Median Proadrenomedullin (nmol/L)	Median Procalcitonin (ng/mL)	Median C-Reactive Protein (μg/mL)
All patients					
Response	70	Initial vs follow-up	1.63 vs 1.29 ($p = 0.002$)	0.77 vs 0.44 ($p = 0.002$)	117.3 vs 53.3 ($p < 0.0001$)
Nonresponse	44	Initial vs follow-up	2.19 vs 4.16 ($p < 0.0001$)	1.02 vs 1.81 ($p = 0.32$)	103.9 vs 96.9 ($p = 0.38$)
All infections					
Response	35	Initial vs follow-up	1.97 vs 1.20 ($p = 0.07$)	1.51 vs 0.45 ($p = 0.009$)	93.3 vs 62.4 ($p = 0.002$)
Nonresponse	28	Initial vs follow-up	2.68 vs 8.41 ($p < 0.0001$)	0.76 vs 2.91 ($p = 0.18$)	119.8 vs 111.0 ($p = 0.17$)
Bacterial infections					
Response	31	Initial vs follow-up	1.97 vs 1.19 ($p = 0.032$)	1.30 vs 0.44 ($p = 0.003$)	91.5 vs 64.5 ($p = 0.006$)
Nonresponse	20	Initial vs follow-up	2.72 vs 6.79 ($p = 0.001$)	0.67 vs 2.91 ($p = 0.65$)	144.9 vs 130.7 ($p = 0.25$)

TABLE 4. Comparison of Proadrenomedullin, Procalcitonin, and C-Reactive Protein Levels in Patients With Sepsis, Systemic Inflammatory Response Syndrome, and Those Without Sepsis/Systemic Inflammatory Response Syndrome

Biomarker Levels	Sepsis ($n = 51$)	SIRS ($n = 41$)	Nonsepsis/SIRS ($n = 22$)	p
Median proadrenomedullin (range), nmol/L	2.22 (0.05–15.24)	1.40 (0.26–16.33)	1.40 (0.34–4.97)	0.025
Median procalcitonin (range), ng/mL	1.30 (0.075–235.0)	1.00 (0.075–24.67)	0.40 (0.075–19.45)	0.068
Median C-reactive protein (range), μg/mL	111.2 (8.4–273.5)	111.2 (5.2–285.2)	97.3 (24.0–228.3)	0.59

SIRS = systemic inflammatory response syndrome.

Pairwise comparisons (proadrenomedullin): sepsis versus SIRS: $p = 0.045$; sepsis versus nonsepsis/SIRS: $p = 0.015$; SIRS versus nonsepsis/SIRS: $p = 0.48$.

prediction improved greatly in patients with documented infections. In those patients, the AUC to predict response was 0.81 (95% CI, 0.71–0.92) for proADM test, 0.73 (95% CI, 0.60–0.85) for PCT tests, and 0.59 (95% CI, 0.45–0.73) for CRP test. Compared with CRP test, proADM test ($p = 0.004$) and PCT test ($p = 0.043$) each had a better performance in predicting response in patients with documented infections.

The median proADM levels at baseline for patients with sepsis, SIRS, and nonsepsis/SIRS were 2.22 nmol/L, 1.40 nmol/L, and 1.40 nmol/L, respectively (**Table 4**). Sepsis group had significantly higher proADM level than SIRS group ($p = 0.045$) and nonsepsis/SIRS group ($p = 0.015$), whereas the latter two groups had comparable proADM levels ($p = 0.48$). By contrast, data showed no significant difference in baseline PCT level ($p = 0.068$) or CRP level ($p = 0.59$) among patients with sepsis, SIRS, and nonsepsis/SIRS. ROC curve analysis showed that proADM test had a numerically but not statistically greater AUC (0.62; 95% CI, 0.51–0.74) than PCT test (0.52; 95% CI, 0.40–0.64) ($p = 0.07$) and CRP test (0.51; 95% CI, 0.39–0.63) ($p = 0.14$) in differentiating sepsis from SIRS.

