ORIGINAL ARTICLE

Comparison of serum procalcitonin level with erythrocytes sedimentation rate, C-reactive protein, white blood cell count, and blood culture in the diagnosis of bacterial infections in patients hospitalized in Motahhari hospital of Urmia (2016)

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ABSTRACT

Blood infection is one of the causes of morbidity in hospitalized patients. While some scholars have identified procalcitonin (PCT) as a potential biomarker for the diagnosis of blood infection, others have questioned its diagnostic value. Thus, the present study was conducted to compare the diagnostic values of PCT with C-reactive protein (CRP), erythrocytes sedimentation rate (ESR), white blood cell (WBC) count, and blood culture in patients with bacterial blood infections. In a prospective case–control study, 45 septic patients (6 months–5 years old), who were hospitalized in Shahid Motahhari Hospital of Urmia over the year 2016 and 45 patients with noninfectious diseases, whose gender and age range were similar to the members of the septic group, were examined. The participants' blood samples were taken for the sake of blood culture and measurement of PCT level, ESR, and CRP. Finally, the collected data were analyzed through the SPSS-21 software. the results indicated that the average PCT, ESR, CRP, and WBC count was significantly higher in septic patients. Moreover, the blood culture of patients with negative or intermediate serum PCT levels was negative, while 50% of blood culture results in patients with positive PCT were positive and the rest were negative. Finally, a significant relationship was detected between the frequency of blood culture results and results of serum PCT tests ($P = 0.003$). serum PCT level can be considered a diagnostic marker of bacterial infections. If used in conjunction with tests of CRP, ESR, and WBC count, the PCT test can enhance the diagnosis of bacterial infections.

Key words: Blood culture, C-reactive protein, erythrocytes sedimentation rate, procalcitonin, sepsis, white blood cell count

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INTRODUCTION

Sepsis is the body's systematic response to infection. As one of the major public health problems in the world,

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sepsis causes hospitalization, or even death, of millions of people each year.[1] Although the mortality rate of sepsis has declined over the past two decades due to various medical advances, it is still high, especially in less developed countries, where blood infections are not detected at the right time.[2,3] To reduce the rate of mortality in patients with sepsis, early diagnosis and immediate interventions, such as appropriate antibiotic therapy and targeted rehabilitation are essential.[4] A large number of suspected cases of blood infection such as bacterial and viral infections, inactive disorders, trauma, and postoperative cares can have common symptoms with systematic inflammatory response syndrome. Therefore, it is difficult to diagnose patients with infection symptoms with sepsis; imaging laboratories are required to work correctly for this diagnosis.[5,6] Blood culture is used to diagnose the pathogen causing sepsis and facilitate the selection of antibiotics; nonetheless, the determination and isolation of organism through blood culture requires several days, and therefore, is not appropriate for the diagnosis of sepsis. Furthermore, microbiological culture is not sensitive and specific enough for the diagnosis of sepsis.[7] The typical laboratory tests for sepsis diagnosis include determining erythrocytes sedimentation rate (ESR), C-reactive protein (CRP), and white blood cell (WBC) count or the percentage of neutrophils, and performing polymerase chain reaction (PCR), which are slow and not sensitive and specific enough.[3] In fact, except for the Procalcitonin (PCT), other tests cannot confirm the existence of blood infection if used alone.[5,7,8] In severe sepsis, WBC count may reduce, and CRP may remain low; hence, the availability of a more sensitive and specific biomarker can be helpful in the diagnosis of sepsis.[9] As biomarkers of sepsis, interleukins, pro-adrenomedullin, atrial natriuretic peptide (ANP), copeptin, provasopressin, interferon gamma, resistin, and plasma renin concentration (PRC) have been examined in recent years.[5,8,10-12] PCT is the peptide precursor of calcitonin secreted from peripheral monocytes and hepatocytes or parafollicular cells (C cells) from the thyroid; PCT is the most prominent biomarker for the diagnosis of bacterial infections, such as sepsis.[13,14] Various studies have reported a low serum PCT level in healthy people and an elevated serum PCT level in patients with bacterial infections.[15-17] Some studies have shown that PCT level can be used for the diagnosis of sepsis and the assessment of its severity.[18,19] In a study, Demirdal *et al*. found a relationship between high PCT level and the severity of sepsis. They concluded that PCT level could be considered a valid indicator for the diagnosis of sepsis.[18] On the other hand, there are studies reporting inconsistent results and questioning the diagnostic and prognostic effectiveness of PCT in bacterial conditions.[20,21] Thus, further studies are needed to confirm the effectiveness of PCT in the diagnosis of blood infections.[5,17] Given the issues mentioned above and the existence of inconsistent results regarding the diagnostic accuracy of PCT in bacterial conditions, the significance of conducting more studies is apparent. This is especially important in the context of the West Azerbaijan Province in Iran, where no such studies have been conducted. Accordingly, the present study was conducted to compare the diagnostic value of PCT with that of ESR, CRP, WBC count, and blood culture in the diagnosis of bacterial infections in patients hospitalized in Shahid Motahhari Hospital of Urmia.

