Journal of Cardiovascular Disease Research

ISSN:0975-3583,0976-2833 VOL12,ISSUE 06,2021

Evaluation of Procalcitonin and C-reactive Protein as prognostic markers in patients with sepsis and septic shock

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ABSTRACT

Background: Sepsis and the inflammatory response that ensues can lead to multiple organ dysfunction syndrome and death. procalcitonin (PCT) and C-reactive protein (CRP) being the most frequently used biomarkers.The aim of the present study was to evaluate the usefulness of procalcitonin and C-reactive protein levels as prognostic markers in patients with sepsis and septic shock .

Patients and methods: The study included 60 patients who were admitted to surgical Intensive Care Unit, Anesthesia and Intensive Care Department, Zagazig University Hospitals. All patients underwent a full clinical examination and data collection about age, sex, BMI, hospital diagnosis, source of sepsis and APACHE II as well as SOFA Scores on ICU admission. Procalcitonin and C-reactive protein levels were estimated in the 1st, 3rd, and 5th ICU day.

Results: As regard to the admitting diagnosis; pneumonia was the commonest cause for sepsis and septic shock with (38 patients - 63.33%) followed by urinary tract infection (16 patients - 26.6) then lower limb cellulitis with (12 patients - 20%) also single source for sepsis and septic shock was found in (31 patients -51.66%) and (29 patients – 48.33%) was diagnosed with two or more sources. There was a correlation between our patients` PCT, CRP and SOFA Score readings with the length of stay in ICU, there was high positive correlation between PCT and length of stay especially in the 3rd day (correlation coefficient = 0.508), in addition there was high significant correlation between SOFA Score and length of stay in ICU especially in the 5th day (correlation coefficient = 0.476).

Conclusion: Kinetic studies of PCT and CRP can improve sensitivity and accuracy when evaluating the prognosis of patients with sepsis and septic shock in addition PCT was found to be better than CRP for prediction of mortality especially in the 5th day PCT value.

Keywords: CRP; PCT ;SOFA Score; Septic Shock

INTRODUCTION

Sepsis is a life threatening organ dysfunction evoked by abnormal host response to infection, and the Sequential Organ Failure Assessment (SOFA) score is used to calculate the degree of organ dysfunction in sepsis **(1)**. Septic shock is defined as a subset of sepsis in which underlying circulatory and cellular metabolism abnormalities are profound enough to substantially increase mortality **(1)**. Degree of shock can be evaluated by measuring mean arterial blood pressure as a circulatory abnormality and serum lactate level as a cellular metabolic abnormality **(2)**.

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 and is challenging for clinicians. Importantly, the inability to accurately diagnose according to exact biochemical indicators often leads to delay or failure to carry out the appropriate clinical treatment, and clinicians cannot assess changes in blood conditions with sufficient time to modify treatment **(3)**.

Blood cultures are the gold standard to diagnose infection, only 30% blood cultures of sepsis patients are positive **(4)**. Early identification of patients at a high risk of dying from sepsis may help initiate rapid and appropriate therapeutic interventions and may decrease the morbidity and mortality caused by sepsis **(5)**.

Non-specific inflammation indexes, such as procalcitonin (PCT) and C-reactive protein (CRP), have been widely used in the clinical setting to identify infections **(4)**.

Procalcitonin (PCT), a prohormone of calcitonin, is encoded by the calcitonin-I (CALC-1) gene on chromosome 11, and comprises 114–116 amino acids. C-reactive protein (CRP) is an acute-phase

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reactive protein that can interact with capsule C polysaccharides of Streptococcus pneumonia. Among the clinically useful biochemical detection indexes, PCT has shown superiority as an important reference marker for infection, as well as antibiotic management guidance **(6)**. Furthermore, some studies have shown that changes in PCT and CRP concentrations are related to the prognosis of patients with sepsis **(7)** and that could be used to improve accuracy of judgment regarding the prognosis of infection **(8)**.

Therefore, this study aimed to evaluate the usefulness of procalcitonin and C-reactive protein levels as prognostic markers in patients with sepsis and septic shock.

PATIENTS AND METHODS

A prospective observational cross-sectional study was included 60 patients admitted to Surgical intensive care unit, Zagazig University Hospitals, Egypt. A written informed consent was obtained from all the patients (or their guardians if unconscious) before inclusion in the study, explaining the value of the study.

