Diagnostic Accuracy of Serum Procalcitonin to Diagnose Sepsis in Advanced Solid Tumor Patients with Fever

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ABSTRACT

Background: *Diagnosis of infection in advanced solid tumor patients can be challenging since signs and symptoms might be overlapping due to paraneoplastic condition. Delay diagnosis of existing infection can lead to more severe conditions and increased mortality. Procalcitonin (PCT) has been used to support the diagnosis of bacterial infection and sepsis. Unfortunately, PCT also increases in malignancy even without an infection. We investigated the diagnostic accuracy of PCT in advanced solid tumor patients with fever to diagnose sepsis.* ***Methods:*** *A cross-sectional study was conducted in solid advanced tumor patients with fever patients who were admitted to Cipto Mangunkusumo Hospitals, Indonesia between June 2016 and April 2018. Sepsis was defined using 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference criteria. The diagnostic accuracy of PCT was determined using the receiver operating characteristic (ROC) curve.* ***Results:*** *A total of 194 subjects were enrolled in this study. 60.3% were female with a mean age of 49.47±12.87 years old. 143 patients (73.7%) with advanced solid tumors. Among this latter group, 39 patients (27%) were sepsis. The ROC curve showed that the levels of PCT for sepsis in advanced solid tumor patients with fever were in the area under the curve (AUC) 0.853 (95%CI 0.785 – 0.921). The Cut-off of PCT in advanced solid tumor patients with fever to classify as sepsis was 2.87 ng/mL, with a sensitivity of 79.5%, and a specificity of 79.8%.* ***Conclusion:*** *PCT has good diagnosis accuracy in advanced solid tumor patients with fever to classify as sepsis, however a higher cut-off compared to non-cancerous patients should be used.*

Keywords: *Procalcitonin, Solid tumor, Advance Stage Cancer, Sepsis, Cut-off.*

INTRODUCTION

Cancer patients have a higher risk of acquiring infection, which may be caused by impaired immunity due to cancer treatment-related adverse events, underlying immune dysregulation, and associated comorbidities. Infections in cancer patients may lead to serious outcomes.[1] Study showed cancer patients with fatal infections had almost three times higher mortality rates compared to general populations.[2] Another study showed infection may be the cause of death in 60% of cancer patients.[3] Sepsis, which is a life-threatening condition due to organ dysfunction caused by a dysregulated host response to infection, was more commonly found among cancer patients.[4] Lower survival rate was found in cancer patients group with sepsis compared to non-cancer patients, therefore early diagnosis and aggressive treatment are important in managing this high-risk group.[5]

Diagnosing infection in patients with cancer was challenging. Fever, which is commonly caused by infections, may also occur in cancer patients and is not related to infectious causes.[6] Several noninfectious causes of fever in cancer patients may be caused due to chemotherapy-induced mucositis, neoplastic fever, drug-induced fever, and others.[7] Inappropriate use of antibiotics in cancer patients with fever may lead to antimicrobial resistance.[8] Therefore, several biomarkers were evaluated to differentiate between infectious and noninfectious causes of fever in cancer patients. Leukocytosis, which is usually an indicator of underlying inflammation or infection, was reportedly found in 4.0-25.6% of patients with solid tumors.[9] Procalcitonin (PCT) has been commonly used as a specific marker for bacterial infection and sepsis, however, studies showed that PCT level may be influenced by solid tumor presence. Therefore, some authors proposed a higher cut-off serum PCT level for diagnosing sepsis in cancer patients. The stage of cancer also proposed may influence the PCT cut-off level. Many variations of cut-off levels were reported between studies, establishing a challenge for PCT level interpretation, especially in advanced-stage tumor patients.[10,11] We aimed to find out the cut-off point of PCT for diagnosing sepsis in advanced solid tumor patients with fever in the Indonesian population.

METHODS

Study Design

A cross-sectional study was conducted on solid tumor patients with fever who were admitted to Cipto Mangunkusumo Hospitals, Jakarta, Indonesia between June 2016 and April 2018. Subjects were chosen consecutively from surgical and non-surgical wards, emergency departments, and outpatients.

