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Assessment of patients with sepsis and septic shock Using Procalcitonin and C-reactive Protein

Abdelhamid Mohammad Abdelhamid, Hassan Mohammad Mageed, Ghada Mohammad Abdel Razik,Sherif M. S. Mowafy

Anesthesia and Surgical Intensive CareDepartment, Faculty of Medicine, Zagazig University, Egypt.

Corresponding author: **Abdelhamid M.Abdelhamid**,

Email: abdulhamidmuhammad326@gmail.com

ABSTRACT

Background: Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection inside ICU. The aim of the present study was to assess the Relation between levels of procalcitonin and C-reactive protein as markers with severity of sepsis and septic shock.

Patients and methods: This observational study was involved 60 patients who diagnosed with sepsis or septic shock and admitted to Surgical intensive care unit, Zagazig University Hospitals, Egypt. Procalcitonin and C-reactive protein levels were estimated in the 1st, 3rd, and 5th ICU day. APACHE II as well as SOFA Scores were estimated on ICU admission.

Results: Patients were classified according to the need for mechanical ventilation (MV group and non-MV group), CRP showed no significant difference between the two groups on the first day (100.51 and 83.21 mg/dl respectively- p=0.108). The remaining readings showed a significant rise in the patients that needed invasive mechanical ventilation. Serum PCT levels showed a significant rise in the MV group throughout the all study readings ($p < 0.001$). Likewise, SOFA score recordings were significantly higher in the MV patients ($p < 0.001$). On assessment of the predictors for vasopressor need, the highest sensitivity was reported for 3rd day CRP (84.1% - cut off = 62.01 mg/dl), and 5th day PCT (84.1% - cutoff = 0.505 ng/ml). Slight decrease in sensitivity (81.8%) was reported with the application of 1st day PCT and 3rd day SOFA.

Conclusion: PCT and CRP can be used as a prognostic markers for evaluating the prognosis of patients with sepsis and septic shock.regarding need for vasopressors the highest sensitivity was reported for 3rd day CRP and fifth day PCT, however the length of stay was found to be highly correlated with 3rd day PCT, also 1st day PCT value was better to Predict need for Mechanical ventilation.

Keywords: Sepsis; SOFA score; PCT; CRP

INTRODUCTION

Sepsis is a common cause of mortality and morbidity worldwide. The prognosis depends on underlying health status and host defences, prompt and adequate control for source of infection, and appropriate and early empiric antimicrobial therapy**(1)**.The site of infection in patients with sepsis may be an important determinant of outcome, with sepsis from a urinary tract infection generally being associated with the lowest mortality rates, while highest mortality in those with sepsis from ischemic bowel also when the source of infection was unknown **(2)**.

Procalcitonin (PCT) and C-reactive protein are acute-phase reactants that are elevated in severe bacterial infections. In most clinical assays, the reference range of PCT is below detectable. Measurement of PCT and C-reactive protein (CRP) at onset and on the following days of treatment can predict survival of patients and can be used as prognostic tools **(3)**.

Appropriate antibiotic therapy has a beneficial impact on bacteremia sepsis. In contrast, prior antibiotic therapy [may be associated with increased mortality, at least among patients with Gram negative sepsis because patients who have received prior antibiotic therapy are more likely to have higher rates of antibiotic resistance, making it less likely that appropriate antibiotic therapy will be chosen empirically for patients with suspected sepsis **(4)**.

Failure to aggressively try to restore perfusion early (ie, failure to initiate early goal-directed therapy) may also be associated with mortality. A severely elevated lactate (>4 mmol/L) is associated with a poor prognosis in patients with sepsis **(5)**.

The most common diagnosis associated with readmission at 90 days included heart failure, pneumonia, acute exacerbations of chronic obstructive pulmonary disease, and urinary tract infection. Sepsis survivors may also be at increased risk of major cardiovascular events and stroke when compared with patients hospitalized with non-sepsis diagnosis **(6)**.Therefore, this study aimed to assess the Relation between levels of procalcitonin and C-reactive protein as markers with severity of sepsis and septic shock.

