



## Original article

# Comparison of diagnostic and prognostic utility of lactate and procalcitonin for sepsis in adult cancer patients presenting to emergency department with systemic inflammatory response syndrome



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## ABSTRACT

**Objectives:** Differentiating sepsis from other noninfectious causes of systemic inflammatory response syndrome (SIRS) in cancer patients is often challenging. Although lactate and procalcitonin have been studied extensively regarding sepsis management, little is known about their utility in cancer patients. This study aimed to compare the diagnostic and prognostic utility of lactate and procalcitonin for sepsis in cancer patients.

**Material and methods:** This prospective case-control study was conducted with adult cancer patients presenting to emergency department (ED) with at least two SIRS criteria. The infection status of each patient was determined retrospectively.

Main diagnostic variables were calculated for diagnostic and prognostic utilities of lactate and procalcitonin.

**Results:** Among 86 patients, mean age was 61. Twenty-two (25.6%) were determined in the sepsis group. In the ROC analysis, a lactate value of 1 mmol/L predicted sepsis with 86.36% (95%CI: 65.1%–97.1%) sensitivity and 28.12% (95%CI: 17.6%–40.76%) specificity. A procalcitonin value of 0.8 ng/mL yielded a sensitivity of 63.64% (95%CI: 40.7%–82.8%) and 76.56% (95%CI: 63.4%–86.2%) specificity for differential diagnosis of sepsis in cancer patients.

Lactate and procalcitonin showed similar abilities in differentiating sepsis from non-infective SIRS in cancer patients [AUROCs of 0.638 (95%CI:0.527–0.739) vs 0.637 (95%CI:0.527–0.738), respectively.  $p = 0.994$ ].

They were also similar in predicting poor clinical outcome with AUROCs of 0.629 (95%CI:0.518–0.731) and 0.584 (95%CI: 0.473–0.69), respectively ( $p = 0.577$ ).

**Conclusions:** The results of this study indicated that, none of the lactate and procalcitonin can be recommended alone to differentiate sepsis from non-infectious SIRS and to predict the poor clinical outcomes in adult cancer patients with SIRS in the ED.

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## 1. Introduction

Sepsis is defined as the presence of probable or documented infection together with systemic inflammatory response syndrome (SIRS).<sup>1</sup> Early diagnosis of sepsis and timely initiation of evidence-

based treatment strategies are known to improve the clinical outcomes and to reduce sepsis-related mortality.<sup>1,2</sup>

The emergency department (ED) is a frequent first point of contact for cancer patients. Cancer patients are ten times more likely to develop sepsis since they are immunocompromised. In addition to be the most common comorbidity in septic patients, cancer is the highest risk factor for mortality in sepsis.<sup>3</sup> Early diagnosis of sepsis and distinguishing it from noninfectious processes are of paramount importance to initiate an appropriate treatment on time in these patients.<sup>4</sup> Besides its low specificity, the

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variable presentation of SIRS in cancer patients makes this distinction challenging for emergency physicians.<sup>5,6</sup> A biomarker can be very helpful in the appropriate management of these patients in the ED and may help to avoid unnecessary diagnostic tests, hospitalization, and unwarranted antimicrobial therapy.

There have been sufficient studies on diagnosis and prediction of severity for procalcitonin and lactate sepsis.<sup>7,8</sup> However, little is known about their utility in cancer patients.<sup>9</sup>

The aim of this study was to compare diagnostic and prognostic values of lactate and procalcitonin levels for sepsis in cancer patients presenting to ED with SIRS.

## 2. Materials and methods

### 2.1. Design and setting

This prospective case-control study was conducted in the ED of a teaching hospital in XXXX, Turkey between February 2014 and August 2014. Institutional ethics committee approval (Project Number: XXXX 2014/45) and written informed consent of patients were obtained.

The study site is a tertiary hospital in which about 2000 cancer patients receive care per year. The ED provides care for about 40,000 patients annually. An average of 10% of the ED patients is cancer patients.

### 2.2. Participants

The study group was composed of adult cancer patients who met at least two of the SIRS criteria presented to ED at times in which the principal investigator (EK) was accessible. Exclusion criteria were hematologic and thyroid malignancies, liver dysfunction, trauma patients, patients who presented to the ED because of seizure or missing data for follow-up. In addition, patients who were treated with intravenous fluid therapy of more than 500cc when they were determined as candidates for study, patients whose blood was obtained for lactate and procalcitonin levels, patients using antibiotics at presentation, or those receiving parenteral fluid therapy at home were also excluded.