METHODOLOGY

In the present prospective case–control study, 45 septic patients, who were hospitalized in Shahid Motahhari Hospital of Urmia, (the experimental group) and 45 patients with noninfectious diseases, whose gender and age range were similar to the members of the experimental group, were included (the control group). Patients who had used antibiotics 24 h before the experiment, those with cancer who were undergoing chemotherapy, and those with immunodeficiency or chronic diseases (chronic renal failure, diabetes, and so forth) were excluded from the study. The demographic characteristics of every participant were recorded. Then, the participants' blood samples were taken for the sake of blood culture and measurement of PCT level, ESR, and CRP. The participants' levels of PCT were measured by the immunoluminescence method and using PCR diagnostic kits (Brahms Diagnostica Hennigsdorf bei Berlin, made in Germany). Finally, the collected data were analyzed using the IBM SPSS Statistics for Windows, Version 21.0 software(IBM Corp., Armonk, NY: USA).

RESULTS

In the present prospective case–control study, 45 septic patients, who were hospitalized in Shahid Motahhari Hospital of Urmia, were entered the study as the experimental group, and 45 patients with noninfectious diseases, whose gender and age range were similar to the members of the experimental group, were included in the study as the control group. Of patients in the experimental group, 25 (55.6%) were male and 20 (44.4%) were female; of patients in the control group, 23 (51.1%) were male and 22 (48.9%) were female. No significant gender-based difference was observed between the two groups ($P = 0.67$). The age range of most patients in the experimental group was 6–18 months, and the age range of most patients in the control group was 19–36 months. No significant age-based difference was observed between the two groups ($P = 0.54$). The means and standard deviation (SDs) of serum WBC count in the experimental and control groups were respectively 17697.77 ± 3651.02 and 7741.33 ± 1988.31 µl. The results showed that serum WBC count was significantly higher in the experimental group ($P < 0.001$) [Table 1]. The means and SDs of serum ESR in the experimental and control groups were respectively 75.28 ± 20.13 and 11.60 ± 5.53 mm/h. Based on the results, serum ESR was significantly higher in the experimental group ($P < 0.001$) [Table 1]. The means and SDs of serum CRP in the experimental and control

Table 1: Comparisons of white blood cell count, erythrocytes sedimentation rate, C-reactive protein, procalcitonin in the two groups

Variable	Mean±SD		*P**
	Case	Control	
WBC (μl)	17,697.77±3651.02	7741.33±1988.31	<0.001
ESR (s)	75.28±20.13	11.60±5.53	<0.001
CRP (mg/l)	55.18±19.17	4.31±3.98	<0.001
PCT (ng/ml)	3.42±3.23	0.3±0.24	<0.001

**t*-test. CRP: C-reactive protein, ESR: Erythrocytes sedimentation rate, WBC: White blood cell, PCT: Procalcitonin, SD: Standard deviation

groups were respectively 55.18 ± 19.17 and 4.31 ± 3.98 mg/L. According to the results, serum CRP was significantly higher in the experimental group (P < 0.001) [Table 1]. The means and SDs of serum PCT in the experimental and control groups were respectively 3.42 ± 3.23 and 0.3 ± 0.24 ng/mL. Based on the results, serum PCT was significantly higher in the experimental group (P < 0.001) [Table 1].

