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The Relationship Between Sepsis Foci and Procalcitonin Values in Intensive Care Patients

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ABSTRACT

Background: Anatomic localizations of septic foci and the relationship between these localizations and procalcitonin (PCT) in the clinical picture of sepsis/septic shock induced by these foci is not a sufficiently investigated topic. We aimed to determine the relationship between sepsis foci and procalcitonin values in intensive care patients.

Methods: Data of the patients who were admitted in the intensive care unit and diagnosed with sepsis/septic shock between 2016 and 2018 were analyzed retrospectively. The patients were grouped based on the localization of the infectious foci as respiratory system, urinary system, blood-catheter, soft tissue and abdominal. Additionally, the patients were grouped also based on number of foci and growing microorganisms. Subsequently, the relationship between septic foci and routine laboratory parameters, primarily PCT, was investigated statistically.

Results: Totally 630 infection periods were analyzed in 424 patients who were diagnosed with sepsis/septic shock in the intensive care unit. Incidence of sepsis/septic shock was 36.5% while mortality rate was 65.6% in these patients. A higher mortality rate was encountered in the infections with two or multiple foci ($p < 0.001$). Multiple-focal infections revealed higher PCT values than the single focal infections ($p = 0.021$). A higher mortality rate was detected in the patients with microbial growth in the respiratory infections than those with urinary and abdominal infections ($p < 0.001$). The patients with microbial growth reported from blood and abdominal cultures revealed higher PCT levels than other patients groups ($p < 0.001$).

Conclusions: Higher procalcitonin levels are related to presence of multiple foci of infection and, as well, to higher mortality rates.

Key words: intensive care units, sepsis, source of infection, procalcitonin.

Introduction

Sepsis is a life-threatening organ dysfunction induced by dysregulated host response. On the other hand, septic shock as a subset of sepsis continues with circulatory and cellular metabolic dysfunction and presents a high mortality rate (1). Sepsis process is affected by the localization of infection. Infection may be associated with the respiratory system, urinary system, soft tissues, abdominal structures and blood stream. When sepsis is suspected, determination of the source of infection is attempted by performing some biochemical, radiological and microbiological studies besides clinical findings of the patients. It has been shown that, septic focus has a critical importance during clinical course and outcomes of the patients (2).

Early and accurate diagnosis is important in sepsis. Several factors such as inaccuracy of the clinical indicators, delayed or failed test results may complicate the process of diagnosis (3). While performing sample cultures; sampling method, sampling localization, contamination of sample and required long duration of incubation for some microorganisms are important factors that may affect test results (4). In addition, there is not a diagnostic biomarker with 100% sensitivity and specificity yet. Conventional laboratory parameters such as C-reactive protein (CRP), leukocytes and sedimentation that are evaluated with clinical signs in diagnosis of the infectious diseases are not adequately sensitive and specific to manage treatment selection. In recent years, use of procalcitonin (PCT) was increased in this field (3,4). All options which may be useful for early

diagnosis should be borne in mind. Concordantly, localization of the infectious focus, number of foci, number of the infectious agents and their species may be crucial. Beside these, determining anatomic localization of the infectious focus and the relationship between the agents may provide a positive effect on treatment by accelerating the diagnosis process without performing advanced investigations.

This study aimed to determine the relationship between anatomic localizations of septic foci, features of infectious agents in these septic foci and PCT and other routine laboratory tests.

Method

The study was approved by The Ethics Committee of Selçuk University Medical Faculty (Number: 2018/238, Date: 27.06.2018). The study was conducted in General Intensive Care Units (ICU) of Konya Numune State Hospital that serves third level ICU care with 30 beds. Data of the patients who were admitted between January 2016 and January 2018 were analyzed retrospectively. Microbiological cultures obtained from all consecutive patients admitted in the ICU during this interval were grouped as respiratory system cultures, urinary system cultures, blood-catheter cultures, soft tissue and abdominal cultures. Sepsis was diagnosed with presence of microbial growth and related clinical findings. Septic period was defined as the time when sepsis treatment was performed. Demographic characteristics, clinical data and results of the patients with sepsis were recorded. Subsequently, groupings were planned according to anatomic localization of the septic focus, number of foci and species of the growing microorganisms. Highest levels of PCT, CRP, creatinine, total bilirubin, lactate and lowest levels of haemoglobin, platelets, glomerular filtration rate (GFR) and albumin were recorded. Both highest and lowest values of the white blood cells were recorded. Statistical analysis was performed to evaluate relationship between laboratory tests and numbers of septic foci, localization of the foci and species of the growing microorganisms regarding septic foci.

Inclusion criteria

1. Age over 18 years
2. Admission for at least 48 hours in the ICU and microbial growth in at least one culture
3. Being diagnosed with sepsis/septic shock and having received treatment for sepsis
4. Independent septic attacks in the same patient were included as separate events.