### 2.3. Protocol

All cancer patients who met the inclusion criteria were recorded regardless of the complaint. Blood samples were taken for lactate and procalcitonin levels immediately, at the time that patients were identified to be eligible for the study. The procalcitonin levels were studied bedside using an immunoassay method and detected by an i-CHROMA Reader (Boditech Med. Inc., KOREA, 2013) device.

For procalcitonin levels, 2 cc blood taken into a mere vacuum tube was centrifuged for 10 min at 4000 rpm, then serum of 150  $\mu$ L was taken and aliquoted into 1.5 mL tubes. An aliquot of 75  $\mu$ L was used for the procalcitonin kit. After waiting 12 min, it was processed in the device and results were obtained in 5 s. The limits of detection were indicated as 0.25–100 ng/mL. The procalcitonin level of greater than 0.5 ng/mL was accepted as probable infection, and the level of greater than 10.0 ng/mL was accepted as severe sepsis or septic shock according to the manufacture protocol.

Lactate levels from radial artery blood administered to a heparin syringe of 2.5 cc was sent to the emergency laboratory pneumatically, followed by analysis with an electrode method by blind technicians using Radiometer ABL 700 Copenhagen (Denmark, 2012) device. The results of lactate levels were obtained as mg/dL, and were converted into mmol/L by multiplying by the constant '0.111' in order to compare with literature.

The presentation characteristics of patients, radiology and laboratory results data with emergency management, lactate levels, and ED outcomes were recorded by the caregiver emergency physician. These doctors were unaware of the procalcitonin levels. However, lactate levels were used in patient care without any changes specific to this study. Hospital database and phone contacts by the principal investigator with patients or their relatives were used for a 28-day follow-up. In addition, radiographic and laboratory data in the form of data were checked from the medical records and ED charts.

Patients whose probable cause of SIRS were assumed to be infection and had been verified clinically infected were accepted as sepsis. In this study, the presence of infection was decided by the lead investigator retrospectively with clinical evidence, laboratory findings, and imaging results based on the criteria of "International Sepsis Forum Consensus Conference on Definitions of Infection".<sup>10</sup> All inpatient and outpatient follow-up data were reviewed for evidence or probability of infection as defined by the consensus. Those for whom infection had not been considered or shown were determined as the 'sepsis negative group'. Intensive care unit (ICU) requirements or mortality were considered as "poor clinical outcome".

### 2.4. Outcome measures

The primary outcome was the detection of sepsis with lactate and procalcitonin levels. The secondary outcome was the comparison of utility of the biomarkers for predicting poor clinical outcomes.

### 2.5. Statistical analysis

Statistical analyses were performed using MedCalc for Windows, version 13.1.0.0 (MedCalc Software, Ostend, Belgium). All continuous variables were presented with 95% confidence intervals (CI). Categorical variables were expressed as percentages or ratios.

Independent samples t-test or Mann Whitney U test were used in the comparison of continuous variables between groups. Chi-square or Fisher's exact test were used in the comparison of categorical variables between groups where appropriate.

Sensitivity, specificity, positive and negative likelihood ratios (LRs) of markers at potential and determined thresholds were calculated with 95% CI. Diagnostic and prognostic performances of markers were assessed with Receiver operating characteristic (ROC) curve analysis. The area-under-the-curve (AUC) comparisons were conducted with nonparametric DeLong method which is used in the comparison of ROC curves of tests performed on the same individual. A p-value of 0.05 was considered statistically significant.

## 3. Results

Among 94 eligible patients, 86 were included in the study (Fig. 1). The median age of was 61 (95% CI: 58–64). The most common malignancy in this study was lung cancer. However, cancer stage data of half of the patients could not be achieved. A total of 39 patients (45.3%) had no comorbid diseases in the study group. The demographic and clinical characteristics are presented in Table 1.

