Procalcitonin, c-reactive protein, leukocyte, mean platelet volume levels in bloodstream infections

Sepsis

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Abstract

Aim: Levels of Serum Procalcitonin (PCT), C-Reactive Protein (CRP), Leukocyte (WBC) and Mean Platelet Volume (MPV) were evaluated in sepsis patients. We evaluated the diagnostic accuracy of different inflammatory markers to discriminate sepsis caused by different pathogens. Material and Method: In this study we included 126 episodes of bacteremia from 126 patients with sepsis. Medical records of patients who had bacteremia caused by Gram-negative bacteria (GN), Gram-positive bacteria (GP) or yeast were reviewed, and information about PCT and other inflammatory markers was recorded. Mann-Whitney U test and Spearman's correlation analysis were used for statistical analysis. Results: 60.4% of the cases (n=76) were GN, 31.7% (n=40) were GP and 7.9% (n=10) were yeast. There was a statistically significant difference between PCT, CRP, and MPV levels according to the microorganism ($p=0.001$, $p<0.01$). There was no statistically significant difference between WBC measurements according to the microorganism ($p>0.05$). Discussion: According to the microorganism, gram positivity cutoff points were determined for PCT as (≤12.17), CRP as (≤9.70) and MPV as (≤9.32). In bilateral comparisons, there was a significant increase in GN and yeast sepsis, while a significantly low level was found in GP sepsis. There was no significant difference between GN and yeast. When the measurements of PCT according to bacterial species are examined, the highest measurement was 44.6 ng/ml with Escherichia coli bacteria, followed by Candida bacteria with 12.6 ng/ml.

Keywords

Microorganisms; Procalcitonin; C-Reactive Protein; Leukocyte; Mean Platelet Volume

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Introduction

Sepsis is defined as a systemic inflammatory response to confirmed or suspected infection. Sepsis is the major cause of morbidity and mortality in intensive care units. Epidemiological data indicate that mortality is higher than 25–30% in patients with sepsis [1]. Twenty-six million people are affected worldwide each year. The annual rate of increase in sepsis cases is reported to be 8-13% [2]. Delayed inadequate antimicrobial therapy and diagnosis are associated with mortality. Choosing antimicrobial therapy according to the causative pathogen of sepsis can significantly improve the prognosis of sepsis [3]. Microbiological examinations represent the current gold standard to identify pathogens. Hence, identifying the pathogen is critical for the successful antimicrobial treatment of sepsis.

Procalcitonin (PCT) and C-reactive protein (CRP) are well-known predictors of sepsis. Serum PCT levels are associated with blood culture positivity in patients with sepsis, but the magnitude of elevation of PCT and CRP levels at the onset of sepsis is unknown in Gram-negative (GN) bacteremia and Gram-positive (GP) bacteremia. PCT is synthesized and released by C-cells from within the thyroid gland, and it is a protein precursor of calcitonin. PCT appears to have higher specificity and sensitivity for predicting bacterial infection than other markers [4,5]. Serum PCT levels differ in patients and are significantly elevated with GN bacteremia [6,7]. CRP, a kind of acute phase reactive protein synthesized by the liver, can regulate inflammatory reaction and defense mechanisms against infectious diseases [8]. Leukocyte (WBC) and Mean Platelet Volume (MPV) give information about the activity of the bone marrow in sepsis. We evaluated the diagnostic accuracy of different inflammatory markers (PCT, CRP, WBC, and MPV) to discriminate sepsis caused by different pathogens.

Material and Method

The blood samples were taken at various clinics. For each blood sample, an aliquot of 5-10 ml whole blood was inoculated into Bactec aerobic and anaerobic bottles that were incubated in a BacT/ALERT 3D automated blood culture system. Aliquots were removed from positive cultures for Gram staining, and they were streaked on solid medium for subsequent analysis. Microorganisms were identified by conventional methods and matrix-assisted laser desorption ionization time of flight mass spectrometry (Vitek MS, bioMérieux, Marcy l'Etoile, France). Microorganisms detected in two or more blood cultures and reported by the clinician as the cause of the sepsis episode were evaluated microbiologically. We included 126 episodes of bacteremia from 126 patients with sepsis in this study. Medical records of patients who had bacteremia caused by GN bacteria, GP bacteria or fungi were reviewed, and information about PCT, CRP, WBC levels and other inflammatory markers was recorded. Serum PCT levels were measured using an automatic analyzer (ARCHITECT ci4100, Abbott, USA) according to the manufacturer's instructions. The lower detection limit of the assay was <0.174 ng/ml. Values were assessed as follows:

<0.174 ng/ml as negative,

0.174-0.5 ng/ml as low risk (possible bacterial or viral infection, partial risk of sepsis and systemic infection),

0.5-2 ng/mL as high risk (leading to severe systemic infection), >10 ng/mL as sepsis and septic shock.