Exclusion criteria

1. Presence of immune system disease (Rheumatoid arthritis, systemic lupus erythematosus, vasculitis etc.)
2. Presence of malignancy
3. Chronic renal failure
4. Postoperative early-term period (first 7 days)
5. Post-traumatic early-term period (first 7 days)
6. Other conditions that may affect procalcitonin metabolism (Burn, severe liver failure, rhabdomyolysis, etc.) (5).

Definition of infection

The patients from whom at least one culture revealed microbial growth of microorganisms accepted as infectious agent by the clinician were included in the study. The decision of the clinician were based on clinical signs of the infection (fever, hypothermia, tachycardia, etc.), changes in the laboratory parameters (PCT, CRP, white blood cell etc.) and radiological results. Growth was regarded as contamination when clinical and laboratory data were not interpreted in favor of infection despite presence of microbial growth in the culture. Surviving Sepsis Campaign 2012 Guideline and Sepsis-3 Definitions were taken into consideration for diagnosis and treatment planning of sepsis and septic shock (1,6).

Pathogen identification and laboratory analysis

Blood-catheter samples sent to the Microbiology Laboratory of Konya Numune State Hospital were incubated in the BacT/ALERT (bioMerieux) Instrument for five days. Blood-catheter and other clinical samples which displayed a positive signal of bacterial growth were planted in 5% sheep blood agar (bioMerieux, France) and eosin methylene blue (EMB) agar (bioMerieux, France) and incubated at 35 °C for 18-24 hours in an aerobic atmosphere. Identification and antimicrobial sensitivity tests of the growing bacteria was performed using VITEK 2 Compact (bioMerieux, France) automated system. Antibiotic sensitivity results were analyzed in accordance with EUCAST (The European Committee on Antimicrobial Susceptibility Testing) recommendations. All samples were examined by also Gram Staining method. Haemoglobin, white blood cells and thrombocyte counts were performed (XN-1000 Haematology analyzer, Sysmex Corporation, Kobe, Japan) in ethylenediamine tetraacetic acid (EDTA) blood samples of the patients. CRP (BN II System, Siemens, Germany), PCT (ADVIA Centaur CP, Siemens, ABD) and other parameters such as creatinine, albumin, total bilirubin and lactate (Cobas ® 6000, Roche Diagnostics) were tested after blood samples sent in the tubes without anticoagulant were centrifuged.

Statistical analysis

Data were statistically analyzed using SPSS Versin 22.0 (Statistical Package for the Social Sciences Inc., Chicago, IL, ABD). Descriptive statistics were performed in all patient groups; numerical data were expressed as median (quarter intervals) while categorical data were presented as percentages. For analysis, patients diagnosed with sepsis/septic shock based on at least one microbial culture growth were sorted into three groups according to numbers of infectious foci (single, double and multiple foci). In addition, infectious foci were sorted into five groups as respiratory system infection, urinary system infection, blood-stream-catheter- infection, soft tissue infection and abdominal infection. Subsequently, statistical analysis was performed to determine the inter-group differences with respect to patient characteristics and laboratory parameters depending both on the number of foci and the source of infection. Patient features were compared using Chi-Square or Fisher's Exact Test for categorical variables and Mann-Whitney U Test for numerical variables. $P < 0.05$ value was accepted as statistically significant.

Results

In the study period, 1,162 patients were monitored and treated in the ICU. Number of the patients for whom microbial growth was reported in the cultures and sepsis treatment was initiated

in accordance with the inclusion criteria was 424. Totally 630 independent septic periods were detected since multiple septic periods were detected in 92 (21.7%) of those patients (Figure 1).

Mean age of the patients was 77 (67-83) and 45.8% of the patients were male. Mean length of ICU stay was 20,5 (9-41) day. Of the patients; 80.4% received mechanical ventilation support. The incidence of acute renal failure was 32.8%. Mortality rate was 65.6% (n: 278) in the study patient group. During the septic periods 38.7% (n: 164) patients died (Table 1).

Number of the patients with single focal infection was found to be higher than the patients with double or multiple focal infections (71.7%, 23.8% and 4.5% respectively). Length of ICU stay was shorter in the single focal infection than the other groups ($p = 0.044$). The frequency of mechanical ventilation raised as number of the infectious foci increased ($p = 0.001$). A higher mortality rate was encountered in patients with double and multi-foci infections ($p < 0.001$). PCT and white blood cell levels were higher in patients with multi-foci infections than with single focal infections ($p = 0.021$ and $p = 0.003$, respectively). It was detected that CRP levels raised as number of the infectious foci increased ($p < 0.001$). Lactate levels were higher in the patients with multi-foci infections than the other groups ($p < 0.001$) (Table 1).

