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Medical Science

PCT, CRP, WBC AND PLTC VALUES FOR DISCRIMINATION OF CULTURE POSITIVE BACTERIAL INFECTIONS IN FEBRILE CHILDREN

KEY WORDS: PCT, CRP, WBC, PLTC, pediatric emergency.

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ABSTRACT

Introduction: Although procalcitonin (PCT) concentration increases in bacterial infections, it does not increase in viral infections and inflammatory diseases. Rapid change and stability of the molecule made PCT as a potentially useful marker for the differentiation of bacterial and viral infections. In the present study, we aimed to compare PCT, CRP, WBC and thrombocyte count values as an infection marker.

Methods: Patients admitted to the pediatric emergency department with fever (≥38.5 °C), and collected blood, urine, stool and CSF samples for culture test were enrolled. 52% of patients were girl. The mean age was 6.77±4.84 years. PCT, CRP, WBC and PLTC values obtained from blood and serum samples at admission to the pediatric emergency department were compared.

Results: The mean PCT concentration was ≥3.375 µg/L in children with positive CSF culture. It was ≥1.95 µg/L in children with positive blood culture which was statistically significant. It was not significant in children with positive urine and stool culture. CRP threshold value was ≥1.285 mg/L in children with a positive CSF culture; it was statistically significant. CRP was not significant in children with a positive blood culture. The WBC value was significantly higher in children with a positive urine culture. PLTC was not statistically significant in whole patients. PCT, WBC, CRP and PLTC values were not significantly differed in children with pathogenic bacterial growth in a stool culture.

Discussion: In our study, PCT value of ≥1.95 µg/L has higher specificity and sensitivity compared to CRP to differentiate various bacterial infections. The threshold value of 3.375 µg/L for PCT was significantly higher specificity, sensitivity for septicaemia and meningeal infections compared to CRP. The threshold value of 1.285 mg/L for CRP was seen in children with positive CSF culture, and it was statistically significant. CRP can be useful in differentiating bacterial and viral infections in children, but PCT has a more significant significance in the pediatric emergency setting, especially for the decision to start early treatment of antibiotic in septicemia and meningitis.

INTRODUCTION

Fever is a physiologic response characterised by an elevation of body temperature above normal daily variation (1). Fever is a common reason for visits to the pediatric emergency departments (EDs), and it is responsible for 15–25% of consultations in primary care and emergency departments (2-4). Commonly, the majority of patients have minor bacterial or viral infections, but it is essential to recognise those having serious bacterial infections to provide appropriate care with antibiotics and early hospitalisation (5). It may be challenging to differentiate bacterial infections from viral infections in EDs accuracy.

Body temperature and other clinical findings often provide inadequate information for diagnosis. Therefore, a more sensitive and specific laboratory markers are needed. Today, blood culture is still the gold-standard method for the bacterial infection diagnosis. However, blood culture has disadvantages such as the lack of rapidity and low diagnostic sensitivity (6,7).

For this reason, increasingly, clinicians have begun proposing other surrogate markers, such as procalcitonin (PCT) and C-reactive protein (CRP). The most commonly used acute phase markers in clinical practice are leukocyte count (WBC), absolute neutrophil count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) levels and procalcitonin levels (PCT) (8-10). C-reactive protein (CRP), an acute-phase reactant which is secreted by the liver in response to a bacterial infection and procalcitonin (PCT), the precursor of calcitonin, which is released from all tissues in response to a bacterial infection are useful for discriminating febrile children with a bacterial infection from those with self-limiting febrile illnesses. However, the superiority of one biomarker than the others has not yet been proven convincingly. It was reported that neither CRP nor PCT could be used as a solitary predictor of bacterial infection without other clinical features or diagnostic markers (11-15).