Infection foci considered by the caregiver physician of patients were as follows: lung (n = 16), bladder (n = 6), gallbladder (n = 2), bowel (n = 2), tonsils (n = 1), and ear (n = 1). A total of 6 out of those (lung-4, bladder-1, bowel-1) were assessed as sepsis negative since it was not supported by clinical, laboratory, and radiological evidences in the retrospective evaluation. As a result, sepsis was observed in 22 (25.6%) of patients in the study group. There was a

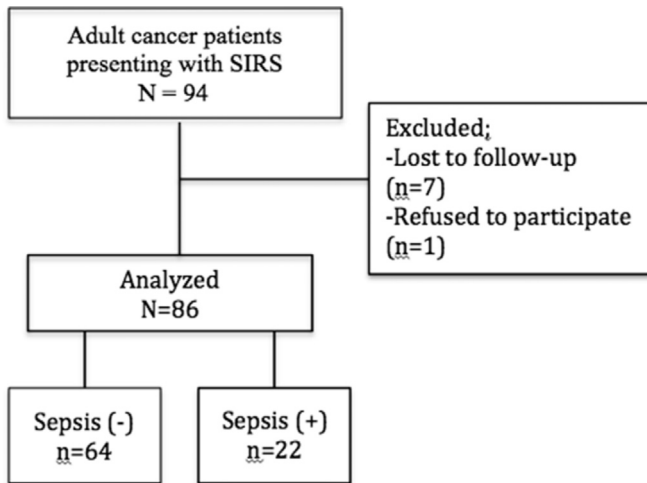


Fig. 1. Patient flow chart.

statistically significant difference in only the mean PaCO<sub>2</sub> and mean WBC between groups when SIRS criteria were examined (Table 2).

There was no significant difference between groups according to sepsis diagnosis in emergency laboratory data including glucose, BUN, creatinine, albumin, AST, ALT, Calcium, Hb, CRP, and the base deficit.

Median lactate levels were found to be similar between the sepsis negative group (median: 1.67 mmol/L, 95% CI: 1.33–1.78) and sepsis positive group (median: 1.89 mmol/L, 95% CI: 1.55–3.46) ( $p = 0.054$ ). Serum procalcitonin levels were significantly higher in the sepsis group (median: 1.01 ng/mL, 95% CI: 0.25–2.48) compared to the sepsis negative group (median: 0.25 ng/mL, 95% CI: 0.25–0.80) ( $p = 0.042$ ). Two patients, whose procalcitonin levels were measured 100 ng/ml, were in sepsis negative group and one of them died in the follow-up.

### 3.1. Diagnostic utility

In the ROC curve analysis, sensitivity was 36.36% (95% CI: 17.2%–59.3%), specificity was 90.62% (95% CI: 80.7%–96.5%), positive LR

Table 1

Demographic and clinical characteristics of patients in the study.

Variable	Total (N = 86)	Sepsis (-) (n = 64)	Sepsis (+) (n = 22)
AGE (mean/median) (95% CI)	61 (54-69)	63 (58.7–65.3)	60 (54.8–64)
Gender (n, %)			
Female	27 (31.4)	23 (35.9)	4 (18.2)
Male	59 (68.6)	41 (64.1)	18 (81.8)
Cancer type (n, %)			
Lung	35 (40.7)	27 (42.2)	8 (36.4)
Breast	8 (9.3)	6 (9.4)	2 (9.1)
Genitourinary	7 (8.1)	4 (6.3)	3 (13.6)
Gastrointestinal	20 (23.3)	15 (23.4)	5 (22.7)
Female genital	5 (5.8)	5 (7.8)	0
Male genital	3 (3.5)	2 (3.1)	1 (4.5)
Airway	3 (3.5)	2 (3.1)	1 (4.5)
Brain	2 (2.3)	1 (1.6)	1 (4.5)
Other	3 (3.5)	2 (3.1)	1 (4.5)
Cancer stage (n, %)			
Unknown	48 (55.8)	36 (56.2)	12 (54.6)
Stage 1	5 (5.8)	2 (3.1)	3 (13.6)
Stage 2	3 (3.4)	3 (4.7)	0
Stage 3	1 (1.1)	1 (1.6)	0
Stage 4	29 (33.7)	22 (34.4)	7 (31.8)
Comorbidity (n, %)			
No	39 (45.4)	30 (46.9)	9 (40.9)
DM	14 (16.2)	12 (18.8)	2 (9.1)
HT	27 (31.3)	19 (29.7)	8 (36.4)
COPD	10 (11.6)	9 (14.1)	1 (4.5)
CHF	8 (9.3)	6 (9.4)	2 (9.1)
CRF	3 (3.4)	0	3 (13.6)
Other	2 (2.3)	1 (1.6)	1 (4.5)
Last CT time (n, %)			
Not receiving	16 (18.6)	11 (17.2)	5 (22.7)
Unknown	13 (15.1)	9 (14.1)	4 (18.2)
Last 2 weeks	20 (23.2)	18 (28.1)	2 (9.1)
2–4 weeks	11 (12.7)	9 (14.1)	2 (9.1)
>1 month	26 (30.2)	17 (26.5)	9 (40.9)
Presentation Complaints (n, %)			
Shortness of breath	32 (37.2)	23 (35.9)	9 (40.9)
Fatigue	11 (12.7)	10 (15.6)	1 (4.5)
Fever	7 (8.1)	4 (6.3)	3 (13.6)
Abdominal pain	7 (8.1)	6 (9.4)	1 (4.5)
General condition disorder	6 (7.0)	6 (9.4)	0
Pain	6 (7.0)	2 (3.1)	4 (18.2)
Inability of nutrition	6 (7.0)	5 (7.8)	1 (4.5)
Hemoptysis	4 (4.7)	3 (4.7)	1 (4.5)
Inability to urinate	3 (3.5)	2 (3.1)	1 (4.5)
Other	4 (4.7)	3 (4.7)	1 (4.5)