Three hundred and four patients with single focal infections and 423 infection periods were sorted into five groups based on the localization of the infectious foci as respiratory system, urinary

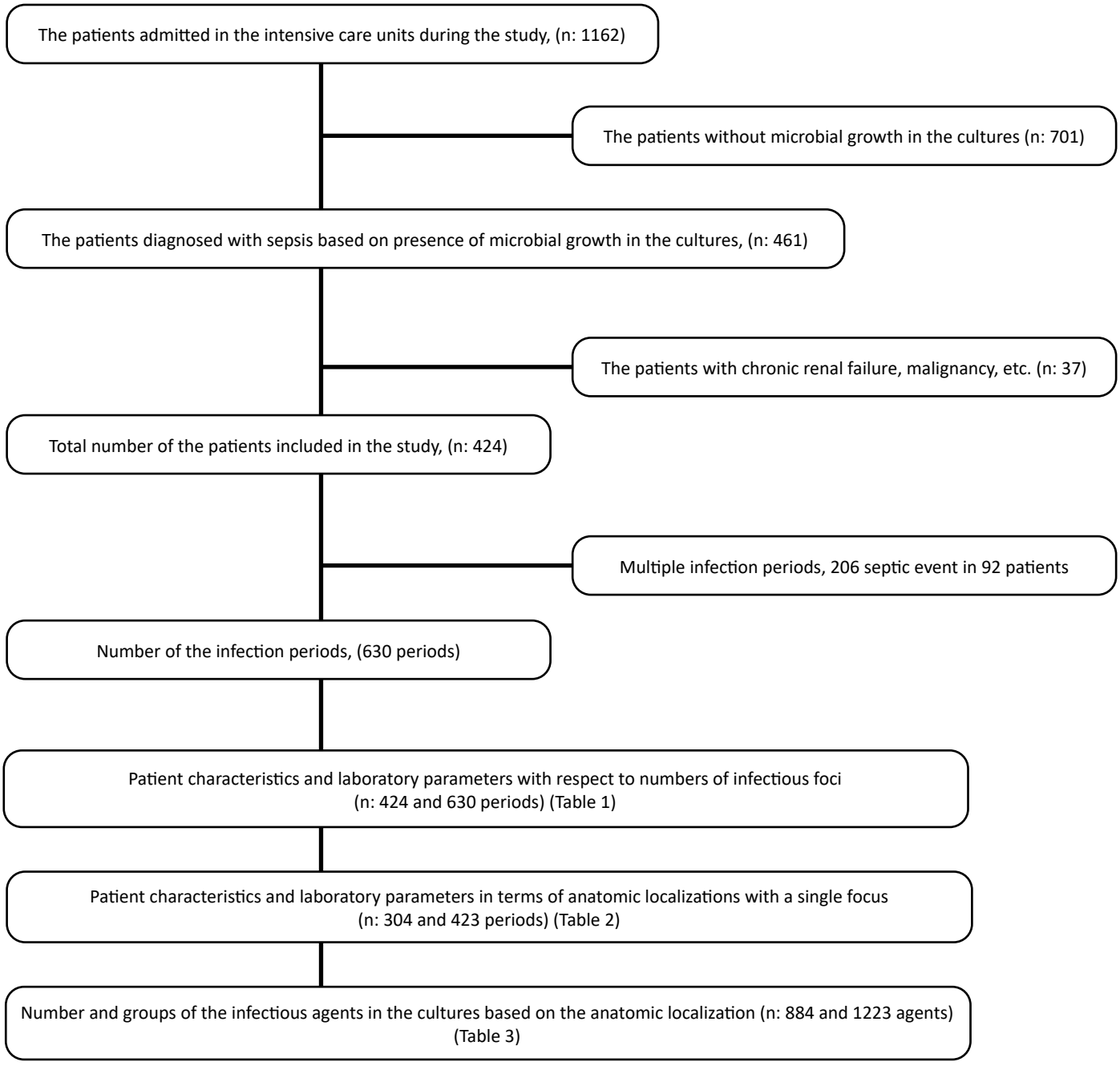

Figure 1. Flow chart of patients.

Table 1. Patient characteristics and laboratory parameters with respect to numbers of infectious foci