The means and SDs of serum WBC count in the male and female participants in the control group were respectively 7568.69 ± 2067.64 and 7921.81 ± 1933.34 μl. Based on the results, serum WBC count was not significantly different between male and female participants in the control group (P = 0.55). The means and SDs of serum WBC count in the male and female participants in the experimental group were respectively 19068 ± 3021.44 and 15985 ± 3712.07 μl. Based on the results, serum WBC count was significantly higher in the male participants in the experimental group (P = 0.004). The means and SDs of serum ESR in the male and female participants in the control group were respectively 11.91 ± 5.74 and 11.27 ± 5.42 s. As the results indicated, the difference in serum ESR was not statistically significant between male and female participants in the control group (P = 0.70). The means and SDs of serum ESR in the male and female participants in the experimental group were respectively 82.20 ± 16.72 and 66.65 ± 21.06 s. As the results indicated, the difference in serum ESR was statistically higher in male participants in the experimental group (P = 0.008). The means and SDs of serum CRP in the male and female participants in the control group were respectively 3.77 ± 4.65 and 4.026 ± 4.04 mg/l. As the results indicated, the difference in serum CRP was not statistically different between male and female participants in the control group (P = 0.34). The means and SDs of serum CRP in the male and female participants in the experimental group were respectively 62.64 ± 16.87 and 45.85 ± 18.08 mg/l. As the results indicated, the serum CRP was statistically higher in the male participants in the experimental group (P = 0.002). The means and SDs of serum PCT in the male and female participants in the control group were respectively 0.23 ± 0.3 and 0.24 ± 0.31 ng/l. As the results indicated, the slight difference in serum PCT between male and female participants in the control group was not statistically significant (P = 0.77). The means and SDs of serum PCT in the male and female participants in the experimental group were respectively 3.51 ± 4.5 and 2.27 ± 2.07 ng/l. As the results indicated, the serum PCT was statistically higher in the male participants in the experimental group (P = 0.01). The average serum WBC count was higher in the age range of 19–36 months than in the age ranges of 6–18 months and 37–60 months. The observed difference in the average serum WBC count was statistically significant between the patients based on their age groups (P = 0.04). The average serum WBC count in the participants of the control group was approximately similar, and the slight difference was not statistically significant (P = 0.96). The average serum ESR was significantly higher in patients, whose age ranged between 19 and 36 months (P = 0.002). The average serum ESR was higher in patients, whose age ranged between 37 and 60 months, but the difference was not statistically significant (P = 0.66). The average serum CRP was significantly higher in patients, whose age ranged between 19 and 36 months (P = 0.01). The average serum CRP was higher in patients, whose age ranged between 19 and 36 months, but the difference was not statistically significant (P = 0.2). The average serum PCT was higher in patients, whose age ranged between 6 and 18 months, but the difference was not statistically significant (P = 0.05). The average serum PCT was higher in patients, whose age ranged between 6 and 18 months, but the difference was not statistically significant (P = 0.05). The percentages of cases with positive serum PCT in the experimental and control groups were respectively 48.9 (n = 22) and 0, indicating a significant difference between the two groups (P < 0.001). The frequency of patients with intermediate PCT level was higher in the experimental group than in the control group, but the frequency of negative PCT was higher in the control group. A significant gender-based difference was observed regarding the positivity of PCT test results in the experimental group, and most of the intermediate PCT levels were observed among female patients in the experimental group (P = 0.01). In the control group, the percentages of positive PCT results in male and female participants were respectively 17.4 (4 people) and 9.1 (2 people). No statistically significant gender-based difference was observed in the control group regarding the positivity of PCT test results (P = 0.11). The frequencies of serum PCT levels were not statistically different between male and female participants in the experimental group; however, intermediate serum PCT levels were mostly observed among male patients (P = 0.66). In patients with positive PCT test result, 50% had negative blood culture results, 27.3% had positive Gram-positive culture, and 22.7% had positive Gram-negative culture. The observed relationship between frequency distributions of blood culture and PCT results was significant (P = 0.003) [Table 2].