Inclusion criteria:

Adult patients older than 18 years. Both sexes were included. Patients who met clinical diagnostic criteria for sepsis or septic shock. Sepsis was defined as evidence of infection plus life-threatening organ dysfunction, clinically 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.

Exclusion criteria:

Patient who exhibited an unrecoverable state of death or dying. Patient who were diagnosed with other cardiovascular or cerebrovascular disease.

Operative Assessement: On admission, the following was done and recorded for all participants (to be repeated when appropriate):detailed medical history; including history of previous ICU admission, associated comorbidities and reason of ICU admission. Full general and local clinical examination were done. Need for vasoactive therapy.

Laboratory investigations

Complete blood picture (CBC), Arterial blood gases analysis (ABGs) on a daily basis, Serum Sodium (Na) and Potassium (K), Liver and Kidney function tests, Serum lactate and C-reactive protein and procalcitonin levels repeated at 1st, 3rd, and 5th days.

Radiological investigations

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 **(9)**.

The sequential organ failure assessment (SOFA) score:

SOFA score was used to demonstrate organ dysfunction, the score is based on six different scores, one for each system; respiratory, cardiovascular, hepatic, coagulation, renal and neurological systems. Each system scored from 0 to 4. A SOFA score of 2 or more indicated organ dysfunction. Sepsis was defined as having SOFA score of 2 or more plus evidence of infection.

Acute Physiology and Chronic Health Evaluation (APACHE II) score:

APACHE II score was recorded within 24 hours from patient ICU admission.

Statistical analysis

Data was coded and entered using the statistical package for the Social Sciences (SPSS) version 26 (IBM Corp., Armonk, NY, USA). Data was summarized using mean, standard deviation, median, minimum and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the non-parametric Mann-Whitney test. For comparing categorical data, Chi square (x2) test was performed. Exact test was used instead when the expected frequency is less than 5. 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.

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RESULTS

The present study showed mean age of the patients was 67.37 ± 12.9, The mean BMI was 28.27 ± 6.52, The mean APACHE II score was 16.93 ± 5.92 on admission, 31.7% of the patients were admitted with sepsis and 68.3% admitted with septic shock **(Table 1)**. Pneumonia was the commonest cause for sepsis and septic shock (63.33%) followed by urinary tract infection (26.6%) then lower limb cellulitis (20%). Also 51.66% of the patients had a single cause for sepsis and 48.33% of the patients had two or more causes for sepsis **(Table 2)**.

During ICU stay 36 patients (60.0%) needed respiratory support with invasive mechanical ventilation, the mean for ventilator days was 7.47 ± 3.36 days, 44 patients (73.3%) were in need for circulatory support with vasopressor, the mean Length of stay in ICU was 9.45 ± 3.50 days, Regarding the outcome, mortality rate was 24 patients (40.0%). The mean Predicted mortality by APACHE II was 28.23% ± 16.39% **(Table 3)**.

Patients were classified according to outcome to survivors and non survivors, there was highly significant statistical difference with increasing of age in non-survivors' group (P = 0.003), also APACHE II score on admission (P < 0.001), length of stay in ICU (P = 0.001), ventilator days (P = 0.018) showed high significant elevation in non survivors when compared to survivors' groups. In addition, need for vasopressors (P < 0.001), two or more causes of sepsis (P = 0.004) and septic shock as admitting diagnoses (P < 0.001) were highly presented in non-survivors' group **(Table 4)**.

There was no significant difference was detected between the survivors and non-survivors regarding first day CRP in the two groups. However, the subsequent readings showed a significant elevation in the non-survivors' group for the third and fifth days respectively. The three procalcitonin readings were significantly elevated in the non-survivors compared to the survivors' group (p < 0.001). Likewise, SOFA score recordings were significantly higher in the non-survivors (p < 0.001) **(Table 5)**.

There was a correlation between our patients` PCT, CRP and SOFA Score readings with the length of stay in ICU, there was high positive correlation between PCT and length of stay especially in the 3rd day (correlation coefficient = 0.508), in addition there was high significant correlation between SOFA Score and length of stay in ICU especially in the 5th day (correlation coefficient = 0.476) **(Figure 1,2,3)**.