	Total	Single focal infection	Double focal infection	Multipl focal infection	p-value
Patient characteristics	n: 424	n: 304 (71.7%)	n: 101 (23.8%)	n: 19 (4.5%)	
Age (Year)	77 (67-83)	77 (67-83)	77 (60,7-82)	81 (70-84)	0.334
Gender (male)	194 (45.8%)	132 (43.4%)	51 (50,5%)	11 (57.9%)	0.259
Length of ICU stay (days)	20,5 (9-41)	17 (8-38)[ab]	27 (15,5-44)[a]	27 (22-51.5)[b]	**0.044**
CCS score	4 (3-5)	4 (3-5)	4 (3-5)	5 (3.5-6)	0.182
APACHE 2 score	25 (20-30)	25 (21-30)	24 (20-30)	24 (19-30)	0.796
SOFA score	4 (3-6)	4 (2-6)	4 (3-5)	5 (3-6)	0.212
Mechanical ventilation	341 (80.4%)	231 (76%)[ab]	91 (90.1%)[a]	19 (100%)[b]	**0.001**
Acute renal failure	139 (32.8%)	101 (33.2%)	31 (30.7%)	7 (36,8%)	0.113
Mortality	278 (65.6%)	184 (60.5%)[ab]	75 (74.3%)[a]	19 (100%)[b]	**< 0.001**
Mortality during septic period	164 (38.7%)	108 (35.5%)	46 (45.5%)	10 (52.6%)	0.089
Laboratory parameters (in events)	**n: 630**	**n: 423 (67.2%)**	**n: 169 (26.8%)**	**n: 38 (6%)**	
Procalcitonin (ng/ml)	2,37 (0.4-10.6)	2,02 (0.37-9,18)[a]	2,42 (0.48-16.6)	6,24 (1.08-35.2)[a]	**0.021**
WBC (max) (x 10^3 /L)	12,4 (9.6-17.4)	12,2 (9.5-16.5)[a]	12,4 (9.4-18.3)	16,3 (11.7-21)[a]	**0.003**
WBC (min) (x 10^3 /L)	4,5 (3.3-5.0)	4,7 (3.3-5.0)	4,05 (2.5-5.4)	5 (5-5)	0.416
CRP (mg/L)	138 (79-187)	123 (67-180)[ab]	146 (106-194)[ac]	191(161-229)[bc]	**< 0.001**
Hemoglobin (g/dL)	10 (9-11.4)	10,1 (9.1-11.6)	9,7 (8.9-11)	9,8 (9.1-10.7)	0.060
Platelets (x 10^3 /µL)	213 (147-292)	216 (144-283)	218 (167-315)	168 (128-274)	0.073
Creatinine (mg/dl)	1,06 (0.5-2.5)	1,20 (0.5-2.5)	0,89 (0.5-2.3)	1,09 (0.4-2.9)	0.241
GFR	60 (21-94)	48 (21-96)	74 (23-94)	55 (18-91)	0.281
Albumin (g/L)	2,5 (2.2-3)	2,5 (2.2-3)	2,5 (2.2-2.8)	2,3 (2.0-2.7)	0.132
Total bilirubin (mg/dl)	0,5 (0.4-0.8)	0,5 (0.4-0.8)	0,6 (0.4-0.8)	0,6 (0.4-1.1)	0.113
Lactate (mEq/L)	1,8 (1-3)	1,6 (1-3)[a]	1,9 (1-3)[b]	2,9 (2-4)[ab]	**< 0.001**

Data are presented as Median [IQR] or n(%)
[a,b,c,d,e,f]Values within the group with the statistical difference are indicated by the same.
IQR: interquartile range; ICU: intensive care unit; CCS: Charlson comorbidity score, APACHE 2: Acute Physiology and Chronic Health Evaluation 2; SOFA: Sequential Organ Failure Assessment; WBC: white blood cell; CRP: C-reaction protein; GFR: Glomerular filtration rate.

system, blood-catheter, soft tissue and abdominal. Single focal infections commonly involved the urinary system by 58.5%. Urinary system infections were more common in the female patients ($p < 0.001$). Incidence of acute renal failure was found to be higher in the abdominal infection group ($p = 0.041$). A higher rate of mechanical ventilation was present in the patients with respiratory infections ($p < 0.001$). Mortality rate was higher in patients respiratory infections than those with urinary and abdominal infections ($p <0.001$). In septic periods, mortality of patients with respiratory system infections was higher than patients with urinary system infections ($p <0.001$). Higher PCT values were encountered in the patients with blood-catheter and abdominal infections than the other groups ($p <0.001$). CRP levels were higher in the patients with microbial growth in the blood-catheter culture than those with microbial growth in the urinary system test cultures while the patients with abdominal infection had higher levels of CRP than both urinary system and soft tissue infections ($p <0.001$). Platelet counts of the patients with microbial growth in the blood-catheter test cultures were lower than the patients with microbial culture growth in the respiratory and urinary systems ($p = 0.002$). Bilirubin levels of the patients with abdominal infection were found to be higher than those with respiratory and urinary system infections ($p < 0.001$). Both APACHE II and SOFA scores did not differ significantly between groups (respectively $p = 0.211$ and $p = 0.113$) (Table 2).