Serum CRP levels were measured using an automatic analyzer (ARCHITECT ci4100, Abbott, USA) according to the manufacturer's instructions. CRP (0-0.5mg/dl), WBC levels and MPV levels were measured using a (Cell-Dyn 3700, Abbott, USA) analyzer. WBC (3.7-9.7 K/ul), MPV (6.1-8.9 fl)

Statistical Analysis

The NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program was used for statistical analysis. Descriptive statistical methods (Mean, Standard Deviation, Median, Frequency, Odds, Minimum, Maximum) were used when study data were evaluated. Kruskal Wallis test was used in the comparison of three groups with no normal distribution. Pearson Chi-square test and Fisher-Freeman-Halton test were used for comparison of qualitative data. Significance was evaluated at $p<0.05$.

Results

The study was carried out between 2016-2017 at the xxx clinic of xxx Training and Research Hospital with 126 participants of whom 40.5% (n=51) were women, and 59.5% (n = 75) were men. The ages of the cases ranged from 0 to 93 years, with an average of 54.92±28.30 years. There was no statistically significant difference between age and sex distributions according to the microorganism ($p>0.05$). Among the 126 bacteremia episodes, 76 (60.4%) were caused by GN bacterial species, 40 (31.7%) by GP bacterial species and 10 (7.9%) by yeasts.

The bacterial species encountered were Klebsiella pneumoniae (n=26), Pseudomonas aeruginosa (n=19), Staphylococcus aureus (n=10), Enterococcus spp. (n=14), Escherichia coli (n=14), coagulase negative staphylococcus (n=10), Acinetobacter baumannii (n=4), Enterobacter aerogenes (n=3), Streptococcus pneumoniae (n=2), Streptococcus pyogenes (n=1), Streptococcus agalactiae (n=3), Salmonella spp. (n=1), Brucella melitensis (n=1), Serratia marcescens (n=4), Candida albicans (n=6), Candida tropicalis (n=2), and Candida parapsilosis (n=3).

Measurements of PCT ranged from 0.1 to 100 ng/dL with an average of 21.31 ± 27.39 ng/dL. According to the measurements of PCT, 15.1% (n=19) were in the low-risk group, 20.6% (n=26) were in the moderate-risk group, 21.4% (n=27) were in the high-risk group and 42.9% (n=54) were in the sepsis group. CRP ranged from 0 to 35.9 mg/dl with an average of 14.75±8.52 mg/dl. WBC measurements ranged from 0.2 to 68.6 K/ul with a mean of 13.8±9.47 K/ul and MPV ranged from 5.5 to 18.5 fl, with a mean of 8.48±2.29.

There was a statistically significant difference between PCT levels according to the microorganism ($p=0.001$, $p<0.01$). We performed binary comparisons to identify the group that caused the significant difference. The PCT low-risk ratio was significantly higher in the GP cases than in the GN and yeast groups ($p=0.002$, $p<0.01$). PCT in the sepsis group was found to be significantly lower than GP and yeast groups in GP cases ($p=0.001$, $p<0.01$). Medium-risk and high-risk rates did not differ by microorganism ($p>0.05$). There was a statistically significant difference between CRP measurements according to the microorganism ($p=0.001$, $p <0.01$). Measurements of GP cases were found significantly lower ($p<0.01$) than in the GN ($p=0.001$)

and yeast groups (p=0.001). There was no statistically significant difference in CRP measurements between GN and yeast groups (p>0.05). There was no statistically significant difference between WBC measurements according to the microorganism (p>0.05). There was a statistically significant difference between MPV measurements according to the microorganism (p=0.001, p<0.01). MPV values of GP cases were found to be significantly (p<0.05) lower than in the GN (p=0.001) and yeast (p=0.015) groups. There was no statistically significant difference between MPV measurements of GN and yeast groups (p>0.05) Table 1.

When the measurements of PVT according to bacterial species were examined, the highest measurement was 44.6 ng/ml with Escherichia coli bacteria, followed by Candida bacteria with 12.6 ng/ml (Figure 1).