Study Participants

Study participants were adult solid tumor patients who had a complete staging confirmed by histological, imaging examinations, and had acute fever during inclusion (temperature > 38.3^{o}C). Patients with any conditions that can influence serum PCT were excluded (medullary thyroid carcinoma, neuroendocrine lung cancers, previous antibiotics therapy within the last 72 hours, shock, recent surgical, multiple trauma, resuscitation, dialysis, cirrhosis, or received any colony-stimulating factors). Informed consent forms were completed by each subject before enrolling in this study. All subjects underwent history taking, physical examinations, chest x-rays, and laboratory examinations (complete blood count, blood glucose, blood urea nitrogen, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), urine analysis, serum PCT, blood and site-specific culture). Patients with any conditions that can influence serum PCT were excluded. Tests of liver ultrasound and hepatitis markers were done in patients with increased ALT, AST, or any suspicion of cirrhosis. Sepsis was defined according to 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference (documented infections and either of the general parameters: fever >38.3^{o}C, hypothermia <36^{o}C, heart rate >90 bpm, tachypnea > 30 bpm, altered mental status, significant edema or positive fluid balance (>20 ml/kg over 24 hours), hyperglycemia plasma glucose >140 in the absence of diabetes, and bacteremia).[12]

Tumor staging was reviewed by a certified oncologist according to the American Joint Committee on Cancer (AJCC) criteria. All subjects were already examined and confirmed histopathologically by an experienced pathologist

from the Department of Pathology Cipto Mangunkusumo Hospital. The types of tumors were grouped into head and neck, colorectal, musculoskeletal, breast, lung, genitourinary, gynecology, and pancreaticobiliary. Tumor staging was grouped into early and advanced stages (locally advanced and metastasis).

Laboratory Examinations

Blood was taken by a certified nurse and processed according to the hospital's standard protocol. PCT levels were measured in the Department of Clinical Pathology Cipto Mangunkusumo Hospital laboratorium using the BRAHMS PCT KRYPTOR® tool, which was calibrated as specified by the manufacturer's protocol. This tool has a lower limit of quantification of 0.02 ng/mL. BACTEC bottles were used for blood culture media. Standard media transport was used for site-specific culture (urine, feces, sputum, etc). All examinations were run through the appropriate machines which were calibrated and generated automatically. We considered that the investigators of the laboratory were blinded, as the laboratory staff were not included in the investigation team and did not know about the subjects.

Statistical Analysis

Analysis was done using the Statistical Package for the Social Sciences (SPSS), v.22 (IBM-corp. Armonk, NY) software. Mann-Whitney test was used to compare WBC and PCT values between groups. The *p-value* <0.05 was considered statistically significant. The cut-off point of PCT level for sepsis in metastatic solid tumor subjects with fever was done by AUC analysis from the ROC curve.

Ethical Consideration and Approval

This study was performed under the Declaration of Helsinki, the World Health Organization, and the ICH guideline for good clinical practice. The study protocol has been approved by the Ethics Committee of the Faculty of Medicine, University of Indonesia (235/UN2. F1/ETIK/2016). All study respondents were given study information, the study purpose, and the confidentiality of the result. All patients provided written informed consent to participate before study inclusion.

RESULTS

194 subjects participated in this study, mean age of 49 years old and predominantly female. Gynecology cancer was the most common type, followed by head and neck, colorectal, breast, genitourinary, and pancreaticobiliary cancer. Subjects were divided into early and advanced stages. We also divided subjects into sepsis and non-sepsis groups. There were 143 patients included in the advanced stage according to AJCC criteria. A total of 39 advanced solid tumor patients were diagnosed with sepsis, mostly caused by pneumonia. Bacteremia was found in 16 patients, among them we found 4 patients with only blood showed positive culture. Subject characteristics are shown in **Table 1** and advanced solid tumor patients with sepsis are shown in **Table 2**.

Table 1. Baseline characteristics of the subjects.

Characteristics	N=194
Age, years, mean±SD	49.47±12.873
Sex, n (%)	
Male	77 (39.7)
Tumor group, n (%)	
Gynecology	49 (25.3)
Head and neck	47 (24.2)
Colorectal	21 (10.8)
Breast	18 (9.3)
Genitourinary	17 (8.8)
Pancreatobilliary	17 (8.8)
Lung	14 (7.2)
Musculoskeletal	9 (4.6)
Stage	
Early	51 (26.3)
Advanced	143 (73.7)
Sepsis, n(%)	49 (25.3)
Procalcitonin, ng/mL, median (min - max)	1.325 (0.04 – 923.10)

Table 2. Characteristics of solid tumor patients with sepsis.

