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Diagnostic utility of C- reactive protein, Pro-calcitonin , Erythrocyte sedimentation rate in early detection of bacterial sepsis

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ABSTRACT

Background: In spite of the advances in critical care medicine, early diagnosis and proper treatment of bacterial sepsis is a challenge in intensive care unit. Procalcitonin (PCT) an innovative and better laboratory marker, has been recently proven to be appropriate and efficient in treating bacterial sepsis. **Aim:** To determine the diagnostic accuracy of Procalcitonin (PCT), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) as individual and combined indicators of bacterial sepsis and compare ESR, CRP, PCT to the gold standard microbiological cultures. **Materials and Methods:** This study was a retrospective study which was conducted during the period of 1 year which was between August 2022 to August 2023. This study was conducted in General surgery department, SVIMS-SPMC(W), Tirupati in a total of 80 patients. **Results:** Majority of patients were in the age group of 51-60 years which constituted 21 patients (26.2%). Majority of patients were males which constituted 66 (82.5%). Females were 14 (17.5%). C-reactive protein was in between 100-150 mg/dl in 16 patients (20%) at admission and after 48 hrs, less than 10 mg/dl C-reactive protein was observed in 6 patients which is considered abnormal. procalcitonin (ng/mL) was greater than 0.25 ng/mL in 69 patients (86.3%) at admission which indicates the presence of infection. After 48 hours, infection was reduced in 54 patients (67.5%). At admission active infection was observed in 27 patients (33.8%) at admission with ESR >100 mm/hr and it was reduced to 8, 10% after 48 hours. 9 positive blood cultures and 3 negative blood cultures were observed in patients with less than 2 ng/mL procalcitonin, 4 positive blood cultures and 3 negative blood cultures were observed in patients with 2-10 ng/mL procalcitonin, 8 positive blood cultures and 1 negative blood cultures were observed in patients with more than 10 ng/mL procalcitonin. **Conclusion:** PCT was more efficient diagnostic tool when compared to CRP and ESR in detecting severity of infection.

Keywords: C reactive protein, sepsis, Procalcitonin (PCT), Erythrocyte Sedimentation Rate (ESR).

INTRODUCTION

Sepsis is a serious life-threatening disease. Its symptoms are highly variable and dependent on the patient's age, the underlying disease, and the type of organism [1]. Several biomarkers have been suggested for the early diagnosis of sepsis, including IL-1b, IL-8, IL-6, TNF-α, and PCT [2].

Microbiological culture is the gold standard test for differentiation of bacterial / non-bacterial aetiology, it is time-consuming and costly resulting in delayed treatments, subsequently leading to poor prognosis along with higher costs on healthcare systems. The results of blood cultures are reported after at least 48 hours. They may be negative in the early stages of SIRS and sepsis, pre-hospital antibiotic usage. Moreover, many organisms require specific media and exclusive culture environments that are not available in most medical centres. The empirical use of antibiotics is effective if the sepsis is of bacterial aetiology. However, for non-bacterial sepsis, such practice would increase antibiotic resistance, morbidity, and eventual mortality. Therefore, identifying a bacterial/non-bacterial aetiology of sepsis is crucial.

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Recent studies have investigated biomarkers such as procalcitonin (PCT), C-reactive protein (CRP) and Erythrocyte sedimentation rate (ESR) for the early detection of bacteraemia in septic patients.

PCT, a calcitonin prohormone, increases significantly in patients with bacterial infections caused by a broad spectrum of gram-positive and gram-negative bacteria [(3)]. CRP rises within hours of onset of an infection or inflammatory condition and returns to normal within three to seven days if the acute process is resolved. ESR, on the other hand, increases in a slower manner and remains elevated for a longer period [(6)]. Erythrocyte sedimentation rate (ESR) is a simple, cheap, and minimally invasive test for assessing the acute and chronic inflammatory response. In addition, ESR is a non-specific measure that can be affected by factors other than inflammation, such as the size, shape, and number of red blood cells; levels of serum fibrinogen and immunoglobulins; renal function; age and sex; pregnancy; and use of medications. This study was conducted to determine the diagnostic accuracy of Procalcitonin (PCT), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) as individual and combined indicators of bacterial sepsis and compare ESR, CRP, PCT to the gold standard microbiological cultures.