PATIENTS AND METHODS

This observational study was involved 60 patients who diagnosed with sepsis or septic shock and admitted to Surgical intensive care unit, Zagazig University Hospitals, Egypt. The whole study design was approved by the Local Ethical Committee and Institutional Review Board, Faculty of Medicine, Zagazig University. Confidentiality and personal privacy were respected in all levels of the study.

Inclusion and exclusion criteria:

Patients older than 18 years who met clinical diagnostic criteria for sepsis or septic shock. Sepsis characterized by an acute change of 2 points or greater in Sequential Organ Failure Assessment (SOFA) score. Septic shock include sepsis with fluid-unresponsive hypotension, serum lactate level greater than 2 mmol/L, and the need for vasopressors to maintain mean arterial pressure of 65 mm Hg or greater. While, patients exhibited an unrecoverable state of death andpatients diagnosed with other cardiovascular or cerebrovascular disease were excluded.

Methods:

On admission, full medical history; general and local clinical examination were done. Laboratory investigations were performed, C-reactive protein and procalcitonin levels repeated at 1st, 3rd, and 5th days. Radiological investigations as chest X ray (CXR).CT chest and other radiological studies for suspected sources of sepsis.

All patients were subjected to the management protocol of Surviving Sepsis Campaign Bundle Update and the local ICU protocol guided by ICU physicians with no intervention from investigators.

The sequential organ failure assessment (SOFA) score was used to demonstrate organ dysfunction, the score is based on six different scores. Each system scored from 0 to 4. A SOFA score of 2 or more indicated organ dysfunction. Acute Physiology and

Chronic Health Evaluation (APACHE II) score was estimated within 24 hours from patient ICU admission.

Statistical analysis:

Data analyzed using the statistical package for the Social Sciences (SPSS) version 26 (IBM Corp., Armonk, NY, USA). Mann-Whitney test, Chi square (x2) test and Exact test were performed.. ROC curve was constructed with area under curve analysis performed to detect best cutoff value of significant parameters for detection of mortality and morbidity. P-values less than 0.05 were considered as statistically significant.