Characteristics	N= 49
Stage	
Early	10 (20.4)
Advanced	39 (79.6)
Infection site, n (%)	
Pneumonia	30 (61.2)
Urinary Tract	11 (22.4)
Skin and soft tissue	4 (8.1)
Intra-abdominal	4 (8.1)
Blood	16 (32.6)
Procalcitonin, ng/mL, median (min-max)	9.04 (0.24 – 923.10)

In the advanced stage solid tumor group (n=143), PCT level was significantly higher among patients with sepsis (n=39) compared to non-sepsis patients (9.03 (IQR 57.45) vs. 0.685 (IQR 1.83) ; p<0.05). PCT concentration was higher among advanced-stage solid tumor patients with sepsis compared to early-stage solid tumor sepsis patients (p<0.05). Meanwhile, WBC levels were not different in all groups. (**Table 3**)

We found PCT has good diagnosis accuracy for sepsis diagnosis in advanced solid tumor patients with fever (AUC 0.853 [95%CI 0.785–0.921]). The cut-off for diagnosing sepsis in advanced solid tumor patients with fever was 2.87 ng/mL, with a sensitivity of 79.5% and specificity of 79.8% (**Figure 1**).

DISCUSSION

Female patients had a higher proportion in this study. This finding may be explained due to WHO GLOBOCAN report in 2020, that the most common cancer in Indonesia was breast (16.6%) and cervix uteri cancer (9.2%).[13] Most of our patients had advanced-stage solid tumors. This finding may be related to a lack of detection, screening programs, and patient awareness and knowledge.[14]

In this study, we found a higher level of PCT was observed in advanced-stage solid tumor patients with sepsis compared to early-stage solid tumor patients with sepsis. Elevated PCT levels may be attributed to numerous factors in cancer patients, including the presence of metastasis or neuroendocrine function of malignant tissue.

Table 3. Serum PCT and WBC in advanced vs. early solid tumor group with sepsis.

Variable	Advanced	Early
	Sepsis (N=39)	Sepsis (N=10)
PCT, ng/ml, median (min-max)	23.14 (0.96 – 923.10)	9.03 (0.24 – 252.7)
WBC, median (min-max)	17,660 (1.440 – 72.470)	21,940 (4.770 – 26.970)

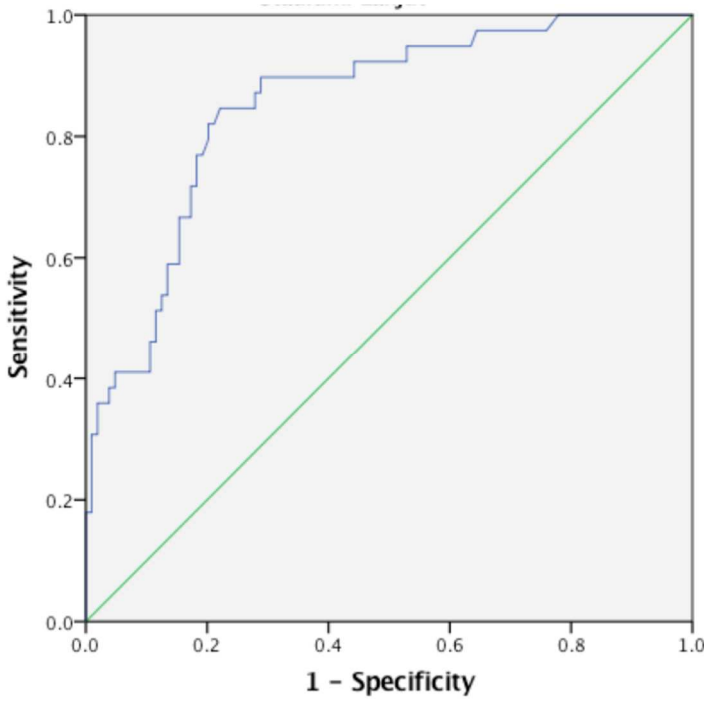

Figure 1. Procalcitonin ROC curve for sepsis in advanced solid tumor patients with fever.