MATERIALS AND METHODS

This study was a retrospective study which was conducted during the period of 1 year which was between August 2022 to August 2023. This study was conducted in General surgery department, SVIMS-SPMC(W), Tirupati in a total of 80 patients with IEC of number-1465. Patients diagnosed to have SIRS, sepsis or septic shock were included in this study. Patients who had age of below 18 years, patients who were on antibiotics at time of blood collection or immunosuppressive drugs; or patients with major trauma, severe burns, or recent surgery were excluded from the study. The study was conducted after approval from Institutional Ethics Committee (IEC), SVIMS. Informed consent form was taken from all the patients. The data included age, sex, co-morbidities, presenting complaints with duration, general condition of the patient. Blood specimens were obtained investigating procalcitonin (PCT) by quantitative immune-chromatography method, C reactive protein (CRP) by nephelometry (CRP <10 mg/dl were considered abnormal) and ESR by Westergren method (ESR >20 mm/1st hour was considered abnormal). The BIOMEURIX BACTALERT culture system was used to process blood cultures.

Antibiotics were commenced after the blood specimens were collected. Before starting the treatment process, the first blood sample was taken on admission followed by a sample taken 48 h after treatment. All the required data were collected from medical records and transform to an excel sheet and individual scores of each patient were calculated and compared.

All data were double checked to exclude any clerical errors. Data were recorded on a predesigned proforma and managed using Microsoft Excel worksheet (Microsoft Corp, Redmond, WA). Descriptive statistics for categorical variables were performed by computing the frequencies (percentages) in each category. For the quantitative variables, approximate normality of distribution were assessed. Variables following normal distribution will be summarized by mean ± standard deviation; the remaining variables were summarized as median [interquartile range (IQR)]. The chi-square test (or Fisher's test for expected value of < 5) was used for analysis of categorical variables. The independent sample t-test was used for analysis of continuous variables with a normal distribution and to compare differences between WBC, ESR, CRP and PCT before and after treatment of SIRS. Mann-Whitney U-test was used for those with a skewed distribution. P values of < 0.05 were considered statistically significant.

RESULTS

This study was conducted in 80 patients.

Table 1: Distribution based on age

Age range (years)	Number of patients	Percentage,%
30-40	7	8.8
41-50	17	21.2
51-60	21	26.2
61-70	19	23.8
71-80	11	13.8
81-90	4	5
Above 90	1	1.2
Total	80	100

Table 1 shows that majority of patients were in the age group of 51-60 years which constituted 21 patients (26.2%).

Table 2: Distribution based on sex

Sex	Number of patients	Percentage,%
Male	66	82.5

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Female	14	17.5
Total	80	100

Table 2 shows that majority of patients were males which constituted 66 (82.5%). Females were 14 (17.5%).

Table 3: C-reactive Protein at admission and after 48 hours

C-reactive protein (mg/dl)	At admission (n,%)	After 48 hours (n,%)
Less than 50	8, 10	31, 38.8
51-100	13, 16.3	25, 31.2
101-150	16, 20	15, 18.8
151-200	12, 15	5, 6.2
201-250	13, 16.3	3, 3.8
251-300	9, 11.2	1, 1.2
>300	9, 11.2	0

Table 3 shows that C-reactive protein was in between 100-150 mg/dl in 16 patients (20%) at admission and after 48 hrs, less than 50 mg/dl C-reactive protein was observed in 31 patients (38.8%). After 48 hrs, less than 10 mg/dl C-reactive protein was observed in 6 patients which is considered normal.

Table 4: Procalcitonin at admission and after 48 hours

Procalcitonin (ng/mL)	At admission (n,%)	After 48 hours (n,%)
Less than 0.25	11, 13.8	26, 32.5
0.25-1	9, 11.2	12, 15
2-20	41, 51.2	38, 47.5
21-40	5, 6.2	1, 1.3
41-60	2, 2.5	2, 2.4
61-80	3, 3.8	1, 1.3
81-100	8, 10	0,0
>100	1, 1.3	0,0

Table 4 shows that procalcitonin (ng/mL) was greater than 0.25 ng/mL in 69 patients (86.3%) at admission which indicates the presence of infection. After 48 hours, infection was reduced in 54 patients (67.5%).