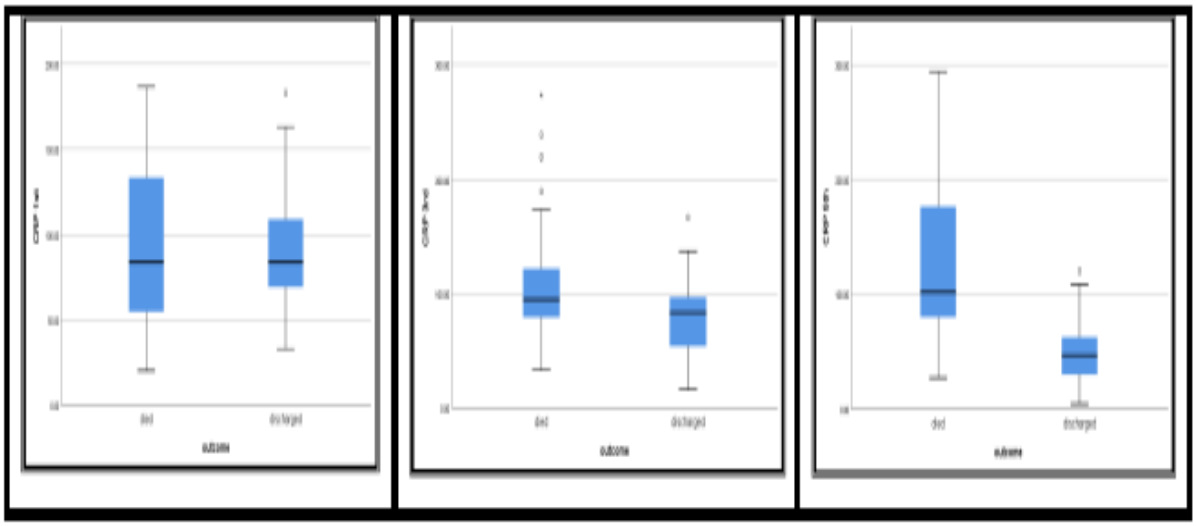
RESULTS

The present study showed subsequent readings of CRP showed a significant elevation in the non-survivors' group for 3rd and5th days respectively**(Figure 1)**. The three procalcitonin readings were significantly elevated in the non-survivors compared to the survivors' group ($p < 0.001$) **(Figure 2)**. SOFA score recordings were significantly higher in the non-survivors ($p < 0.001$) **(Figure 3)**.

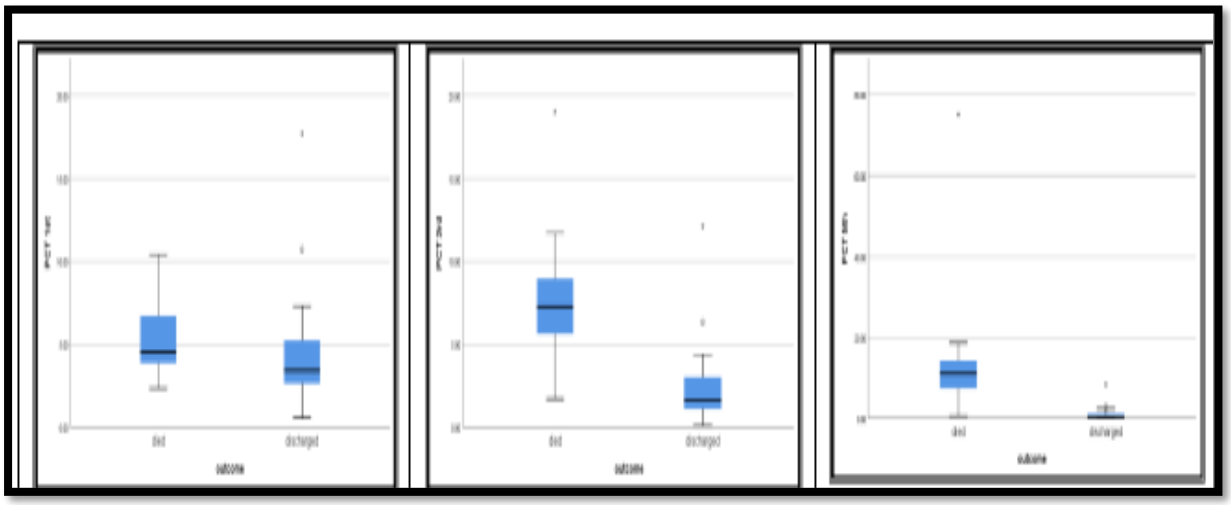
On classifying our patients according to the need for vasopressor; the first group included patients that needed it, while the other one included patients didn`t need vasopressors. First-day CRP show no significant difference between the two groups ($p = 0.207$). Conversely, both 3rd and 5th day readings were significantly elevated in the first group that needed vasopressors. Regarding PCT, it showed significant elevation in patients who needed vasopressor use ($p < 0.001$).SOFA score showed significant increase in patients who needed vasopressors ($P < 0.001$) **(Table1)**.

Patients were classified according to the need for mechanical ventilation (MV group and non-MV group), CRP showed no significant difference between the two groups on the first day (100.51 and 83.21 mg/dl respectively- p=0.108). The remaining readings showed a significant rise in the patients that needed invasive mechanical ventilation. Serum PCT levels showed a significant rise in the MV group throughout the all study readings ($p < 0.001$). Likewise, SOFA score recordings were significantly higher in the MV patients ($p < 0.001$) **(Table 2)**.