The cultures revealed single agent double agents and multipl agents infections by 69.4%, 23.5% and 7.1%, respectively. Single-agent infection rate was lowest in soft tissue cultures (22%), while polymicrobial infection rate was found mostly in soft tissue and abdomen cultures (28% and 26.9% respectively). Gram negative bacteria, Gram positive bacteria and fungal agents were determined in the cultures by 77.4%, 10.9% and 11.7%, respectively. The highest rates of Gram negative infection were encountered in the respiratory system and soft tissue (95.7% and 89.4%, respectively) while highest rates of Gram positive infection were reported from the abdominal and blood-catheter samples (21.6% and 19.8%, respectively) ($p <0.001$). Highest incidence of fungal infections (22.5%) was encountered in the urinary system ($p < 0.001$) (Table 3).

Discussion

We have conducted our study by evaluating a very comprehensive data and found that during sepsis PCT levels increase as number of the infectious foci increase and this elevation is related to increased mortality rate. Additionally, abdominal and blood-catheter infections seem to trigger higher levels of PCT while higher mortality rates were determined to be higher in patients with sepsis originated from respiratory system. Respiratory system cultures revealed higher rates of gram negative growth. Soft tissue and abdominal infections demonstrated higher rates of polymicrobial growth.

Table 2. Patient characteristics and laboratory parameters in terms of anatomic localizations with a single focus

	Total patients	Respiratory system infection	Urinary system infection	Blood stream -catheter infection	Soft tissue infection	Abdominal infection	p-value
Patient characteristics (Median IQR), %	n: 304	n: 75 (24.7%)	n: 178 (58.5%)	n: 23 (7.6%)	n: 6 (2%)	n: 22 (7.2%)	
Age (year)	77 (67-83)	73 (64-81)	80 (69-85)	77 (62-84)	76 (69-82.5)	73 (65-79)	0.205
Gender (male)	134/304 (44.1%)	50/75 (66.7%)[a]	57/178 (32%)[ab]	10/23 (43.5%)	3/6 (50%)	14/22 (63.6%)[b]	< 0.001
Length of ICU stay (days)	17 (8-38)	17 (8-34)	20 (8.7-40.2)	17 (9-38)	26 (14-35)	7,5 (4-16.2)	0.064
CCS score	4 (3-5)	3 (2-5)	4 (3-5)	5 (2-6)	6 (2.7-7.5)	4 (2.7-5)	0.188
APACHE 2 score	25 (21-30)	24 (22-30)	26 (21-31)	24 (22-29)	26 (20-32)	22 (18.5-29)	0.211
SOFA score	4 (3-6)	4 (2-6)	4 (2-5)	5 (3-6)	5 (3-6)	5 (2-6)	0.113
Mechanical ventilation	231 (76%)	72 (96%)[abcd]	127 (71.3%)[a]	17 (73.9%)[b]	4 (66.7%)[c]	11 (50%)[d]	< 0.001
Acute renal failure	101/304 (33.2%)	26/75 (34.7%)	50/178 (28.1%)[a]	9/23 (39.1%)	3/6 (50%)	13/22 (59.1%)[a]	0.041
Mortality	184 (60.5%)	61 (81.3%)[ab]	93 (52.2%)[a]	15 (62.2%)	5 (83.3%)	9 (40.9%)[b]	< 0.001
Mortality during septic period	145(47.6%)	57 (76%)[a]	62 (34.8%)[ab]	11 (47.8%)	5 (83.3%)[b]	9 (40.9%)	< 0.001
Laboratory parameters (Median, IQR)	**n: 423**	**n: 102 (24.1%)**	**n: 254 (60%)**	**n: 29 (6.9%)**	**n: 16 (3.8%)**	**n: 22 (5.2%)**	
Procalcitonin (ng/ml)	2,02(0.37-9.18)	3,86 (0.8-8.67)[ab]	1,07 (0.28-6.54)[cd]	6,89 (1.88-59.76)[ace]	0,97 (0.3-1.73) [ef]	20,6 (2.37-39.4)[bdf]	< 0.001
WBC (max)(x10³ /L)	12,2 (9.5-16,5)	14 (10.4-19.5)	11,0 (9.2-15.2)	15 (12.1-18.2)	11,26 (6.6-14.9)	12,7 (7.4-21.5)	0.121
WBC (min)(x10³ /L)	4,7 (3.3-5.0)	4,7 (4.3-4.9)	5 (3,6-5,4)	4,8 (4.7-4.9)	3,2 (0.7-5.7)	3,3 (1.6-4.2)	0.104
CRP (mg/L)	123 (67-180)	148 (101-188)	104 (58-153)[ab]	147 (115-200)[a]	137 (79-184)[c]	185 (143-319)[bc]	< 0.001
Hemoglobin (g/dL)	10,1 (9.1-11.6)	10 (8.7-11.5)	10 (9.2-11.5)	10 (8.5-12.2)	9,6 (8.6-10)	12 (10.7-13.6)	0.536
Platelets (x10³ /µL)	216 (144-283)	227 (156-297)[a]	229 (157-284)[b]	141 (99-216)[ab]	182 (94-300)	194 (126-261)	0.002
Creatinine (mg/dl)	1,2 (0.52-2.51)	1,55 (0.59-2.91)	1,04 (0.49-2.2)	0,9 (0.5-2.68)	1,07 (0.43-2.4)	2,7 (1.77-3.64)	0.774
GFR	48 (21-96)	41 (16-95)	63 (23-98)	65 (22-89)	54 (22-97)	22 (11-33)	0.217
Albumin (g/L)	2,5 (2.2-3)	2,4 (2.1-3.0)	2,6 (2.3-3.2)	2,5 (2.2-2.8)	2,1 (1.8-2.6)	2,8 (2.2-3.1)	0.132
Total bilirubin (mg/dl)	0,5 (0.4-0.8)	0,5 (0.4-0.6)[a]	0,5 (0.37-0.8)[b]	0,6 (0.5-0.8)	0, 7(0.3-0.87)	0,9 (0.5-1.3)[ab]	0.001
Lactate (mEq/L)	1,7 (1-3)	2 (1-3)	1,5 (1-3)	2 (1-3)	1,5 (1-3)	1,5 (0.9-2.7)	0.229