DISCUSSION

This is the largest study and only study to date investigating the clinical utility of proADM and PCT in comparison to CRP in critically ill patients with cancer. Based on our data, proADM and PCT were found to have better performance in predicting BSI and mortality compared with CRP in febrile patients with cancer admitted to the ICU. Both biomarkers had promising role in predicting response to antimicrobial therapy and were superior to CRP particularly in patients with documented infections. However, proADM's level significantly and uniquely increased in patients who did not respond to antimicrobial therapy, and proADM test was superior to PCT in predicting response among all febrile patients included. Thus, proADM may be a more plausible prognostic biomarker of nonresponders in critically ill patients with cancer than PCT and CRP. This may help to improve the management of critically ill patients and febrile patients with cancer, which may translate into improved outcomes, reduced mortality, and prevention of unnecessary diagnostic and therapeutic measures.

CRP is an acute-phase protein that is used as a biochemical inflammatory marker. CRP concentration level during the infection phase depends on tissue destruction, the extent of malignant disease, and the duration of fever, and it does not increase by a significant amount in the 24–48 hours after the onset of inflammation. CRP as marker of inflammation was widely used in the 1990s in the diagnosis of sepsis. However, in more recent years, CRP has proven to be less useful than PCT due to its lack of specificity for sepsis and even infection (25, 26). PCT and CRP are widely used as rapid and easily accessible variables for predicting bacteremia. However, several studies have demonstrated that PCT exhibits better clinical performance in recognizing bacterial sepsis than CRP (27, 28). Furthermore, in a previous study, Jeong et al (7) demonstrated that PCT had better diagnostic ability than CRP to differentiate true bloodstream infection from both contaminated and local infections. Furthermore, Meynaar et al (29) showed that PCT was more useful when compared with CRP and interleukin-6 in differentiating between sepsis and SIRS in critically ill patients.

PCT and proADM are recently introduced blood biomarkers that have shown promising results to meet the diagnostic and prognostic needs in the critically ill patients. They exemplify a class of circulating substances referred to as "hormokines" because they normally follow hormonal behavior, that is, expression in neuroendocrine cells and systemic action; yet, in response to inflammation or other physiological stress, they follow cytokine behavior (30). PCT and proADM also represent biomarkers that can be incorporated into personalized medicine (31), an emerging paradigm based on the traditional but increasingly important concept of antimicrobial stewardship that aims at reducing the potential toxic (side) effects and development of antibiotic resistance associated with the unnecessary empiric use of antimicrobials. Hence, interventions would be limited to the patients likeliest to truly need them. Toward this aim, our analysis provides novel and clinically important information.

Our study is the first study to look at proADM and PCT as predictors of BSI, mortality, and antimicrobial response in comparison to CRP in a large cohort of critically ill patients with cancer. We found proADM and PCT to be better predictors

compared with CRP in patients with cancer with documented BSIs and infections, adding a new role for both biomarkers in this patient population. Therefore, proADM and PCT might be useful in helping clinicians in early discontinuation of antimicrobial therapy when patients respond clinically if they have low initial levels.

In this current study, serum PCT in critically ill patients with cancer was also found to be a predictor of BSI. This finding is consistent with our previously published data in patients with hematologic malignancy (17), and with other studies on different patient populations (9, 32), in which PCT was found to play a role in discriminating true BSI from contamination (33) and was described as a good predictor of sepsis. PCT has been extensively studied for its role in guiding antibiotic therapy (10–15). Our results confirm the validity of using PCT to assess response and guide therapy in critically ill patients with cancer. PCT levels have been previously shown to be high in advanced metastatic stages of cancer in the absence of infection (34). Therefore, because PCT levels can be high at baseline because of the tumor burden itself, the concurrent use of proADM levels at baseline and after 4 days of antimicrobial therapy may be useful for determining whether the fever is related to sepsis and BSI or a noninfectious cause, such as cancer metastasis.