DM: Diabetes mellitus; HT: Hypertension; COPD: Chronic obstructive pulmonary disease; CHF: Congestive heart failure; CRF: Chronic renal failure; CT: Chemotherapy; CI: confidence interval.

**Table 2**  
The mean values of SIRS criteria in groups.

Variable	Total N: 86	Sepsis (–) n: 64	Sepsis (+) n: 22	p Value
Pulse rate (beats/min) [mean (95% CI)]	115.5 (110.9–120.1)	114.0 (108.4–119.6)	119.8 (112.1–127.5)	0.278 <sup>a</sup>
Temperature (°C) [mean (95% CI)]	36.5 (36.2–36.7)	36.5 (36.3–36.8)	36.4 (35.8–37.0)	0.710 <sup>a</sup>
Respiratory rate/min [median (95% CI)]	26.0 (24.4–28.0)	25.5 (24.0–28.0)	28.0 (25.0–32.0)	0.241 <sup>b</sup>
PaCO <sub>2</sub> (mmHg) [median (95% CI)]	33.8 (32.0–35.3)	35.0 (33.1–37.0)	30.5 (27.2–33.0)	0.005 <sup>b</sup>
WBC(10 <sup>3</sup> /uL) [mean (95% CI)]	11.1 (9.1–13.0)	8.7 (6.4–9.8)	17.9 (12.2–23.5)	0.003 <sup>a</sup>

WBC: White blood cell; paCO<sub>2</sub>: partial carbon dioxide pressure; SD: standard deviation; CI: confidence interval.

<sup>a</sup> Provided via t-test.

<sup>b</sup> Provided via Mann–Whitney U test.

was 3.88 (95% CI: 2.2–6.8), and negative LR was 0.7 (0.3–1.6) at the cutoff value of lactate set at 2.98 mmol/L in diagnosis of sepsis patients. The analysis demonstrated an AUC of 0.638 (95% CI: 0.527–0.739) ( $p = 0.061$ ) for lactate to diagnose sepsis.

With regard to sepsis diagnosis, for a level of 0.8 ng/mL, procalcitonin provided a sensitivity of 63.64% (95% CI: 40.7%–82.8%) and a specificity of 76.56% (95% CI: 64.3%–86.2%) and a positive LR of 2.72 (95% CI: 1.9–3.8) with a negative LR of 0.47 (95% CI: 0.2–1). The AUC was 0.637 (95% CI: 0.527–0.738) ( $p = 0.0496$ ).