CRP can be useful to discrimination between bacterial and viral infection in children but serum level of CRP increases within 12-48 hours. Because PCT, a 14-kDa protein prohormone of calcitonin rises within 6-8 hours, earlier than CRP, it may be more useful in the early diagnosis of severe infections in children such as sepsis and meningitis. Because it can increase nearly a 1000-fold in the very invasive bacterial infections. (16,17). Therefore, we aimed to compare CRP, WBC, PLTC and PCT values in febrile children with positive blood, urine, stool and CSF culture and to determine the specific cut-off values for these infection markers. Also, we aimed to clarify which acute phase marker is better for early diagnosis.

MATERIAL AND METHODS

This prospective observational study was conducted at Eskisehir Osmangazi University Faculty of Medicine, Pediatric Emergency Department in Eskisehir, Turkey between March 2018 and September 2018. The institutional review board approved the study and written informed consent was obtained from parents or caregivers. This study was supported by Eskisehir Osmangazi University Scientific Research Projects Commission (Project number: 2017-1640).

Patients admitted to the pediatric emergency department for fever were selected. Using infrared thermometry, forehead skin temperature was measured three times by a paediatrician. It was positioned 5 cm in front of the subject's forehead, and the mean temperature was calculated. The mean patient temperature of >38.5 C° was accepted as febrile.

All patients with fever lasting longer than seven days, known acquired or congenital immunodeficiency, any chronic pathology and children treated with antibiotics or vaccination during the previous two days were excluded from the study. After consent was obtained, samples were taken for CRP, PCT, WBC, PLTC and blood, stool, urine and CSF culture. Blood, stool and urine culture were studied in all cases, but CSF culture was studied in selected cases based on the clinical examination findings. A hundred patients aged 0 to 18 years with positive blood, urine, stool or CSF culture were included the analysis. Children were detailed examined, and complete history and demographic information were taken. Also, the degree and duration of fever were recorded. Decisions on antibiotic treatment and hospitalisation were made by emergency staff physician based on clinical assessment and the presence of risk factors.

Procalcitonin was measured by automatic immunofluorescence assay (Brahms Diagnostica, Berlin, Germany) following the manufacturer's instructions. CRP was analysed using

nephelometric assay according to the instructions of the manufacturer (Siemens Healthcare Diagnostics, Marburg, Germany). WBC and PLTC analysis were performed in blood samples with ETDA using an automated cell counter (Beckman Coulter, Miami, FL, USA).

Statistical Analysis

All statistical analysis were performed by commercial SPSS 17.0 software. Normally distributed data were expressed as mean standard deviation (±SD); nonnormally distributed data were expressed as median and frequency, and categorical variables were reported as percentages. For nonnormally distributed data, the comparison was performed employing Mann–Whitney U or Kruskal Wallis tests when appropriate and comparison of normally distributed data were performed using independent-samples t-test. Receiver operating characteristic (ROC) analysis was used for the diagnostic performance of CRP, WBC, PCT and PLTC and Based on ROC analysis, the best statistical cut-off values for each parameter was calculated. The sensitivity and specificity were assessed. Results were assessed with a 95 % confidence interval. $P<0.05$ was considered statistically significant. Parameters displaying $P<0.01$ were considered advanced statistically significant.

RESULTS

Totally 100 patients were analysed. Fifty-two of cases were girl (52%), and 48 (48%) were boy. The mean age was 6.77±4.84 years (between 2 months and 18 years).

For the whole cohort, the mean CRP concentration was 3.153±4.974 mg/L (range 0.24 to 21.0), the mean WBC value was 9922.1±5633.9 mm^3 (range 400 to 32.000) the mean PCT value was 2.688±11.12 µg/L (range 0.2 to 94) and the mean PLTC value was 296600±142553 $\times 10^3$/µL (range 7000 to 760000).

Thirty-six patients had a positive urine culture, 21 had positive blood culture, 14 had a positive stool culture, 10 had a positive CSF culture. Both blood and urine cultures were positive in 12 patients, both CSF and blood cultures were positive in 3 patients, both blood and stool cultures were positive in 2 patients, and both urine and stool cultures were positive in 2 patients.