The average serum WBC count, ESR, and CRP were significantly different regarding blood culture results in the experimental group. The average serum WBC count was significantly lower in patients with negative blood culture results than in the other two groups ($P < 0.001$). The average serum WBC count was higher in patients with positive Gram-positive blood culture results [Table 3]. The average serum ESR was significantly lower in patients with negative blood culture results than in the other two groups [Table 3]. The average serum CRP was significantly lower in patients with negative blood culture results than in the other two groups ($P = 0.004$). The average serum CRP was higher in patients with positive Gram-positive blood culture results ($P < 0.001$) [Table 3].

DISCUSSION AND CONCLUSION

Early diagnosis and proper treatment of sepsis are the most important factors in reducing the rate of mortality.[22] Biomarkers have been used for the early diagnosis, primary treatment, and determination of the severity of sepsis. The sensitivity of biomarkers has considerably improved in recent years, but they still have weaknesses and require further examination.[23] The present study was conducted to compare the effectiveness of serum PCT with serum ESR, CRP, WBC count, and blood culture in the diagnosis of bacterial infection in patients hospitalized in infection control department of Motahhari Hospital of Urmia in 2016. According to the results, the average serum PCT, CRP, ESR, and WBC count was significantly higher in the experimental group than in the control group. The blood culture test results of six patients were positive Gram-positive (13.3%), of five patients were positive Gram-negative (11.1%), and the rest were negative. In patients with negative or intermediate serum PCT, the blood culture test results were negative. Half of the patients with positive serum PCT also had positive blood culture test results, and the rest had negative results. The observed relationship between frequency distributions of blood culture and PCT results was significant. Similar results were reported in another study done by Samraj *et al.*, who found that the average serum levels of their examined biomarkers were significantly higher in patients with positive blood culture test results.[24] In the present study, the relationships between PCT and age and PCT and gender were not statistically significant. As mentioned in the result section, the average serum PCT was significantly higher in the experimental group. Unfortunately, due to the low sensitivity and a high number of false-negative blood culture results, indices such as sensitivity, specificity, and positive/negative predictive values of the examined markers could not be evaluated in comparison with the blood culture test results, as the "gold standard" for the diagnosis of infection. Barati *et al*. reported the more significant role of PCT, compared to serum CRP, ESR, and WBC count, in the diagnosis of severe burn wound infections. They found that serum PCT was higher in septic patients than in nonseptic ones. They, however, found no significant difference in serum CRP, ESR, and WBC count between septic and nonseptic patients.[25] Barati *et al.* reported results are rather similar to the present study's finding concerning the more central role of PCT in the diagnosis of bacterial infections. In line with results of the present study, Nakajima *et al*. found that PCT level was significantly higher in septic patients compared to patients with pneumonia and healthy controls. They reported that the average WBC count and CRP level were not statically different between the three groups. Thus, they concluded that serum PCT was a potentially useful marker for the determination of the type of pathogen causing sepsis, which was higher than the rest of microorganisms in the group with Gram-negative culture.[9] In Lipińska-Gediga' *et al*. study on patients diagnosed with either severe sepsis or septic shock, although serum WBC count and CRP level were higher in patients with septic shock than in patients with severe sepsis, the difference was not statistically significant. This finding was also true when comparing deceased and surviving patients, but the difference was not still statistically significant. Hence, serum PCT changes were lower in surviving patients than in deceased ones, and the difference was statistically significant. However, the difference was not statistically significant during any time interval between patients surviving from severe sepsis and

Table 2: Frequencies of positive, intermediate, and negative procalcitonin results in the experimental group based on blood culture results

PCT and blood culture results	Negative	Intermediate	Positive	P
Negative	7 (100)	16 (100)	11 (50)	0.003*
Positive Gram-positive	0	0	6 (27.3)	
Positive Gram-negative	0	0	5 (22.7)	

*Fisher's exact test. PCT: Procalcitonin

Table 3: Comparison of average serum white blood cell count, erythrocytes sedimentation rate, and C-reactive protein based on blood culture results in the experimental group

Results of the examined variable culture	Mean±SD			P*
	Negative	Positive Gram-positive	Positive Gram-negative	
WBC	16,525±3321.49	21,725±1743.5	20,840±1858.22	<0.001
ESR	69.88±20.3	93.2±5.15	90.60±3.97	0.004
CRP	48.94±17.66	76.2±7.08	72.40±6.87	<0.001