For prediction of mortality as show in table (9) that SOFA Score on the 5th day was the best predictor (cut off = 7.5 - AUC = 1) then 3rd day SOFA (AUC = 0.970), regarding changes in the serum PCT and CRP levels in survivors and non survivors groups we found that PCT is better than CRP as predictor for mortality especially in the 5th day (cut off = 3.69 ng/ml - AUC = 0.967), then 1st day PCT (AUC = 0.701) however 5th day CRP is the best to predict mortality (sensitivity 75% - AUC = 0.848) among CRP readings **(Table 6,Figure 4)**.

Table (1): Demographic data among the studied patients

Characteristics		Participant no. = 60 patients
Age in years		67.37 ± 12.9
BMI kg/m²		28.27 ± 6.52
APACHE II score (points)		16.93 ± 5.92
Sex	Male	27 (45.0%)
	Female	33 (55.0%)
Diagnosis	Sepsis	19 (31.7%)
	septic shock	41 (68.3%)

data expressed as: mean ± standard deviation, number and percentage

Table (2): causes of sepsis and septic shock

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Causes	Participant no. = 60 patients (%)
Pneumonia	38 (63.33%)
UTI	16 (26.66%)
LL cellulitis	12 (20%)
Diabetic foot	11 (18.3%)
Peritonitis	9 (15%)
Infected bed sores	6 (10%)
CRBSI	2 (3.3%)
Patients with single source	31 (51.66%)
Patients with multiple sources	48.33%) 29

No. = number, UTI = urinary tract infections, LL = lower limb, CRBSI = catheter related blood stream infections, Data expressed as number and percentage

Table (3): Description of patient's data

Data collected		Participant (60 patients)
Need for mechanical ventilation	Yes	36 (60.0%)
	No	24 (40.0%)
ventilator days		7.47 ± 3.36
need for vasopressor	Yes	44 (73.3%)
	No	16 (26.7%)
Length of stay		9.45 ± 3.50
Condition on ICU discharge	Non-survivor	24 (40.0%)
	alive	36 (60.0%)
Predicted mortality by APACHE II		28.23% ± 16.39%

Data expressed as: number and percentage, mean ± standard deviation

Table (4): Relations between collected data to mortality

Variables		outcome		P value
		Non-survivor (no. = 24 patients)	Survivors (no. = 36 patients)	
		Mean (± SD) or (%)	Mean (± SD) or (%)	
Sex	Male	10 (37.0%)	17 (63.0%)	0.672
	female	14 (42.4%)	19 (57.6%)	
BMI kg/m²		28.22 ± 7.92	28.32 ± 36.70	0.784
Age in years		72.27 ± 10.12	62.47 ± 80.00	0.003
APACHE II (points)		20.43 ± 5.10	14.17 ± 25.00	< 0.001
Predicted mortality by APACHE II		38.16% ± 15.39	21.81% ± 53.30	< 0.001
Length of stay		11.20 ± 3.56	8.10 ± 15.00	0.001
ventilator days		8.52 ± 3.45	5.60 ± 9.00	0.018
Need for vasopressors	Yes	23 (63.9%)	13 (36.1%)	<0.001
	no	1 (4.2%)	23 (95.8%)	
No. of sources	2 sources or more	17 (70.8%)	12 (33.3%)	0.004

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	single source	7 (29.2%)	24 (66.7%)	
Admitted diagnosis	Sepsis	1 (5.3%)	18 (94.7%)	< 0.001
	Septic shock	23 (56.1%)	94.7%) 18	

No. = number, SD = standard deviation, (%) = percent from total number, Data expressed as: mean ±standard deviation, number and percentage, P < 0.05 high significant

Table (5): CRP, PCT and SOFA Score in survivors and non-survivors

Variables		outcome		P value
		Non-survivor (no. 24 patients)	Survivors (no = 36 patients)	
CRP (mg/dl)	1st day	95.01 ± 50.12	92.64 ± 35.76	0.964
	3rd day	112.53 ± 62.65	78.99 ± 30.30	0.042
	5th day	128.53 ± 75.37	50.76 ± 30.41	< 0.001
PCT (ng/ml)	1st day	5.53 ± 2.29	4.21 ± 3.10	0.009
	3rd day	7.41 ± 3.61	2.37 ± 2.17	< 0.001
	5th day	13.45 ± 13.85	0.96 ± 1.47	< 0.001
SOFA Score	1st day	8.50 ± 2.64	5.67 ± 2.47	< 0.001
	3rd day	10.71 ±2.53	4.33 ± 1.88	< 0.001
	5th day	13.37 ± 2.72	2.33 ± 1.62	< 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