The effect of positivity of blood culture on PCT level was statistically significant (p=0.000). The optimum cut-off value of positivity of blood culture for PCT level was 1.95. The sensitivity was 66.7%, and specificity was 88.2%. Also, the effect of positivity of CSF culture on PCT level was statistically significant (p=0.000) The optimum cut-off value of positivity of CSF culture for PCT was 3.375. The sensitivity was 80.0%, and specificity was 95.6%. The effect of positivity of urine culture on WBC level was statistically significant (p=0.000). The optimum cut-off value of positivity of urine culture for WBC was 9370. The sensitivity was 78.6%, and specificity was 58.3%. The effect of positivity of CSF culture on CRP level was statistically significant (p=0.045). The optimum cut-off value of positivity of CSF culture for CRP was 1.285. The sensitivity was 80.0%, specificity was 57.8%. ROCs for laboratory values for the prediction of culture positivity are shown in Figure 1, 2, 3 and 4.

The mean PCT concentration was ≥3.375 µg/L in children with positive BOS culture. It was ≥1.95 µg/L in children with positive blood culture (with higher sensitivity and specificity) It was not significant in children with positive urine and stool culture. CRP threshold value was ≥1.285 mg/L in children with a positive CSF culture. It was not significant in children with positive blood culture. The WBC value was significantly higher in children with a positive urine culture (≥9370 $\times 10^3$/µL). PLTC was not statistically significant in whole patients. PCT, WBC, CRP and PLTC values were not significantly differed in children with pathogenic bacterial growth in a stool culture. The sensitivity, specificity, cut-off and AUC rates for CRP, WBC, PCT and PLTC according to the positivity of culture are shown in Table 1.

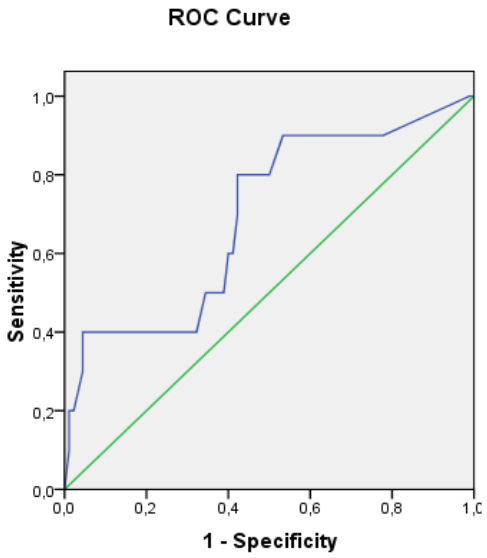

Figure 4. ROC for CRP for prediction of CSF culture positivity.

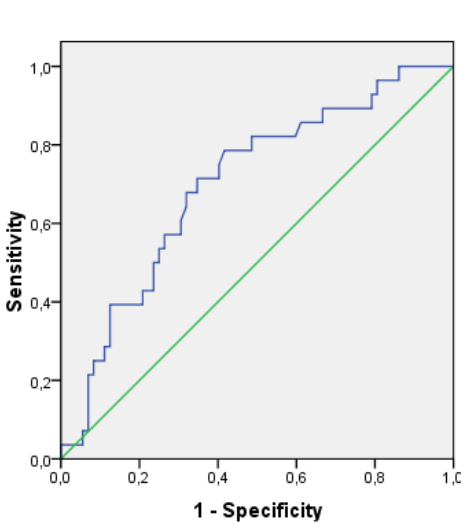

Figure 3. ROC for WBC for prediction of urine culture positivity.