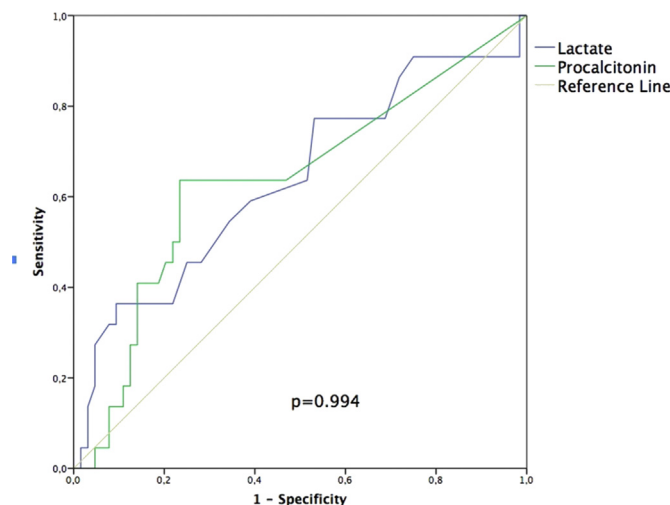
For sepsis diagnosis, the comparison of ROC curves with DeLong method revealed a difference of 0.00071 (95% CI: –0.178–0.180) between AUCs of lactate and procalcitonin (Fig. 2).

The diagnostic values of lactate and procalcitonin levels at the potential cutoffs are presented in Table 3.

A total of 49 patients (57.0%) in study group were discharged upon the completion of emergency care. A total of 32 patients (37.2%) out of remaining 37 were hospitalized in the wards and 5 (5.8%) were hospitalized in the ICU. At the end of twenty-eight days follow-up, 49 (57%) patients did not suffer poor clinical outcomes while, 21 (24.4%) ICU requirements and 32 (37.2%) mortalities were observed. There was no significant relationship between poor clinical outcomes and sepsis diagnosis ( $p = 0.816$ ). Mortality was not associated with the presence of sepsis either ( $p = 0.544$ ).

### 3.2. Prognostic utility

The 28-day mortality prediction abilities of lactate and procalcitonin were found to be similar and insufficient. The AUC was



**Fig. 2.** The comparison of ROC curves of serum lactate and procalcitonin levels in sepsis diagnosis.

0.676 (95% CI: 0.566–0.733) for lactate and 0.548 (95% CI: 0.437–0.655) for procalcitonin ( $p = 0.099$ ).

In the prediction of poor clinical outcomes including mortality or ICU requirements, sensitivity was 51.35% (95% CI: 34.4%–68.1%), specificity was 81.63% (95% CI: 68%–91.2%), positive LR was 2.8 (95% CI: 2–3.9), and negative LR was 0.6 (95% CI: 0.3–1.2) for lactate value of 1.89 mmol/L. The AUC was 0.629 (95% CI: 0.518–0.731). At a cutoff value of procalcitonin set at 2.47 ng/mL based on the ROC curve's optimal threshold the sensitivity, specificity, positive and negative LR were 29.73% (95% CI: 15.9%–47%), 91.84% (95% CI: 80.4%–97.7%), 3.64 (95% CI: 2.2–6) and 0.77 (95% CI: 0.3–2), respectively, for predicting poor clinical outcomes. The AUC was found 0.584 (95% CI: 0.473–0.69) for procalcitonin. The ROC curve comparison showed 0.0444 (95% CI: –0.112–0.2) difference between AUCs in the prediction ability of the 28-day poor clinical outcomes (Fig. 3). The test characteristics of lactate and procalcitonin at potential thresholds for poor clinical outcomes are presented in Table 4.

## 4. Discussion

Based on the results of this study, none of the lactate and procalcitonin values can be suggested alone to distinguish sepsis from noninfectious SIRS in adult cancer patients to guide decision making in the ED. This study sought to search for a screening test to alert physicians regarding sepsis in cancer patients. But sensitivities of lactate and procalcitonin decreased to nearly 70% at low thresholds (1 mmol/L and 0.25 ng/mL, respectively). So, none of them promised to serve as a rule-out test. Furthermore, none of them was superior to the other or suggested utility in predicting poor clinical outcomes.

Procalcitonin has been shown to be valuable in the diagnosis and demonstration of the severity and prognosis of sepsis in literature.<sup>11–14</sup> Lactate has also been suggested as a useful marker in the diagnosis and prognosis of sepsis in many studies. However, cancer patients were excluded in most of those studies.<sup>15,16</sup> This study investigated the diagnostic value of these markers in cancer patients where structural and functional immunosuppression presented together in the pathophysiology of sepsis. Although the pathogenesis of lactate in the tumor tissue has been better understood, the pathogenesis of increased blood levels has not been elucidated.<sup>17</sup> In addition, lactate levels reported in septic cancer patients were not different from the mean levels of septic patients without malignancy in the literature.<sup>18,19</sup> In this case, we believe that our findings based on measured lactate levels in cancer patients in this study are valuable.