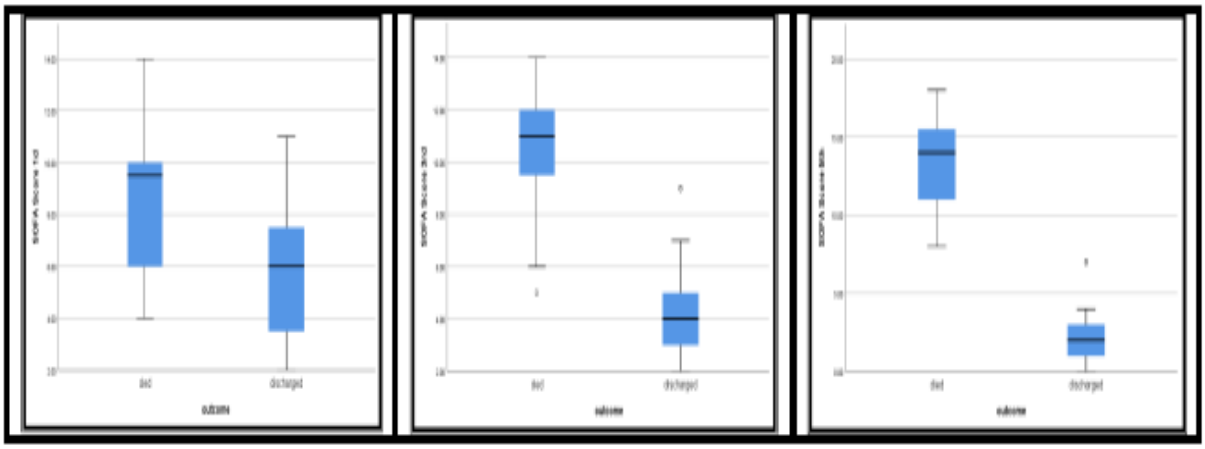
On assessment of the predictors for vasopressor need, the highest sensitivity was reported for 3rd day CRP (84.1% - cut off = 62.01 mg/dl), and fifth day PCT (84.1% - cut off = 0.505 ng/ml). Slight decrease in sensitivity (81.8%) was reported with the application of 1st day PCT and 3rd day SOFA**(Figure 4)**.The need for mechanical ventilation was best predicted by 1st day PCT, which had sensitivity and specificity of 80.6 and 66.7% respectively, using a cut-off value of 3.45ng/ml. Other lower prediction accuracy was noted with the application of SOFA, and it yielded sensitivities ranging between 75 and 77.8%**(Figure 5)**.



Figure(1):1st, 3rd and 5th days CRP in survivor and non-survivor groups



Figure(2):1st, 3rd and 5th days PCTin survivor and non-survivor groups



Figure(3):1st, 3rd and 5th days SOFA Score in survivor and non-survivor groups

Table (1): CRP, PCT and SOFA Score readings in patient who needed and those who didn`t need vasopressors use

variables		Need for vasopressors		
		Yes patients) (no.= 44	No (no.= 16 patients)	P value
CRP (mg/dl)	1st day	97.77 ± 44.24	82.10 ± 32.23	0.207
	3rd day	102.22 ± 50.94	65.41 ± 27.22	0.005
	5th day	97.15 ± 68.82	39.85 ±22.98	< 0.001
PCT (ng/dl)	1st day	5.42 ± 2.75	2.85 ± 2.29	< 0.001
	3rd day	5.45 ± 3.77	1.44 ± 1.42	< 0.001
	5th day	7.95 ± 11.88	0.45 ± 0.66	< 0.001
SOFA Score	1st day	7.80 ± 2.63	4.06 ± 1.39	< 0.001
	3rd day	8.20 ± 3.59	3.25 ± 1.00	< 0.001
	5th day	8.68 ± 5.68	1.44 ± 1.03	< 0.001

No. = number, CRP = C-reactive Protein, PCT= Procalcitonin, SOFA = Sequential organ failure assessment, Data expressed as : mean ± standard deviation, P < 0.05 is significant