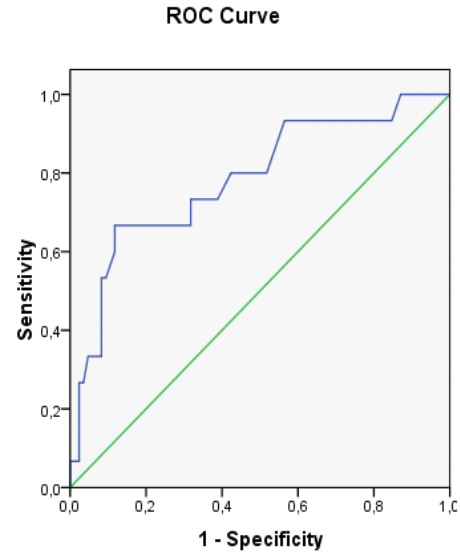

Figure 1. ROC for PCT for prediction of blood culture positivity.

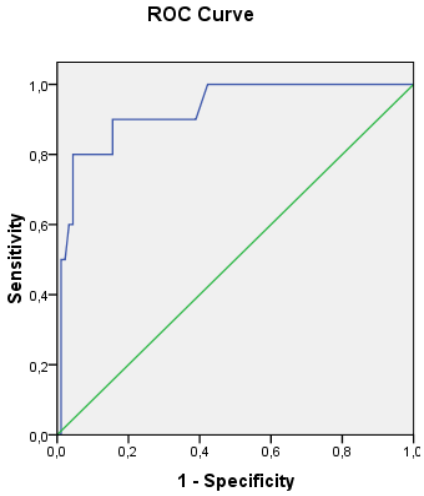

Figure 2. ROC for PCT for prediction of CSF culture positivity.

Table 1. Sensitivity, specificity, cut-off and AUC rates for laboratory values according to the positivity of culture.

Marker	Culture positivity	AUC	p	Cut off	Sensitivity	Specificity
CRP	Blood	0,611 (0,455 - 0,767)	0,172	-		
	Urine	0,614 (0,498 - 0,730)	0,078	-		
	Stool	0,444 (0,280 - 0,609)	0,548	-		
	CSF	0,694 (0,517 - 0,871)	0,045	1,285	80,0%	57,8%
WBC	Blood	0,495 (0,326 - 0,664)	0,954	-		
	Urine	0,700 (0,588 - 0,811)	0,002	9740	78,9%	58,3%
	Stool	0,552 (0,373 - 0,731)	0,574	-		
	CSF	0,553 (0,339 - 0,766)	0,585	-		
PCT	Blood	0,784 (0,649 - 0,918)	0,000	1,95	67,7%	88,2%
	Urine	0,597 (0,474 - 0,719)	0,134	-		
	Stool	0,403 (0,234 - 0,573)	0,298	-		
	CSF	0,927 (0,837 - 0,999)	0,000	3,375	80,0%	95,6%
PLTC	Blood	0,643 (0,476 - 0,810)	0,078	-		
	Urine	0,378 (0,257 - 0,498)	0,058	-		
	Stool	0,437 (0,274 - 0,601)	0,498	-		
	CSF	0,687 (0,476 - 0,897)	0,054	-		

DISCUSSION

At pediatric EDs, early diagnosis of bacterial infections still poses a major challenge. Bacterial infections can cause fetal outcomes if untreated. Sometimes complaints are similar in patients with viral and bacterial infections. Therefore, high sensitivity and specificity markers or certain approaches are needed the distinction between these two conditions. The growth of the causative organism in culture is gold-standard for diagnosis (6, 18). However, it is known that culture techniques may not be sufficient in some cases including long growth time for bacteria some types, expensive tissue culture procedures for viruses, negative culture of certain microorganisms, taking culture samples after starting antibiotics or sent to the laboratory in unsuitable conditions (19,20).

Procalcitonin and CRP have commonly investigated marker for the differentiation of bacterial and viral infections. Higher sensitivity and specificity rates were reported for them (21,22). CRP is a good index but may not be elevated in the first 24 hours of serious bacterial illness. CRP would also be raised in many viral diseases, whereas PCT rises only slightly in response to viral infections. Compared with CRP, the increase of PCT in the circulation was found more rapid and more specific (23,24). It has been reported that PCT has better diagnostic accuracy to detect severe bacterial infections in children with fever without source than does CRP (12).