In this study, both proADM and PCT were predictive of BSI but not localized bacterial infections. This is unlike what we found in patients with hematologic malignancy where proADM was able to predict localized infections (17). Furthermore, we found no significant difference in PCT and proADM levels between patients with pneumonia and those with other localized infections. Both biomarkers had similar sensitivities and specificities for BSI (67% sensitivity and 68% specificity for proADM at a cutoff of 2.2 nmol/L and 67% sensitivity and 72% specificity for PCT at a cutoff of 1.9 ng/mL). In addition, both proADM and PCT were better than CRP in predicting favorable response to antibiotic therapy among patients with infections.

proADM and PCT tests also had good performance in predicting patients' mortality within 2 months after their fever onset. We found that proADM and PCT levels at follow-up (4–7 d after fever onset) were both significantly higher in patients who died during that time period than those who did not, whereas CRP level at follow-up showed no statistical difference.

In a rat model of lipopolysaccharide-induced endotoxin shock, proADM gene transcription was increased in the lungs, adrenal glands, and aorta, with an associated increase in plasma adrenomedullin and proadrenomedullin N-terminal 20 peptide (35). In a cohort of 101 critically ill patients admitted to the ICU with various diagnoses including seven patients with leukemia, admission levels of proADM were found to be significantly higher in patients with sepsis than in healthy control individuals. Therefore, proADM may add a diagnostic value for clinicians treating immunocompromised patients with cancer, in whom signs and symptoms of BSI and sepsis can be subtle (i.e., fever and leukocytosis are not always present). proADM can also serve as a biomarker to help triage patients with cancer in the emergency room and alert clinicians in general wards to transfer patients to the ICU early for intensive resuscitative therapy including antimicrobial treatment.

proADM has also been shown to have prognostic implications in critically ill patients. Admission plasma proADM was found to be significantly higher in nonsurviving ICU patients than in survivors (16, 36). This was consistent with our findings that showed proADM and PCT tests had better mortality prediction than CRP. However, the proADM levels in these studies were analyzed only at admission (16, 36) or at one point in time during the course of sepsis (37). No follow-up data were available to determine the association between serum proADM levels and fatal outcome. Furthermore, the number of patients with cancer in those studies was small. In our study, we compared serum proADM at two different time points after the onset of a new fever in patients with cancer admitted to the ICU (day 1 and then between day 4 and 7) and found that proADM levels significantly decreased among those who experienced a response to antimicrobial therapy and increased among those who did not respond. This finding, in addition to the other observations in our study, demonstrates that proADM is a better predictor of response to antimicrobial therapy than PCT in febrile critically ill patients with cancer and indicates that proADM is a highly useful prognostic biomarker in critically ill patients with cancer and has a promising role in guiding antimicrobial therapy. This is particularly true because most febrile patients with cancer are continued on a multitude of antimicrobials for prolonged time periods, resulting in a markedly increased prevalence of drug resistance.

In critically ill patients with cancer, combinations of antibiotics are used for prolonged periods of time because it is difficult to differentiate sepsis-related fever from fever caused by other inflammatory conditions, such as acute respiratory distress syndrome and pancreatitis, or due to the tumor burden itself. Based on our data, consideration should be given to the use of these two biomarkers as they might complement one another. If used with follow-up levels, these two biomarkers could benefit critically ill patients with cancer, especially in the judicious use of antibiotics through a stewardship program.

Our study has several limitations. First, our patients had all been on prophylactic antibiotics, which may have interfered with the microbiologic yield and could account for the negative cultures. Second, this was a single-center study, which may have limited the generalizability of the results. Third, due to the observational design of this study, clinical data were collected retrospectively, which could have masked confounding variables.

CONCLUSIONS

In conclusion, both biomarkers proADM and PCT have a promising role, and they are more useful than CRP in assisting clinicians in recognizing BSIs and predicting mortality as well as response to antimicrobial therapy in critically ill patients with cancer with documented infections. They have a good prognostic value and can potentially guide the duration to

antimicrobial therapy and assess treatment response in critically ill patients with cancer. However, proADM might have a slight advantage over PCT in predicting nonresponders and also in predicting response in all febrile critically ill patients with cancer. Further prospective randomized trials are needed to confirm whether bedside monitoring of these markers translate into improved clinical outcomes.

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