Table 5: ESR at admission and after 48 hours

ESR (mm/hr)	At admission (n,%)	After 48 hours (n,%)
Less than 20	1, 1.2	5, 6.3
21-40	2, 2.5	9, 11.2
41-60	6, 7.5	18, 22.5
61-80	8, 10	17, 21.2
81-100	36, 45	23, 28.8
>100	27, 33.8	8, 10

Table 5 shows that at admission active infection was observed in 27 patients (33.8%) at admission with ESR >100 mm/hr and it was reduced to 8, 10% after 48 hours.

Table 6: Blood culture

Microorganisms in blood culture	Number of patients	Percentage
Acinetobacter	2	2.5
Enterococcus Faecalis	4	5
Escherichia Coli	3	3.8
Klebsiella	2	2.5
Staphylococcus Aureus	10	12.4
Staphylococcus Haemolyticus	3	3.8
Staphylococcus Hominis	1	1.2
Streptococcus	3	3.8
No growth	52	65

Table 6 shows that no growth was observed in 52 patients (65%), Staphylococcus Aureus (10,12.4%), Enterococcus Faecalis (4,5%), Escherichia Coli (3,3.8%), Staphylococcus Haemolyticus (3,3.8%), Streptococcus (3,3.8%), Acinetobacter (2,2.5%), Klebsiella (2,2.5%), Staphylococcus Hominis (1,1.2).

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Table 7: Comparison of bio markers at the time of admission

Tests	Sensitivity (Cl)	Specificity (Cl)	PPV (Cl)	NPV (Cl)	Accuracy
PCT	92%	94.8%	89.3%	96.5%	96.5%
CRP	98.7%	98.7%	98.7%	98.7%	98.7%
ESR	98.5%	97.5%	97.5%	98.7%	98.1%
PCT & CRP	95.35%	96.75%	94%	97.6%	97.6%
PCT & ESR	98.5%	97.5%	97.5%	98.7%	98.1%
PCT, CRP & ESR	96.4%	97%	95.1%	97.9%	97.7%

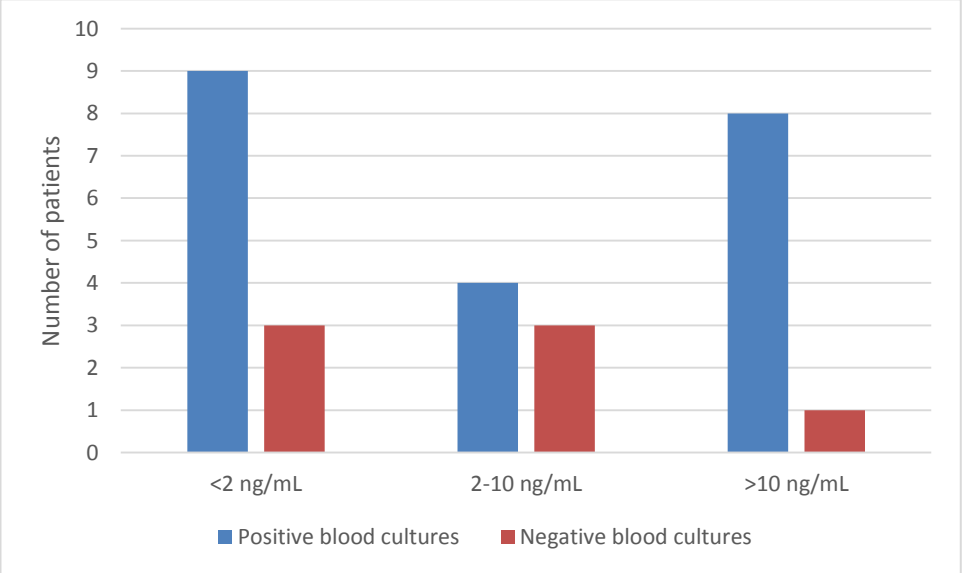
Diagnostic accuracy of CRP was higher (98.7%) with greater specificity (98.7%), sensitivity (98.7%).

Table 8: Comparison of bio markers after 48 hrs

Tests	Sensitivity (Cl)	Specificity (Cl)	PPV (Cl)	NPV (Cl)	Accuracy
PCT	91.67%	95.8%	78.57%	98.5%	95.2%
CRP	94.7%	98.1%	98.2%	94.6%	95.7%
ESR	97.5%	97.3%	97.5%	97.3%	97%
PCT & CRP	95.18%	97.2%	88.63%	98.55%	96.95%
PCT & ESR	94.58%	96.55%	88%	97.9%	96.3%
PCT,CRP & ESR	95.9%	97.2%	91.59%	98%	97.1%

Diagnostic accuracy of PCT,CRP and ESR was higher (97.1%) with greater specificity (97.2%), sensitivity (95.9%) after 48 hrs.