Table (2): CRP, PCT and SOFA Score in MV group and non-MV group

variables		Need for invasive mechanical ventialtion		
		Yes (no. = 36 patients)	No (no. = 24 patients)	P value
CRP (mg/dl)	1st day	100.51± 45.90	83.21± 32.67	0.108
	3rd day	103.63 ± 54.50	75.57 ± 31.82	0.033
	5th day	107.55 ± 70.64	43.35 ± 26.45	< 0.001
PCT (ng/dl)	1st day	5.29 ± 2.14	3.91 ± 3.58	0.001
	3rd day	5.82 ± 3.77	2.22 ± 2.51	< 0.001
	5th day	9.25 ± 12.75	1.00 ± 1.74	< 0.001
SOFA SCORE	1st day	8.19 ± 2.59	4.71 ± 1.85	< 0.001
	3rd day	8.94 ± 3.43	3.79 ± 1.64	< 0.001
	5th day	9.86 ± 5.52	2.08 ± 1.86	< 0.001

No. = number, CRP = C-reactive Protein, PCT= Procalcitonin, SOFA = Sequential organ failure assessment, Data expressed as : mean ± standard deviation, P < 0.05 is significant

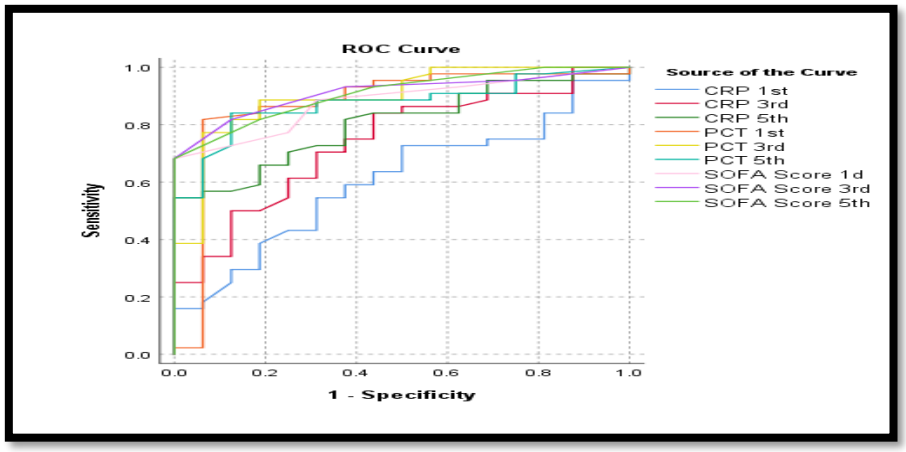


Fig. (4): ROC curve for prediction of vasopressors needs using SOFA, PCT and CRP.

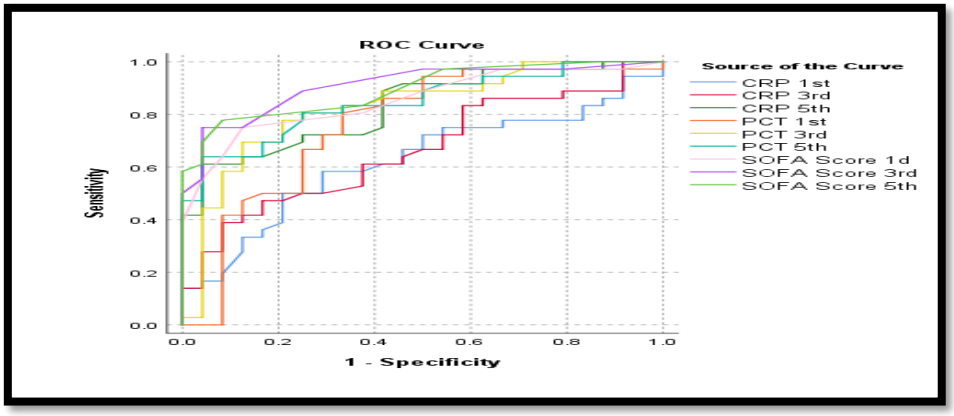


Fig. (5): ROC curve for prediction of MV need using SOFA, PCT and CRP.