In the GP case group, the cutoff point for PCT was determined as 12.17 and below. For PCT the cutoff value was 12.17; sensitivity was 82.50%; specificity was 51.32%; positive predictive value was 47.14; and negative predictive value was 84.78 Table 2. In the obtained ROC curve, the underlying area was determined as 67.1%, and the standard error was 5.1% (Figure 2). The cutoff point for CRP in the GP case group was determined as 9.70 and below. For CRP the cutoff value was 9.70; sensitivity was 60%; specificity was 78.95%; the positive predictive value was 60; and the negative predictive value was 78.95. In the obtained ROC curve, the underlying area was 71.4% and the standard error was 5.5% (Figure 3). The cutoff point for MPV in the GP case group was determined as 9.32 and below. For MPV the cutoff value was 9.32; sensitivity was 97.37%; specificity was 41.67%; the positive predictive value was 46.84; and the negative predictive value was 96.77. In the obtained ROC curve, the underlying area was 71.1%,and the standard error was 4.9% (Figure 4). The proportion of those with PCT measurements

Table 2. Cutoff Detection and ROC Curve Results for PCT, CRP and MPV According to Microorganism (GP, GN)

	Diagnostic Scan					ROC curve		
	Cut off	Sensitivity	Spesifisity	Positive Predictive Value	Negative Predictive Value	Area	95% Confidence Interval	P volue
PRC	≤12.17	82.50	51.32	47.14	84.78	0.671	0.571-0.771	0.001**
CRP	≤9.70	60.00	78.95	60.00	78.95	0.714	0.607-0.821	0.001**
MPV	≤9.32	97.37	41.67	46.84	96.77	0.711	0.615-0.806	0.001**

Table 1. PCT, CRP, WBC, MPV values according to microorganism groups

		GN (n=76)	GP (n=40)	Yeast (n=10)	P volue
PCT (ng/ml)	Low risk	7 (9.2)	12 (30.0)	0 (0)	[b]0.002**
	Moderate risk	18 (23.7)	8 (20.0)	0 (0)	[b]0.263
	High risk	12 (15.8)	12 (30.0)	3 (30.0)	[b]0.150
	Sepsis	39 (51.3)	8 (20.0)	7 (70.0)	[b]0.001**
	Min-Max (Median)	0.2-100 (14.2)	0.1-55.9 (2)	3.3-55.9 (12.5)	
	Mean±Std	27.21±30.67	9.75±16.89	22.74±21.38	
CRP (mg/dl)	Min-Max (Median)	0-34.1 (15.2)	0.4-35.9 (9.2)	10.7-32 (20.4)	[a]0.001**
	Mean±Std	16.12±7.42	10.51±9.06	21.24±7.08	
WBC (K/ul)	Min-Max (Median)	0.2-68.6 (11.7)	5.6-53.5 (11,1)	1.2-22.7 (15)	[a]0.483
	Mean±Std	14.06±10.38	13.35±8.51	13.65±5.70	
MPV (fl)	Min-Max (Median)	5.5-18.5 (8.5)	5.5-10.9 (7)	6.9-12.4 (9.5)	[a]0.001**
	Mean±Std	9.00±2.55	7.31±1.19	9.38±1.85	

[a]Kruskal Wallis Test [b]Fisher Freeman Halton Test **p<0.01

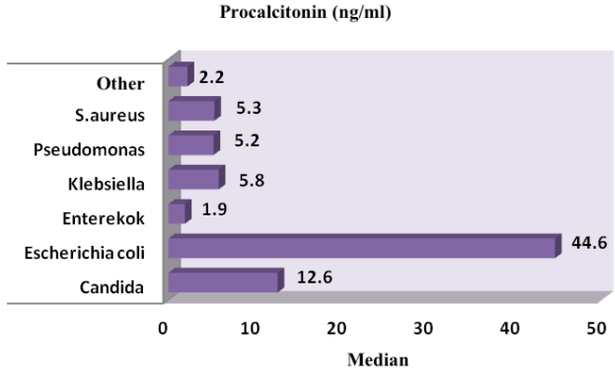

Figure 1. Distributions of procalcitonin measurements according to Bacterial species