In the present study, the mean PCT concentration was ≥3.375 µg/L in children with positive BOS culture. It was ≥1.95 µg/L in children with positive blood culture which was statistically significant. It was not significant in children with positive urine and stool culture. CRP threshold value was 1.285 mg/L in children with a positive CSF culture; it was statistically significant. CRP was not found significant in children with positive blood culture. The WBC value was significantly higher in children with a positive urine culture. PLTC was not statistically significant in whole patients. PCT, WBC, CRP and PLTC values were not significantly differed in children with pathogenic bacterial growth in a stool culture.

CRP level increases in many cases with tissue damage, such as acute infections, rheumatic diseases, malignancies and acute myocardial infarction. (25) In general, high CRP value is detected in severe acute bacterial infections, and it may be lower in viral infections. (26) It can be detected as high in some diseases including adenovirus, cytomegalovirus, influenza, mumps, measles and other viruses related infections. However, the low level of CRP does not eliminate the possibility of bacterial infection. CRP level may be low in the first 12 hours after onset of the illness. However, serial CRP measurements should be used if a bacterial infection is clinically suspected (27) Tayyil et al. reported that the sensitivity and specificity were 75% and 68.7%, respectively for CRP (>50 mg/L) to detect bacterial infection.(28) Ip et al. reported that the sensitivity and specificity of CRP (>10 mg/L) were 95% and 55%, respectively.(29) Yo et al. found that the sensitivity was 74% and the specificity was 76% for CRP (>9.83 mg/L) to detect severe bacterial infection.(12). In our patients, a cut-off value of 1.285 mg/L for CRP was demonstrated 80% sensitivity and 57.8% specificity (for CSF culture positivity). As it is shown in these studies, the sensitivity and the specificity of different values are variable; and suggesting that it is difficult to give a certain amount for the distinction between bacterial and viral infections.

Procalcitonin concentrations were strongly correlated with disease severity in several bacterial infections such as meningitis or urinary tract infection (30-32). Also, it was reported that serum PCT, CRP and WBC levels were significantly higher in bacterial meningitis group than the viral group, and it continued to remain significantly higher on the 3rd day of treatment.(33) It was also reported that serum PCT, CRP and WBC levels were significantly reduced after 72 hours of treatment in bacterial meningitis group (20). Similarly, CRP and PCT levels were significantly higher in patients with positive BOS culture in our study. In our patients, a cut-off value of 1.95 µg/L for PCT was demonstrated 67.7% sensitivity and 88.2 % specificity (for blood culture positivity). But, the threshold of 3.375 µg/L for PCT had higher sensitivity (80%) and specificity (95.6%) (for CSF culture positivity).

In a study by Virkki et al., the proportion of patients with increased WBC was similar in bacterial and viral pneumonia (34). Moulin et al. measured the sensitivity as 65.1% and specificity as 79.3% for WBC to distinguish bacterial and viral pneumonia (35). In our study, the cut-off value of WBC for prediction of urine culture positivity was 9740 $\times 10^3$/ L, and WBC was significantly higher only in patients with positive urine culture with higher sensitivity (78.9%) but lower specificity (58.3%). Majority of these patients had urinary tract infection. Compared to the literature, relatively lower specificity levels in our study may be due to different bacterial infection from other studies. Our WBC result indicated that WBC may not be essential for early prediction of bacterial infection, especially very severe bacterial infections.

CONCLUSION

In conclusion, PCT value of ≥1.95 µg/L has higher specificity and

sensitivity compared to CRP to differentiate various bacterial infections. The threshold value of 3.375µg/L for PCT was significantly higher specificity, sensitivity for septicaemia and meningeal infections compared to CRP. The threshold value of 1.285 mg/L for CRP was seen in children with positive CSF culture, and it was statistically significant. CRP can be useful in differentiating bacterial and viral infections in children, but the PCT has a more significant significance in distinguishing the bacterial and viral infections in the paediatric emergency setting, especially in the decision to start early treatment of antibiotic in septicemia and meningitis.

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