DISCUSSION

Sepsis and septic shock are the most common causes of death in hospital. Currently, the diagnosis of such diseases is primarily based on biochemical indexes or pathogen detection through bacterial culture. Relevant biochemical tests lack high specificity, which leads to increased uncertainty in the diagnostic process**(7).**

Patients with sepsis and septic shock often exhibit cardiovascular and cerebrovascular diseases or endocrine diseases, the diagnostic process is highly complex and variable. Rapid and accurate disease diagnosis, as well as timely medical intervention, can help clinicians confirm the disease in an appropriate timeframe and make necessary treatment decisions **(8)**.

C-reactive protein (CRP) is a traditional biomarker which is elevated in inflammatory states including rheumatoid arthritis and infection. Aside from its roles as a biomarker, CRP also functions as a part of the defense mechanism against inflammation and pathogen invasion **(9)**.

Procalcitonin is used as an indicator for antibiotics treatment because the level of PCT is elevated in bacterial infections. Accordingly, high early levels of PCT in sepsis have been suggested to be associated with unfavorable prognosis (**10).**

The main aim of this study was to assess the Relation between levels of procalcitonin and C-reactive protein as markers with severity of sepsis and septic shock. The current study showed that during ICU stay 36 patients (60.0%) need respiratory support with invasive mechanical ventilation, the mean for ventilator days

was 7.47 (range 2-16), 44 patients (73.3%) were in need for circulatory support with vasopressor, the mean Length of stay was 9.45 (range 5 - 16), Regarding the outcome, ICU mortality was 24 patients (40.0%) and 36 patients (60.0%) were discharged. The mean Predicted mortality by APACHE II was 28.23 % (range 7.6% - 63.90%).

In the study of **Schuetz et al. (11)** revealed among the 820 patients enrolled, there were 184 deaths account for 22% also among the 646 patients in the ITD (intention-to-diagnose) population, there were a total of 107 deaths 17% mortality rate. The median stay in the ICU was 4 days and patients stayed for a median of 11 days in the hospital.

In the study of **Poddar et al. (12)** found all patients required organ support in the ICU; 160 (94.1%) required mechanical ventilation, 154 (91.7%) required vasoactive drugs, 84 (49.1%) required renal replacement therapy (at least one session) and 130 (76.02%) required transfusion of any blood product.

Furthermore, **Huanget al. (13)** revealed that the average length of ICU stay was 12.5± 9.1 days, and the average total length of hospital stay was 23± 14.9 days. Ten patients required endotracheal tube insertion (20.8%), and the overall mortality was 16.7% (8 patients, 7 of whom had septic shock).

In the study of **Sep Net Critical Care Trials (14)** revealed ICU and hospital mortality of septic shock was 44.3 and 50.9 %, respectively. The median lengths of stay in the ICU and in the hospital were longer in patients with septic shock. The subgroup of patients with septic shock was treated in the ICU for 12 days and in the hospital for 24 days.

Based on **Pittard et al. (15)** study, seven hundred and fifty-four patients were screened and a total of 186 with septic shock identified. There was a hospital mortality rate of 23.7% and ICU mortality of 17.7%. Most admissions were from inter-hospital transfers, followed by admissions through the emergency department. A greater proportion of non-survivors were mechanically ventilated (P=0.027), tended to have higher SOFA scores (P=0.023), APACHE III scores (P=0.0001), and had a longer duration of vasopressor therapy (P <0.002).

The current study showed the first day value of CRP show no significant difference regarding ICU mortality, need for vasopressor, need for invasive mechanical ventilation and length of stay, however the third and fifth CRP value as well as PCT readings were higher in non-survivor, patients who needed vasopressors and mechanical ventilations also who stayed longer in our ICU.