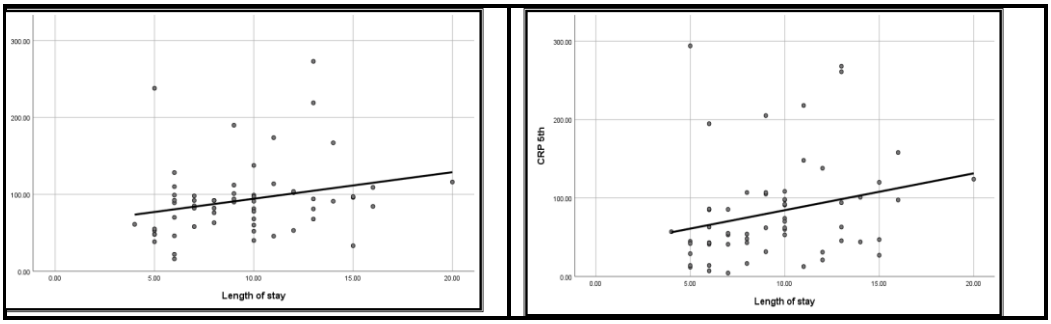

Figure (1): Relationship between 3rd day and 5th day CRP and length of stay.

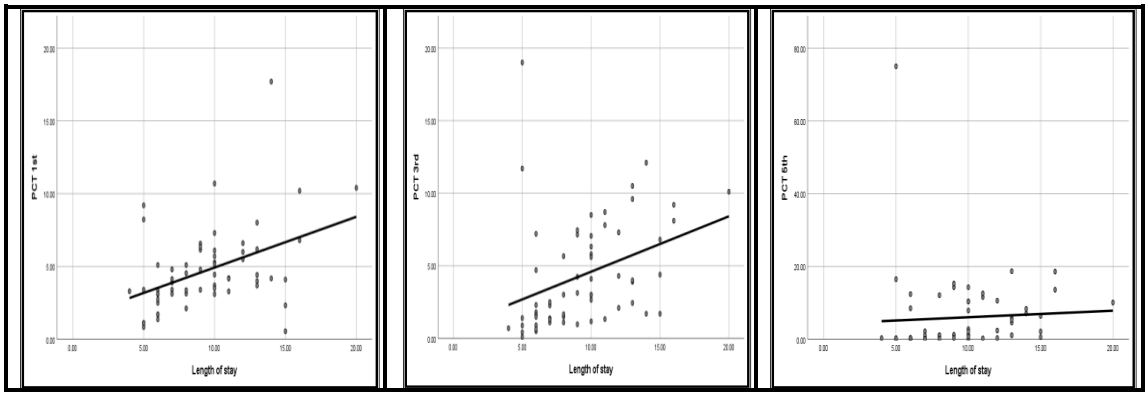

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Figure (2): Relationship between 1st,3rd and 5th days PCT and length of stay

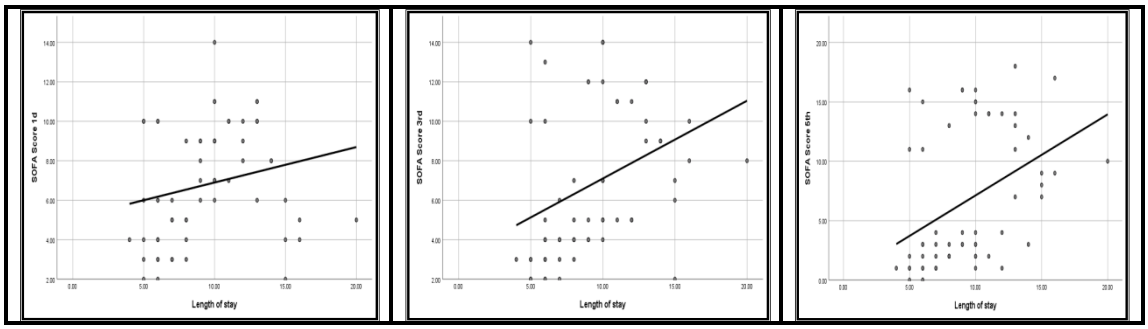

Figure (3): Relationship between 1st,3rd and 5th days SOFA Score and length of stay.