*One-way ANOVA test. CRP: C-reactive protein, ESR: Erythrocytes sedimentation rate, WBC: White blood cell, SD: Standard deviation those surviving from septic shock. They also reported that serum PCT level had a diagnostic value from the 3rd day and its diagnostic value was higher in comparison with changes in clinical statuses of septic patients.[26] The mentioned study confirmed the diagnostic value of PCT; however, in the present study, serum PCT level was only examined once and for the initial diagnosis of bacterial infection. Faqi *et al*. also found that PCT is a better predictor of bacteremia than CRP and ESR (based on the indices of sensitivity and specificity); however, using PCT results in conjunction with results of CRP and ESR enhances its predictive value in the diagnosis of bacteremia and sepsis.[27] Serum CRP and ESR are widely used in the diagnosis of infections; nonetheless, some scholars have questioned their value due to the instability of their diagnostic power.[28] Those results are also consistent with the results of the present study. In this study, patients with negative or intermediate PCT levels had a negative blood culture result; 50% of patients with positive PCT had negative blood culture, and the rest had a positive blood culture. The observed relationship between frequency distributions of culture and PCT results was significant. Nakajima *et al*. examined serum PCT level in patients with a positive blood culture result and found that PCT level was significantly higher in the group of Gram-negative bacilli than in the group of Gram-positive cocci. However, they reported no significant difference in the average WBC count or CRP levels between the two groups. They used the indices of sensitivity, specificity, and positive/negative predictive values and found a correlation of 87% between blood culture and PCT results.[9] Accordingly, they found higher correlations between serum PCT level and sepsis (than local infections) and serum PCT level and infections caused by Gram-negative cocci (than Gram-positive cocci).[9] According to the results of other studies, blood culture seems to have a low sensitivity to sepsis.[7] This low sensitivity of blood culture to sepsis can be a limitation when considering it the "gold standard" for the diagnosis of infections. In a study, done by Delèvaux *et al*., serum CRP, WBC count, and PCT were higher in patients with bacterial infections than in patients with nonbacterial inflammatory diseases; but, PCT values were more distinctive in the diagnosis of bacterial infections than values of CRP and WBC count.[29] CRP and ESR are widely used in the diagnosis of infections; however, some studies have questioned their value due to the instability of their diagnostic power.[21,28,30] In many studies, levels of serum PCT have been measured during and after patients' admission to the hospital. Thus, it has been concluded that PCT can be an infection marker for follow-up treatments and that certain levels of PCT are always a sign of bacterial infection or a clue for the initiation of antibiotic therapy.[26,29,31] As biomarkers of sepsis, interleukins, pro-adrenomedullin, ANP, copeptin, provasopressin, interferon gamma, resistin, and PRC have been examined in recent years.[5,8,10-12] However, PCT has the most important role in the diagnosis of sepsis. Various studies have reported that serum PCT level is low in healthy people.[15,16] Results of the present study confirmed the importance of PCT in the diagnosis of bacterial infections. In a review study, Nelson *et al*. explained that PCT is a valuable marker for the diagnosis of sepsis, but they did not approve the cost-effectiveness of PCT test for the diagnosis of sepsis if used extensively.[25] In another review study, Tang explained that serum PCT level cannot differentiate sepsis from the systemic inflammatory syndrome.[7] Several biomarkers are currently used for the diagnosis of sepsis; nonetheless, their applicability is restricted in many cases due to the lack of sensitivity to and specificity in detecting infections and the complexity of inflammatory and immune processes. This is why patients are usually classified into homogeneous groups for specific treatments.[24] The current study was conducted to compare serum PCT with ESR, CRP, WBC count, and blood culture in the diagnosis of bacterial infections. The results of this study can be used in the diagnosis, prognosis, and treatment of bacterial infections.

Recommendations

It is necessary to conduct more research on PCT as a diagnostic and predictive parameter for blood infections. In the present study, problems associated with the blood culture systems and costs of conducting PCT testing led to some limitations with regards to the study's samples. Accordingly, it is recommended to conduct similar studies on larger samples sizes to obtain results with higher validity.

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Conflicts of interest

There are no conflicts of interest.

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