This can be seen in the study by Matzaraki et al that found that PCT level was correlated with different tumor stages. They found higher PCT levels in healthy solid tumor patients with generalized metastatic disease compared to the healthy control group or solid tumor without metastases group.[11] Chaftari et al also found higher PCT levels in stage IV cancer patients compared to stage I-III cancer non-febrile patients (0.190 vs. 0.127 ng/ml, p<0.0001). However, they also stated that febrile cancer patients with sepsis had higher PCT levels compared to non-infectious febrile cancer patients (0.49 vs. 0.31 ng/ml, p:0.003), implying the usefulness of PCT in predicting sepsis in cancer patients.[15] Procalcitonin secretion was induced through two mechanisms. The first pathway was due to direct stimulation by lipopolysaccharides (LPS) or other toxins that produced by pathogens. The second pathway was by indirect stimulation of inflammatory cytokines such as IL-6, and TNF-α.[16] Solid tumors may produce inflammatory cytokines which may affect the tumor microenvironment and produce a chronic inflammatory state.[17] Michalaki et al found that significantly higher levels of IL-6 and TNF-α in metastatic disease compared to localized disease (9.3 ±7.8 vs. 1.3 ±0.8 pg/ml; p<0.001 and 6.3±3.6 vs. 1.1.±0.5 pg/ml; p<0.001).[18] This finding may explain why higher median level of PCT in patients with advanced-stage solid tumors although without infection.

Interpretation of PCT level to determine sepsis may be difficult, due to higher level PCT baseline level in tumor patients. Therefore, the usual cut-off level of PCT in the general population may not apply to cancer patients, especially those in an advanced stage. Advanced-stage cancer may decrease the specificity of PCT in determining infection. The reported cut-off level of PCT in cancer patients varied between studies.[19] Our study found that a cut-off point of 2.87 ng/mL had an overall good performance in detecting sepsis among febrile advanced-stage tumor patients. Azis et al previously reported PCT cut-off for determining sepsis in metastatic cancer patients was 1.14 ng/ml (sensitivity 86% and specificity 88%). They also found higher PCT levels in metastasis cancer patients with sepsis compared to non-metastasis cancer patients without sepsis (3.48 vs.2.92 ng/ml). The different cut-off levels may be explained due to Azis et al only included patients with metastasis, while our study included all advanced-stage cancer patients.[10] Vincenzi et al showed a PCT cut-off of 1.52 ng/mL had a sensitivity of 61.6%, and specificity 70.1% to detect bacteremia in advanced stage solid tumor patients with fever patient. However, the proposed cut-off by Vincenzi et al was determined based on hemoculture positive or negative, they did not evaluate whether the patient's condition which already in a septic condition or not.[20] Similarly, Blouin et al found that a cut-off value of 1.7 ng/mL (sensitivity 61% and specificity 74%) was able to detect bacteremia in cancer patients. However, this study did not account for the possibility of receiving treatment before drawing PCT samples from the patients.[21] Vassallo et al found that a PCT cut-off of 0.52 ng/ml (sensitivity 75% and specificity 55%) was a sensitive marker to differentiate between infection and tumor-associated fever in solid tumor patients. However, the determined cut-off did not differentiate between sepsis condition or localized infection.[19] Ding et al reported a lower cut-off value for PCT, namely 0.105 ng/mL (sensitivity 79.7% and specificity 80.4%). Unfortunately, the cut-off of this study also did not differentiate between sepsis and localized infection.[22]

The strength of our study was our study method which had tight inclusion criteria to minimize bias of PCT level. We did not use retrospective data which was mainly utilized in other studies; therefore, we can accurately determine the sepsis condition and relationship with the PCT level at admission. However, our study had also several limitations. First, we did not use the SEPSIS-3 criteria for diagnosing sepsis in our study, due to the timing of the SEPSIS-3 criteria guidance released and the starting date of our study.[23] Second, we did not determine the type of bacteria that caused sepsis in our studies. Gram-negative bacteremia is generally thought to produce more LPS than gram-positive and, therefore may variably affect

the PCT level. We propose a prospective study to determine the accuracy of our cut-off PCT level using real-world data.

CONCLUSION

PCT has good diagnosis accuracy for sepsis diagnosis in advanced solid tumor patients with fever. The cut-off for diagnosing sepsis in advanced solid tumor patients with fever was 2.87 ng/mL, with sensitivity and specificity of 79.5% and 79.8%, respectively.

LIST OF ABBREVIATIONS

AJCC American Joint Committee on Cancer
ALT Alanine Aminotransferase
AST Aspartate Aminotransferase
AUC Area Under Curve
PCT Procalcitonin
ROC Receiver Operating Characteristics

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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