[a,b,c,d,e,f]Values within the group with the statistical difference are indicated by the same.
IQR: interquartile range; ICU: intensive care unit; CCS: Charlson comorbidity score; APACHE 2: Acute Physiology and Chronic Health Evaluation 2; SOFA: Sequential Organ Failure Assessment; WBC: white blood cell; CRP: C-reaction protein; GFR: glomerular filtration rate.

Table 3. Number and groups of the infectious agents in the cultures based on the anatomic localization

	Total Patients	Respiratory system infection	Urinary system infection	Blood stream -catheter- infection	Soft tissue infection	Abdominal infection	p-value
Number of agents	n: 884	n: 263 (29.8%)	n: 438 (49.6%)	n: 107 (12.1%)	n: 50 (5.6%)	n: 26 (2.9%)	
Single agent cultures	614 (69.4%)	170 (64.6%)[a]	331 (75.5%)[b]	89 (83.2%)[c]	11 (22%)[abc]	13 (50%)	< 0.001
Double agents cultures	207 (23.5%)	72 (27.4%)	92 (21%)	12 (11.2%)[a]	25 (50%)[a]	6 (23.1%)	0.028
Multipl agents cultures	63 (7.1%)	21 (8%)ad	15 (3.5%)[be]	6 (5.6%)[cf]	14 (28%)[abc]	7 (26.9%)[def]	< 0.001
Agents grouping	**n: 1,223**	**n: 377 (30.8%)**	**n: 560 (45.8%)**	**n: 131 (10.7%)**	**n: 104 (8.5%)**	**n: 51 (4.2%)**	
Gram negative	947 (77.4%)	361 (95.7%)[abe]	363 (64.8%)[ac]	96 (73.2%)[bd]	93 (89.4%)[cdf]	34 (66.6%)[ef]	< 0.001
Acinetobacter baumannii	254 (20.7%)	145 (38.5%)	45 (8%)	28 (21.4%)	30 (28.9%)	6 (11.8%)	
Psedomonas aeruginosa	193 (15.7%)	79 (20.1%)	60 (10.7%)	19 (14.5%)	21 (20.2%)	5 (9.8%)	
Klebsiella pneumoniae	234 (19.1%)	72 (19.1%)	113 (20.2%)	23 (17.5%)	20 (19.2%)	6 (11.8%)	
Escherichia coli	118 (9.6%)	11 (3.0%)	85 (15.2%)	6 (4.6%)	4 (3.8%)	12 (23.5%)	
Proteus mirabilis	79 (6.4%)	19 (5.1%)	40 (7.1%)	7 (5.3%)	10 (9.6%)	3 (5.9%)	
Serratia marcescens	31 (2.5%)	16 (4.3%)	5 (0.9%)	6 (4.6%)	4 (3.8%)	0 (%)	
Other	45 (3.5%)	19 (5.2%)	15 (2.7%)	7 (5.3%)	4 (3.8%)	2 (3.9%)	
Gram positive	133 (10.9%)	14 (3.7%)[abd]	71 (12.7%)[a]	26 (19.8%)[bc]	11 (10.6%)[ce]	11 (21.6%)de	< 0.001
Fungal	143 (11.7%)	2 (0.5%)[ac]	126 (22.5%)[abd]	9 (6.9%)[b]	0 (%)	6 (11.8%)cd	< 0.001

[a,b,c,d,e,f]Values within the group with the statistical difference are indicated by the same, Other: Enterobacter, Providencia etc.