Figure-1: Procalcitonin Vs Blood cultures after 48 hrs.



9 positive blood cultures and 3 negative blood cultures were observed in patients with less than 2 ng/mL procalcitonin, 4 positive blood cultures and 3 negative blood cultures were observed in patients with 2-10 ng/mL procalcitonin, 8 positive blood cultures and 1 negative blood cultures were observed in patients with more than 10 ng/mL procalcitonin.

DISCUSSION

The present study was conducted in 80 patients and it was observed that procalcitonin (ng/mL) was greater than 0.25 ng/mL in 69 patients (86.3%) at admission which indicates the presence of infection. After 48 hours, infection was reduced in 54 patients (67.5%). Diagnostic accuracy of CRP was higher (98.7%) with greater specificity (98.7%), sensitivity (98.7%) at the time of admission. Diagnostic accuracy of PCT,CRP and ESR was higher (97.1%) with greater specificity (97.2%), sensitivity (95.9%) after 48 hrs. All 3 parameters serum PCT, CRP and ESR values in cases with sepsis and were significantly higher from that of the cases. These results are in correlation with Waheeda Nargis *et al*[3] study, which reported that the diagnostic accuracy of PCT was higher (75%) with greater specificity (72%), sensitivity (76%), positive and negative predictive values (89% and 50%), positive likelihood ratio (2.75) as well as the smaller negative likelihood ratio (0.33). Both serum PCT and CRP values in cases with sepsis, severe sepsis and septic shock were significantly higher from that of the cases with SIRS and no SIRS ($P < 0.01$). In Simon L *et al*[4] study; similar results were observed that PCT level was more sensitive (88% [95% confidence interval [CI], 80%-93%] vs. 75% [95%

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CI, 62%-84%]) and more specific (81% [95% CI, 67%-90%] vs. 67% [95% CI, 56%-77%]) than CRP level for differentiating bacterial from non-infective causes of inflammation. The Q value for PCT markers was higher (0.82 vs. 0.73). The sensitivity for differentiating bacterial from viral infections was also higher for PCT markers (92% [95% CI, 86%-95%] vs. 86% [95% CI, 65%-95%]); the specificities were comparable (73% [95% CI, 42%-91%] vs. 70% [95% CI, 19%-96%]). The Q value was higher for PCT markers (0.89 vs. 0.83). PCT markers also had a higher positive likelihood ratio and lower negative likelihood ratio than did CRP markers.