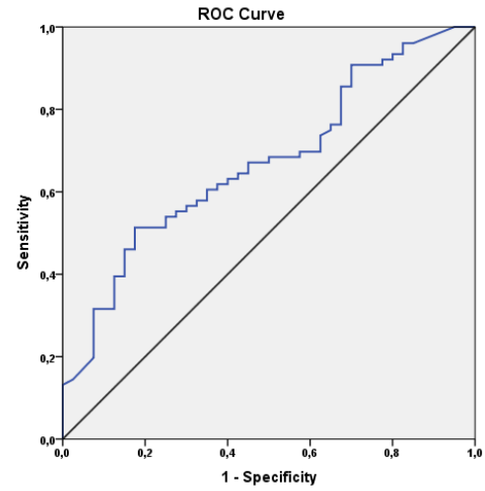

Figure 2. ROC curve for procalcitonin level according to GP case group

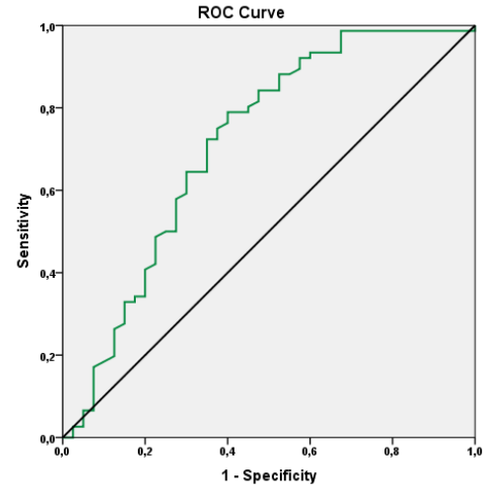

Figure 3. ROC curve for CRP level according to GP case group

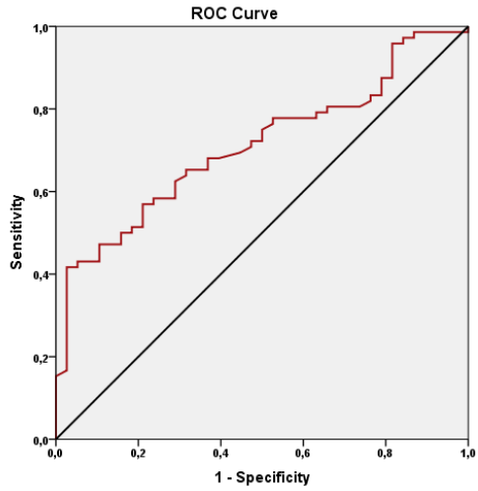

Figure 4. ROC curve for MPV level according to GP case group

of 12.17 and below was found to be statistically significantly higher in the GP case group than in the GN group (p=0.001; p<0.01). The proportion of those with a CRP score of 9.70 or less in the GP group was found to be statistically significantly higher than in the GN group (p=0.001, p<0.01). The proportion of those with an MPV score of 9.32 and below was found to be statistically significantly higher in the GP group than in the GN group (p=0.001, p<0.01) Table 3.

Table 3. Microorganism (GP, GN) PCT, CRP and MPV Evaluation

		GN(n=76)	GP(n=40)	cp
PCT (ng/ml)	≤12.17	37 (48.7)	33 (82.5)	0.001**
	>12.17	39 (51.3)	7 (17.5)	
CRP (mg/dl)	≤9.70	16 (21.1)	24 (60.0)	0.001**
	>9.70	60 (78.9)	16 (40.0)	
MPV (fl)	≤9.32	42 (58.3)	37 (97.4)	0.001**
	>9.32	30 (41.7)	1 (2.6)	