Sepsis incidence of 36.5% in our ICU was compatible with the mean values of 30-40% stated in the literature data (7). A meta-analysis involving a 20-year data has reported a 28-day mortality rate of 33.2% for severe sepsis and septic shock (8). In a study comprised of 198 ICU's in 24 European countries, a ICU mortality rate of 27% was reported in sepsis patients whereas the patients without sepsis had a mortality rate of 14% (7). Several studies have shown that mortality rate in the hospital is associated with anatomic localization of the focus in sepsis (9,10). It has been suggested in also our study that mortality rate increased as number of septic foci increased. In another study, total hospital mortality rate was 22.6% whereas this rate raised to 40% for sepsis due to multiple sources and unknown cause. Mortality rate was approximately 30% in sepsis induced by a focus in the respiratory system or intravascular device (15%, 7% and 0% by foci in the abdomen, genitourinary system and skin/soft tissue, respectively) (2). Another study has sorted 7974 patients into 20 anatomic groups with septic shock based on clinical diagnosis or foci of the isolated pathogens. General hospital mortality rate was 52% while mortality rate ranged between 21% to 85% depending on infectious focus. Highest mortality rate was found in the ischemic intestinal disorders while the lowest mortality rate was encountered in the urinary tract infections associated with obstructive uropathy. Mortality rate was 54% in patients with a respiratory infectious focus (10). However, in our study, both total mortality rate and also specific mortality rate during the septic periods were higher in patients with respiratory system infections. Urinary system infections were more commonly diagnosed in females and showed lower mortality rates. It is noticeable that this patient group presented with lower rates of Gram negative infection and higher rates of fungal infections and that single focal infections showed higher incidence in this group. Some studies have analyzed the role of anatomic foci with respect to the results of severe sepsis and reported that urosepsis has a better prognosis; however abdominal foci indicate a worse prognosis (11,12). Whereas, both abdominal and urinary tract infections demonstrated lower mortality rates than pneumonia in our study.

PCT is an important acceptable biomarker during severe bacterial infections and sepsis (13). PCT can be used in not only diagnosis of infection but also in predicting severity of the underlying disease, treatment response and results (14,15). It has been stated in the literature that use of PCT for these purposes is more specific than CRP (16). PCT has a higher sensitivity and specificity than CRP especially during bacterial infections (17). A meta-analysis has demonstrated that PCT was superior to CRP in the differential diagnosis of systemic inflammatory response syndrome (SIRS) and sepsis (18). It is usually recommended that these biomarkers should be supported with other markers such as leukocyte count and interleukin-6 levels. Leukocyte count which is commonly used may have important limitations, especially in immunocompromised patients (16). Higher levels of both PCT and white blood cells were encountered in the multifocal infections in our study. Significantly higher levels of PCT were encountered in the bloodstream-catheter and abdominal infections. The reduction in the levels of white blood cells was not significant. PCT values should be analyzed more comprehensively depending on various infectious, host and pathogen sites (19). CRP, being a conventional non-specific biomarker, is commonly used for sepsis in clinical routine (19). It has been reported that CRP level is not a useful biomarker in sepsis since CRP levels may increase due to non-septic reasons and also show occasionally moderate level elevations (20). Contrarily, CRP levels increased more significantly as number of the infectious foci increased. CRP levels during infections involving the soft tissues and urinary system were found to be lower than the infections involving blood-stream and abdomen. Coagulation parameters, D-dimer, lactate level and thrombocyte count are the other routine laboratory tests which may be used in diagnosis of sepsis (20). Lactate which is an indicator of impaired oxidative metabolism and tissue perfusion anomalies in the clinical picture of sepsis and septic shock demonstrated significantly high levels in the multifocal sepsis in our study. Platelet levels significantly decreased in patients with microbial growth in the blood cultures.

Other important prominent issues of our study were length of ICU stay, need for mechanical ventilation and clinical picture of acute renal failure. The length of ICU stay was longer in sepsis. The length of this period varied depending on the infectious focus. Sepsis patients with multifocal infections have been reported to show 2 to 5-fold increased length of ICU stay (2). In our study, increased length of ICU stay was detected in the double or multifocal infections. However, anatomic localization of the foci had no impact on length of ICU stay. Additionally, increased numbers of infectious foci and localization in the respiratory tract were associated with increased need for mechanical ventilation support. The development of acute kidney injury is another important issue in sepsis. Higher cut-off values of serum PCT levels are recommended in the patients with impaired renal function (17,21). Serum PCT levels may increase regardless of presence of bacterial infection in renal failure which is accepted as a proinflammatory condition (22). In our study, incidence of acute renal failure increased only in the sepsis patients with abdominal foci. The studies conducted until today have not adequately investigated the impact of the infectious foci on organ dysfunction. A study has shown that number of organs involved during multiple organ failure (≥ 2 organs) was 50-60% in the sepsis patients with pulmonary focus, unknown etiology and multifocal infection (2). However, sequential organ failure assessment (SOFA) score as an important component of Sepsis-3 Definition was not found to be correlated with localization and number of the infectious foci in our study.