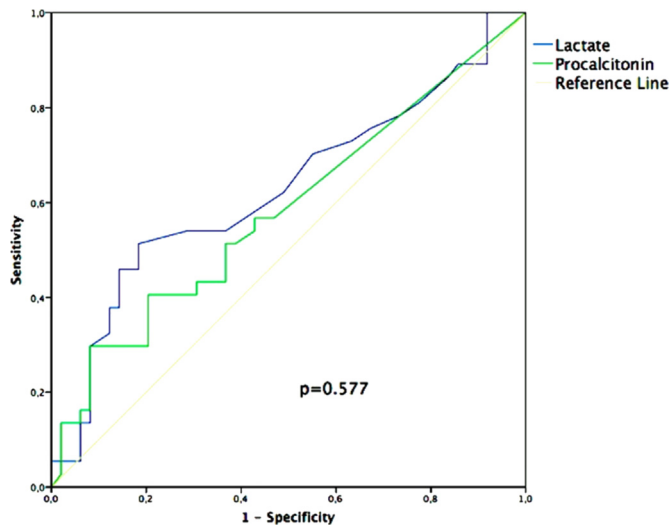
In their study investigating the use of lactate levels on sepsis screening in ED patients without malignancy, Singer et al found that lactate levels were similar between sepsis negative and positive patients (1.35 mmol/L vs1.48 mmol/L), which is consistent with our results. They also reported a lower AUC of 0.59

**Table 3**

The test characteristics of lactate and procalcitonin at potential thresholds for sepsis diagnosis.

	Sensitivity % (95% CI)	Specificity % (95%CI)	(+) LR (95% CI)	(-) LR (95% CI)
Lactate > 1 mmol/L	86.36 (65.09–97.09)	28.12 (17.60–40.76)	1.20 (0.96–1.51)	0.48 (0.16–1.49)
Lactate > 2 mmol/L	37.04 (19.40–57.3)	79.66 (67.17–89.02)	1.82 (0.90–3.69)	0.79 (0.58–1.08)
Lactate > 4 mmol/L	22.73 (7.82–45.37)	95.31 (86.91–99.02)	4.85 (1.26–18.65)	0.81 (0.64–1.02)
Lactate > 2.98 mmol/L	36.36 (17.2–59.3)	90.62 (80.7–96.5)	3.88 (2.2–6.8)	0.70 (0.3–1.6)
Procalcitonin > 0.5 ng/mL	63.64 (40.66–82.80)	68.75 (55.94–79.76)	2.04 (1.26–3.30)	0.53 (0.30–0.94)
Procalcitonin > 2 ng/mL	36.36 (17.20–59.34)	85.94 (74.98–93.36)	2.59 (1.14–5.87)	0.74 (0.53–1.03)
Procalcitonin > 10 ng/mL	9.09 (1.12–29.16)	92.19 (82.7–97.41)	1.16 (0.24–5.57)	0.99 (0.85–1.15)
Procalcitonin > 0.8 ng/mL	63.64 (40.7–82.8)	76.56 (64.3–86.2)	2.72 (1.9–3.8)	0.47 (0.2–1)

CI: confidence interval; LR: likelihood ratio.

**Fig. 3.** The comparison of ROC curves of serum lactate and procalcitonin levels for poor clinical outcomes.

than this study for sepsis diagnosis. The authors reported 34.0% sensitivity and 82.0% specificity at the limit of 2.0 mmol/L, and emphasized the low sensitivity of the lactate levels in the diagnosis of sepsis.<sup>20</sup> They reported a specificity close to our results (95.3%) at the predictive value of 4.0 mmol/L in the same study, and suggested that sepsis could not be excluded with normal lactate levels.

The studies regarding the utility of lactate for diagnosis and prognosis of sepsis in cancers patients have been limited in literature.<sup>9</sup> Among 1129 septic cancer patients in an ICU, Hajjar et al reported that the mortality was 28.7%, mean lactate levels were different between surviving and dead patients (2.4 mmol/L vs 3.7 mmol/L), and found that the lactate levels could predict mortality in multiple regression analysis.<sup>18</sup> The lactate levels of sepsis patients in our study were lower than that. This result was expected

since our sepsis positive patient group was composed of milder forms since we did not group according to the severity of sepsis.