cPearson Chi-Square Test **p<0.01

Discussion

Empirical antimicrobial therapy is crucial for the prognosis of patients with sepsis, and inadequate or inappropriate antimicrobial therapy reduces the probability of survival [1]. Therefore, surrogate biomarkers are needed to make the appropriate choice more rapidly. In other studies, some authors have previously shown that in a population with proven sepsis, PCT was significantly higher in patients with bacteremia than in those without proven sepsis [9-11]. PCT levels have been shown to distinguish between bacteremia and noninfectious inflammatory states quickly and accurately in critically ill patients [5]. The mechanism underlying different PCT levels in response to GP and GN bacteria remains confusing. Differences in the membrane composition of GN and GP bacteria might partly explain this. The major membrane component of GN bacteria is lipopolysaccharide (LPS) layer (the major component of endotoxin) and that of GP bacteria is peptidoglycan layer (PGN). The PCT elevation could be, at least in part, related to the characteristics of the pathogen in the systemic bacterial infection. It has been shown in vitro that PCT value was significantly higher in the supernatants of cultured human cells stimulated with LPS than in those stimulated with muramyl dipeptide, a component of the outer membrane of the GP bacteria [12]. In a study, the positive value of PCT in the bacterial infection rate was much higher than that of CRP and WBC, and the difference had a statistical significance (p<0.05). It indicated that PCT was more sensitive than CRP and WBC in the early stage of bacterial infection, which was consistent with the findings of She et al. [13]. Compared to other biomarkers, PCT as a novel inflammatory biomarker has a high value in identifying bacterial infection, and it is an ideal biomarker for distinguishing bacterial and nonbacterial infection [14]. According to several studies, low concentrations of PCT in critically ill patients might suggest fungal infection. Thus, PCT levels could be used specifically and sensitively to distinguish GN sepsis from fungal sepsis [15,16,17]. The diagnostic accuracy of PCT for this differentiation was determined by ROC analysis, revealing an optimal cutoff value of 3.11 ng/mL, resulting in 93.3% specificity and 63.9% sensitivity [16]. In a similar study, Leli et al. [18] found that an optimal PCT cutoff value of 1.6 ng/mL could be used to distinguish GN infections from fungal infections with 96% specificity and 77% sensitivity. Martini et al. [19] also demonstrated that an optimal PCT cutoff value of 2 ng/mL could be used to distinguish Candida sepsis from bacterial sepsis with 92% sensitivity and 93% specificity. The studies cannot explain whether the severity of sepsis would influence the diagnostic accuracy of PCT in discriminating between different causative pathogens or not. Further research is warranted. Furthermore, patients treated with broad-spectrum antibiotics and invasive surgeries have a greater risk of developing fungal infections, and therefore such patients with elevated PCT levels should be screened for fungal infections [19]. PCT levels have been shown to be able to distinguish GN bacterial sepsis from GP bacterial and fungal sepsis [15,16,20]. Charles et al. reported that an optimal PCT cutoff value of 16 ng/mL resulted in 75.0% sensitivity and 82.2% specificity in distinguishing GN sepsis from GP sepsis. Further studies are warranted to elucidate the underlying mechanisms of the significant increase in PCT concentrations in patients with E. coli or K. pneumoniae sepsis [5].

In our study, while PCT levels were found to be low in GP sepsis, they were determined to be high in GN sepsis and yeast sepsis (Table 2).

Performing tests for detecting the acute phase reactants, particularly CRP, can aid in the differential diagnosis. CRP levels in viral infections usually rise slightly. CRP level is usually significantly higher in bacterial infections. A very high CRP level (greater than 100 mg/L) is more likely to occur in bacterial infection than in viral infection. If CRP level is >100 mg/L in adults, the probability of the bacterial infection is 80-85% [21]. This level was reported to be 40 mg/L for children [22]. This feature is helpful in differential diagnosis of viral and bacterial lower and upper respiratory tract infections [23,24]. However, it should also be kept in mind that markedly increased CRP level can be found in viral infections.

Since markedly increased CRP level can be found in Crohn's disease, it helps to distinguish Crohn's disease from ulcerative colitis [25]. Although CRP levels can be used to accurately distinguish causative pathogens, confounding factors limit the

broader application of this marker. Serum CRP concentrations were found to be influenced by myocardial diseases [26] and autoinflammatory diseases [27]. In one study, serum PCT levels were higher in GN sepsis than GP sepsis in 72 h. There were no differences in CRP levels. The separation of PCT and CRP phenomenon is helpful for early diagnosis of GP sepsis [28]. These confounding factors were not excluded in this study. Hence, CRP levels were considered inferior to PCT levels in distinguishing causative pathogens of sepsis [28].

In our study, CRP levels were significantly higher in GN and fungal sepsis, but they were low in GP sepsis (Table 2). WBC values are not distinguishing in GN, GP and fungal sepsis. It has been determined that MPV is not determinative of sepsis and SIRS discrimination [29]. While there was a significant correlation between PCT, CRP, and MPV, there was no correlation with WBC. Correlations with PCT, CRP, and MPV were observed in our study.

In conclusion, PCT can be used to distinguish between viral, inflammatory, and bacterial, as well as to induce empirical therapy in GP and GN sepsis. However, there is a need for more large-scale studies of the role of PCT in identifying yeast sepsis.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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