Different microorganisms stimulate release of PCT to various levels by various pathways and via release of different cytokines (5,23). Some studies have suggested that, severity of the clinical condition may be differentiated using PCT and additionally it may be helpful in predicting type of the microbial agent (16). It has been considered according to the results of a study, that high levels of PCT encountered in the polymicrobial bloodstream infections may commonly be associated with Gram negative bacteria (15). Also in our study, different levels of PCT were detected in the distinct infectious foci. Underlying reason of this situation may be growth of the distinct microorganisms in different foci. We have determined in our study that these infections events involved multifocal agents depending on the foci. It is stated in the literature that Gram negatives induce higher PCT levels. (24,25). In our study, it was found that gram negative growth rates were lower in abdominal and blood infections where PCT levels were higher. A study has

reported higher levels of PCT in the patients with abdominal or urinary tract infection than the patients with pneumonia (5). This result was compatible with higher levels of PCT in the abdominal infections in our study; whereas it was inconsistent with PCT levels in the urinary tract infections. As depicted in Table 3, lower PCT levels were found in urinary tract infections compared to bloodstream an abdominal infections and, this finding may due to higher rates of fungal infection in this localization in our study. High level of PCT in the postoperative complicated abdominal infections is associated with mortality (26). Strong evidence on utilization of PCT levels to track treatment response during abdominal sepsis, the second most common source of infection during sepsis after the respiratory system, is rare. On the other hand, it has been reported that PCT may be helpful to evaluate antibiotic response in patients with pulmonary infections, resulting in decreased treatment durations (27).

Higher levels of PCT were encountered during abdominal infections than the pulmonary infections in our study. PCT should not be used for diagnosis of infection alone, since local bacterial infections or bacterial colonizations do not usually induce PCT (20). In also our study, PCT levels were lower in the patients with soft tissue infection.

Although some studies have reported that PCT levels do not vary in presence of Gram negative and Gram positive agents, a larger number of studies have suggested that PCT levels increased more significantly in Gram negative infections (14). Inflammatory cascades are complicated processes in sepsis while Gram positive, Gram negative and fungal agents which play important roles in these processes may activate these cascades in distinct ways (16). Some bacterial antigens (Lipopeptides, peptidoglycan, flagellin and bacterial DNA etc.) are present in both Gram positive and Gram negative bacteria. Besides, some agents such as LPS and lipoteichoic acid are specific for Gram-negative and Gram-positive bacteria, respectively (28). The previous researches had suggested that once the inflammation cascade was triggered, the response progressed independently from the triggering infectious agent. This belief has led scientists to focus on the immunological component of sepsis, resulting in trial of many immunomodulatory agents with no benefit (2,29). According to the results of a study; PCT levels induced by *Escherichia coli* were higher than *Acinetobacter baumanni* or *Burkholderia cepacia* whereas PCT levels induced by *Klebsiella pneumoniae* were higher than *Acinetobacter baumanni*. According to the same study, PCT levels for *Staphylococcus epidermidis, Staphylococcus aureus and Enterococcus faecium* from Gram positive bacteria were higher than those for *Staphylococcus hominis or Staphylococcus haemolyticus*. PCT levels in the infections caused by *Enterococcus faecium* were higher than *Enterococcus faecalis* (5). So it may not be appropriate to use PCT to differentiate between gram negative and gram positive bacterial infections. In another study, the members of *Enterobacteriaceae* such as *Escherichia coli and Klebsiella pneumoniae* caused production of higher level of IL-6. It is known that this cytokine, IL-6 induce PCT (28). A study which analyzed bloodstream infections showed that *Acinetobacter baumannii* was the most commonly encountered Gram negative agent by 23.6%. Incidence of *Staphylococcus aureus* and *Methicillin resistant staphylococcus aureus* were 9.1% and 20%, respectively (30). The most commonly determined agents were *Acinetobacter baumannii* (20.7%) and *Klebsiella pneumoniae* (19.1%) in our study. In our test cultures, highest rate of Gram negative growth (95.7%) was detected in the pulmonary system while highest rate of Gram positive growth (21.6%) and fungal infection (22.5%) were determined in the abdomen and urinary system, respectively. The importance of microbial load and is triggering the inflammatory cascade has important role on the levels of PCT. (2,10). More comprehensive studies would contribute to the adequate clarification of this issue.

Conclusion

Serum PCT levels vary depending on anatomic localizations and it is and additional biomarker in clinical and microbiological diagnosis of sepsis. Higher procalcitonin levels are related to presence of multiple foci of infection and, as well, to higher mortality rates. Clarification of the role of anatomic septic focus may be crucial in predicting mortality rate of sepsis and determination of prognosis.

AUTHOR CONTRIBUTIONS:

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