The other marker, assessed in this study was procalcitonin. Procalcitonin has been suggested to be used in early diagnosis and exclusion of infection in cancer patients in literature.<sup>21</sup> However, basal procalcitonin levels have been reported to be associated with total and cancer mortality in a prospective cohort study that was in the secondary analysis qualification and included 3322 patients.<sup>22</sup> Based on those findings, it has been proposed that procalcitonin can exacerbate procarcinogenic inflammatory response, impair anti-tumor immune mechanisms, and act as disease mediator in cancer.<sup>22</sup> However; if this assumption is correct, procalcitonin levels would be expected to be high in all cancer patients. Yet, normal procalcitonin levels were measured in half of the patients in our study.

Although procalcitonin is accepted as a marker that can distinguish infectious and noninfectious processes in febrile neutropenic patients,<sup>23</sup> it showed the lowest diagnostic accuracy with an AUC of 0.71 in immunocompromised and neutropenic patients.<sup>24</sup> In detection of infection among febrile neutropenic patients with solid tumors, its sensitivity was lower than our results (41.5%) and the specificity was much higher (92.0%). Mortality was predicted with 100% sensitivity and 83% specificity with 0.5 ng/mL procalcitonin level. Those findings were interpreted just as a support for decision-making, not a guide.<sup>25</sup> The current study suggested much lower prognosis prediction as that study was conducted on only febrile neutropenic patients.

The AUC for sepsis diagnosis was calculated in 66 patients as 0.75 for only SIRS criteria, 0.67 for only procalcitonin, and 0.92 when evaluated together in a study suggesting procalcitonin as a probable indicator of early sepsis in SIRS patients without malignancy in ED. The authors concluded that immediate bedside measurement of procalcitonin in ED may be helpful for emergency physicians.<sup>26</sup> In another study comparing procalcitonin results and judgment of emergency physician in detection of the presence of infection in the ED, procalcitonin could diagnose the presence of infection with 63.0% sensitivity and 79.0% specificity at the limit of 0.5 ng/mL in a population, one-third of which was composed of

**Table 4**

The predictive values of lactate and procalcitonin at potential thresholds for poor clinical outcomes.

	Sensitivity % (95% CI)	Specificity % (95% CI)	(+) LR (95% CI)	(-) LR (95% CI)
Lactate > 1 mmol/L	78.38 (61.79–90.17)	26.53 (14.95–41.08)	1.07 (0.84–1.35)	0.81 (0.38–1.76)
Lactate > 2 mmol/L	48.65 (31.92–65.60)	81.63 (67.98–91.24)	2.65 (1.35–5.21)	0.63 (0.45–0.88)
Lactate > 4 mmol/L	13.51 (4.54–28.77)	93.88 (83.13–98.72)	2.21 (0.56–8.65)	0.92 (0.80–1.07)
Lactate > 1.89 mmol/L	51.35 (34.40–68.10)	81.63 (68.00–91.20)	2.80 (2.00–3.90)	0.60 (0.30–1.20)
Procalcitonin > 0.5 ng/mL	43.24 (27.10–60.51)	63.27 (48.29–76.58)	1.18 (0.70–1.98)	0.90 (0.63–1.28)
Procalcitonin > 2 ng/mL	29.73 (15.87–46.98)	87.76 (75.23–95.37)	2.43 (0.99–5.96)	0.8 (0.63–1.01)
Procalcitonin > 10 ng/mL	13.51 (4.54–28.77)	95.92 (86.02–99.50)	3.31 (0.68–16.13)	0.9 (0.78–1.04)
Procalcitonin > 2.47 ng/mL	29.73 (15.90–47.00)	91.84 (80.40–97.70)	3.64 (2.20–6.00)	0.77 (0.30–2.00)

CI: confidence interval; LR: likelihood ratio.



immunosuppressed cancer patients. The sensitivity decreased to 36.0% and specificity increased to 93.0% at the limit of 2.0 ng/mL. In addition, the superiority of procalcitonin levels over emergency physician judgments could not be shown. The authors also proposed the cutoff value of 0.2 ng/mL for emergency settings arguing that much lower predictive values rather than the one in intensive care units must be used in order for procalcitonin to be used as early finding of infection.<sup>14</sup> We did not calculate test characteristics at the limit of 0.2 ng/mL, since the lower limit of the kit used in this study was 0.25 ng/mL.