In Assicot M *et al*[5] study, similar results were observed that investigation was performed on 79 children (newborn to age 12 years) in hospital with suspected infections prospectively. Very high serum concentrations of procalcitonin were observed in 19 patients with severe bacterial infections had at diagnosis (range 6-53 ng/mL) in comparison with 21 children found to have no signs of infection (baseline concentrations < 0.1 ng/mL). During antibiotic therapy, Serum procalcitonin values decreased rapidly. 11 patients with peripheral bacterial colonisation or local infections without invasive sepsis and 18 (86%) of 21 patients with viral infections had concentrations within or slightly above the normal range (0.1-1.5 ng/mL). Among 9 severely burned patients studied in an intensive care unit, the post-traumatic course of procalcitonin concentrations (range 0.1-120 ng/mL) was closely related to infectious complications and acute septic episodes. procalcitonin concentrations were observed, and Concentrations of mature calcitonin were normal in all subjects. Brunkhorst FM *et al*[6] reported similar results that 50% of the patients had elevated PCT levels above 2 ng/mL at the onset of infection. The model of multivariate analysis of all tested parameters on days 0-5 stratified for clinical outcome (change in clinical classification or death) showed local significance for APACHE II score only. It gave similar conclusions as the present sudy that change in PCT on admission and at the end of the observation period significantly indicated a clinical change. Naher BS *et al*[7] reported that sepsis was more prevalent in low birth weight and preterm newborns. As a risk factor of sepsis, premature rupture of membrane (PROM) was found to be the commonest maternal clinical condition. In the different categories of sepsis, there was positive correlation between serum PCT and CRP and values of serum PCT as well as CRP differed significantly indicating relation to the severity of sepsis. PCT is a useful, sensitive and independent biomarker of neonatal sepsis. CRP measurement along with PCT measurement may increase the specificity. Karlsson S *et al*[8] reported contrary results compared to the present study that the median PCT serum concentration on day 0 was 5.0 ng/ml (interquartile range (IQR) 1.0 and 20.1 ng/ml) and 1.3 ng/ml (IQR 0.5 and 5.8 ng/ml) 72 hours later. Hospital mortality was 25.6% (62/242). Median PCT concentrations in patients with community-acquired infections were higher than with nosocomial infections (P = 0.001). Blood cultures were positive in 28.5% of patients (n = 69), and severe sepsis with positive blood cultures was associated with higher PCT levels than with negative cultures (P = < 0.001). Patients with septic shock had higher PCT concentrations than patients without (P = 0.02). PCT concentrations did not differ between hospital survivors and nonsurvivors (P = 0.64 and P = 0.99, respectively), but mortality was lower in patients whose PCT concentration decreased > 50% (by 72 hours) compared to those with a < 50% decrease (12.2% vs. 29.8%, P = 0.007). A substantial concentration decrease was more important for survival than absolute values and PCT concentrations were higher in more severe forms of severe sepsis. Hur M *et al*[9] reported that the mean concentrations of CRP in five categories of PCT were 15.4 mg/dL, 42.1 mg/dL, 101.2 mg/dL, 125.0 mg/dL, 167.1 mgd/L, respectively (P<0.0001). Both PCT and CRP showed significant differences between the two positive and negative groups of blood culture (PCT, 8.47 vs 2.44 ng/mL, P=0.0133; CRP, 110.48 vs 59.78 mg/L, P<0.0001). The areas under the ROC curves (95% confidence interval) for PCT and CRP were 0.720 (0.644-0.788) and 0.558 (0.478-0.636), respectively, and showed a significant difference (P=0.005). Similar conclusions were made that the diagnostic utility of PCT is superior to that of CRP for the patients with blood culture-positive sepsis. Luzzani A *et al*[10] reported that a total of 800 patient days were classified into the four categories. The median plasma PCT concentrations in noninfected (systemic inflammatory response syndrome) and localized-infection patient days were 0.4 and 1.4 ng/mL (p <.0001), respectively; the median CRP plasma concentrations were 79.9 and 85.3 mg/L (p =.08), respectively. The area under the receiver operating characteristic curve was 0.756 for PCT (95% confidence interval [CI], 0.675-0.836), compared with 0.580 for CRP (95% CI, 0.488-0.672) (p <.01). The median plasma PCT concentrations in nonseptic (systemic inflammatory response syndrome) and septic (sepsis, severe sepsis, or septic shock) patient days were 0.4 and 3.65 ng/mL (p <.0001), respectively, whereas those for CRP were 79.9 and 115.6 mg/L (p <.0001), respectively. The area under the receiver operating characteristic curve was 0.925 for PCT (95% CI, 0.899-0.952), compared with 0.677 for CRP (95% CI, 0.622-0.733) (p <.0001). The linear correlation between PCT plasma concentrations and the four categories was much stronger than in the case of CRP (Spearman's rho, 0.73 vs. 0.41; p <.05). A rise in sepsis-related organ failure assessment score was related to a higher median value of PCT but not CRP. Similar conclusion was made that PCT is a better marker of sepsis than CRP.

In Janjam Harikrishna et al[11] study among patients 275 cases significantly higher median serum PCT levels was evident in bacteraemia compared to leptospirosis (*P*=0.002), dengue (*P*<0.001), scrub typhus (*P*<0.001) and evident focus of infection without bacteraemia (*P*=0.036). Sensitivity and specificity of serum PCT levels in predicting bacteraemia were 81.1 and 63.3 per cent, respectively. 91 (18.9%) patients had a poor outcome and these had significantly higher median serum PCT levels compared to survivors (n=389) [9.46 (2.03-44.4) vs. 1.23 (0.34-7.645); *P*<0.001]. At a cut-off value of

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>3.74 ng/ml, serum PCT levels at initial presentation predicted in-hospital mortality with a sensitivity and specificity of 67 and 67.5 per cent was noted.

CONCLUSION

This study concluded that PCT, CRP and ESR was used in detection of severity of sepsis and PCT was a better diagnostic tool when compared to CRP and ESR in detecting severity of infection in comparison with blood cultures.

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