In **Davidson et al. (16)** study on Post-operative support requirements for patient with delayed sternal closure due to wound infection, demonstrated by higher median vasoactive-inotropic score (VIS) at 24, 48, and 72 hours' post-operation, and longer median intubation time, cardiac intensive care unit (CICU) stay, and hospital stay. Spearman correlation testing was utilized to assess for associations between PCT and CRP at 24 and 72 hours and post-operative support. PCT at 72 hours showed a statistically significant moderate positive correlation with VIS at 24 and 72 hours ($r=0.48$, $p<0.0001$; $r=0.44$, $p<0.0005$), as well as weaker correlations with intubation time ($r=0.40$, $p<0.005$), peak lactate ($r=0.40$; $p<0.005$), and length of CICU ($r=0.39$; $p<0.005$) and hospital stay ($r=0.29$; $p<0.05$). PCT at 24 hours was also weakly correlated with VIS at 24($r=0.40$, $p<0.005$) and 72 hours ($r=0.31$, $p<0.05$), intubation time ($r=0.29$, $p<0.05$). CRP did not demonstrate a statistically significant positive correlation with any measure of post-operative support.

The need for mechanical ventilation was best predicted by 1st day PCT, which had sensitivity and specificity of 80.6 and 66.7% respectively, using a cut-off value of 3.45 ng/ml.

In the study of **Aygun, (17)** revealed a statistically significant relationship between PCT levels in the first laboratory analysis performed during admission regarding ventilator support, inotropic drug use, mortality, acute respiratory failure, hospitalization in the intensive care unit, p values were $p \leq 0.001$, $p \leq 0.001$, $p \leq 0.001$, $p \leq 0.001$, $p = 0.002$, respectively. There was a statistically significant relationship between CRP levels during admission and MV support, inotropic drug use, mortality, acute renal failure (ARF), hospitalization in the intensive care unit, CRRT. p values were $p = 0.001$, $p = 0.040$, $p = 0.000$, $p = 0.022$, $p \leq 0.001$, $p \leq 0.001$, respectively. According to logistic regression analysis, the odds ratios were OR: 2.364 for mortality. Analysis of ROC curves of correlation between mortality and biomarkers. PCT at a cut-off value of 6.38 ng/dl has a sensitivity of 81.8% and a specificity of 80.8% (area under curve 0.838). CRP showed 63.6% sensitivity and 61.0% specificity.

In the study of **Ruiz-Rodríguez et al. (18)** found procalcitonin clearance was higher in survivors than in non-survivors, with significant differences at 24 h (73.9 [56.4–83.8] % vs 22.7 [−331–58.4], $p < 0.05$) and 48 h (81.6 [71.6–91.3] % vs −7.29 [−108.2–82.3], $p < 0.05$). The area under the ROC curve was 0.74 (95%CI, 0.54–0.95, $p < 0.05$) for procalcitonin clearance at 24 h, and 0.86 (95%CI, 0.69–1.0, $p < 0.05$) at 48 h.

Furthermore, **Poddar et al. (12)** revealed that receiver operating characteristic curves were constructed to identify the most discriminatory values of change in procalcitonin and change in SOFA score. The area under the curve (AUC) for change in PCT to predict survival was 0.64 (95% confidence interval [CI]: 0.54–0.73; $P = 0.007$) as compared to 0.78 (95% CI: 0.71–0.86; $P < 0.01$) for change in SOFA score. Percentage change in PCT gives a C–statistic of 0.73 (95% CI: 0.65–0.82; $P < 0.01$). 50% and 75% fall in PCT value yielded 68% and 47% sensitivity and 64% and 93% specificity respectively to predict survival at 28 days. Among those patients in whom the absolute fall in procalcitonin was >1 ng/ml, a 70% fall in procalcitonin predicted survival with 75% sensitivity and 64% specificity.

CONCLUSION

PCT and CRP can be used as a prognostic markers for evaluating the prognosis of patients with sepsis and septic shock.regarding need for vasopressors the highest sensitivity was reported for 3rd day CRP and fifth day PCT, however the length of stay was found to be highly correlated with 3rd day PCT, also 1st day PCT value was better to Predict need for Mechanical ventilation.

No Conflict of interest.

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