Debiane et al reported the AUC in cancer patients as 0.52 for distinguishing sepsis from SIRS and as 0.77 for mortality and suggested procalcitonin as a promising marker in terms of prognosis.<sup>9</sup> In addition, they suggested that using procalcitonin together with another infection marker may increase the diagnostic utility considering that increased procalcitonin might arise from tumor load. Freund et al<sup>8</sup> similarly suggested that using lactate and procalcitonin together would be more useful clinically instead of comparing the markers in their study conducted with 462 participants (84 of which were immunocompromised or cancer patients). The authors reported the AUC as 0.565 and 0.748, respectively at the predictive values of 1.4 mmol/L for lactate and 0.25 ng/mL for procalcitonin in which ROC curve presents the best performance in sepsis diagnosis. The authors found the AUC as 0.679 and 0.664, respectively at markers' predictive values of 2.0 mmol/L and 0.8 ng/mL in the study using the same definition for poor clinical outcome as our group. The study determined that procalcitonin was superior in diagnosis of sepsis and lactate was superior in prediction of severe sepsis. For prognostic values, they could increase the sensitivity to 72.0% and negative predictive value to 88.0% even evaluating that any of the markers were high. All these findings supported our results suggesting that none of the markers are sensitive enough to rely on.

In their prospective study Shomali et al<sup>27</sup> found sensitivity as 67.0%, specificity as 62.0%, and the negative predictive value as 90.0% for procalcitonin value of 0.5 ng/mL in diagnosis of bacteremia. The striking feature of that study was the detection of significantly higher procalcitonin levels in patients with metastatic cancer compared to the levels in non-metastatic patients.<sup>27</sup> We could not analyze the patients in cancer stage subgroups. In this context, it is possible that procalcitonin may suggest higher utility in a non-metastatic cancer population.

When we compared lactate and procalcitonin, we observed no difference in the diagnosis of sepsis and prediction of poor outcomes. In addition, they had no sufficient diagnostic and prognostic value alone in distinguishing cancer-induced inflammatory response findings, clinical sepsis in the early period to guide ED management of cancer patients. Although the lactate levels higher than 1 mmol/L did not have ideal sensitivity in SIRS patients with cancer, we believe that those levels were sufficient to draw attention of emergency physicians to sepsis possibility to initiate early treatment.

#### 4.1. Limitations

The small sample size may have limited to reach statistical significance in this single center study. Because of time restriction and overcrowding in the ED, there might be some patients overlooked. The authors were aware that SIRS is not a reliable criterion in cancer patients.<sup>28</sup> Nevertheless, it was preferred for homogeneity for inclusion criteria to provide reliable comparison among studies.<sup>29</sup>

A single measurement of lactate and procalcitonin might have also contributed to the interpretation of the results. Only one measurement was performed in this study in order to

investigate a biomarker at triage as a strong clue for sepsis in cancer patients.

The researcher who decided the presence of infection was not blind to the procalcitonin levels. This might have led to a bias in sepsis diagnosis or in the differentiation of positive and negative groups. Lack of a gold standard in the determination of bacteremia and infection, low rates of blood culture results, and the possibility of unnoticed occult infection foci might also cause an incorrect classification of patients.

Medications used by patients in the study group were not evaluated in terms of the possible cause of lactate elevation. In this study, 16.0% of the patients were diabetic and might be using metformin. However, the literature has supported that prescribed doses of metformin do not lead to significant lactate elevation.<sup>30</sup>

The markers could not be assessed in the subgroup analysis due to the lack of data in patients' tumor stage. The subgroup analyses may provide more valuable information on the usefulness of markers in cancer patients, since both procalcitonin and lactate are markers that may be affected by tumor stage and tumor aggressiveness.

## 5. Conclusions

The results of this study revealed that the lactate and procalcitonin levels cannot be used reliably in differentiating sepsis from noninfectious SIRS or predicting clinical outcomes in cancer patients in the ED. Considering that cancer patients are at high risk for sepsis and poor clinical outcomes, further extensive studies to assess cancer stages, sepsis severity classes, and early diagnostic biomarkers should be conducted.

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