Table (6): Prediction of mortality using SOFA, PCT and CRP

Variables		Cut off	Sensitivity %	Specificity %	Area Under the Curve (AUC)	95% Confidence Interval		P value
						Lower Bound	Upper Bound	
CRP (mg/dl)	1st day	---	---	---	0.497	0.336	0.657	0.966
	3rd day	93.15	54.2	69.4	0.656	0.508	0.803	0.038
	5th day	85.75	75	86.1	0.848	0.747	0.950	< 0.001
PCT (ng/dl)	1st day	3.45	87.5	55.6	0.701	0.569	0.833	0.003
	3rd day	4.545	83.3	94.4	0.912	0.834	0.990	< 0.001
	5th day	3.69	95.8	97.2	0.976	0.938	1.013	< 0.001
SOFA Score	1st day	8.5	62.5	83.3	0.784	0.665	0.903	< 0.001
	3rd day	7.5	87.5	94.4	0.970	0.934	1.005	< 0.001
	5th day	7.5	100	100	1.000	1.000	1.000	< 0.001

CRP = C-reactive Protein, PCT= Procalcitonin, SOFA = Sequential organ failure assessment, P < 0.05 is significant

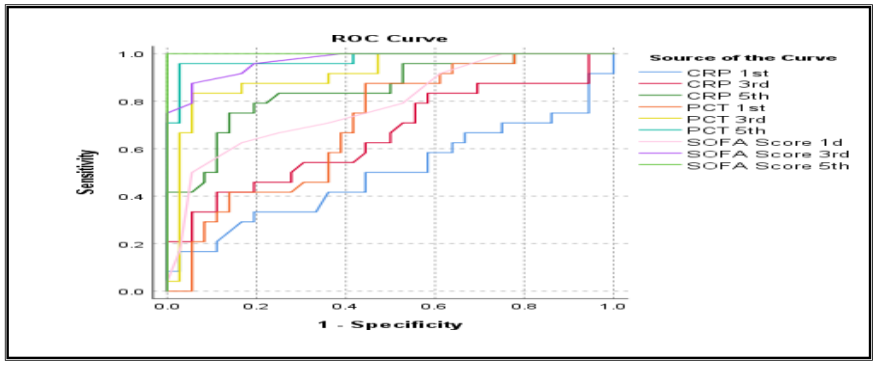

Figure (4): ROC curve for prediction of mortality using SOFA, PCT and CRP.

DISCUSSION

Sepsis and septic shock is challenging for clinicians. Importantly, the inability to accurately diagnose according to exact biochemical indicators often leads to delay or failure to carry out the appropriate clinical treatment, and clinicians cannot assess changes in blood conditions with sufficient time to modify treatment **(10).**

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Bacterial culture has high specificity, but requires an extended incubation period; this leads to treatment delay, as well as antibiotic misuse and abuse. For example, according to the specificity of the biochemical indicators to determine the severity of infection, timely control of infection can be achieved through effective antibiotics or surgery to reverse the progress of the disease; clinicians can also monitor changes in disease (**3)**.

The main aim of this study was to evaluate the usefulness of procalcitonin and C-reactive protein levels as prognostic markers in patients with of sepsis and septic shock. The present study showed that as regard diagnosis; pneumonia was the commonest cause for sepsis and septic shock with (38 patients - 63.33%) followed by urinary tract infection (16 patients - 26.6) then lower limb cellulitis with (12 patients - 20%) also single source for sepsis and septic shock was found in (31 patients -51.66%) and (29 patients – 48.33%) was diagnosed with two or more sources. Our results were supported by study of **Azevedo et al., (11)** reported that nineteen patients were in medical and nine were in surgical ICU; in 13 patients (46.4%) the source of sepsis was pulmonary, abdominal in seven patients (25.0%), urinary infection in five (17.9%) and soft tissue in three patients (10.7%). Fifteen patients had sepsis and septic shock.

However, in the study of **Siddiqui et al.(12)** stated in 26.9% of patients, the primary diagnosis was cardiovascular disease, while 19.7% had pneumonia or bronchiolitis, 11.3% suffered from sepsis or septic shock, 10.1% from central nervous system (CNS) infections and 10.1% had CNS disease, 5.3% had gastrointestinal disorders, 0.6% kidney disease and 15.5% suffered from miscellaneous causes as the study was performed in pediatric ICU.

The present study showed that according to outcome, there was highly significant increase of age in non- survivors' group (P=0.003), also APACHE II score on admission ($P < 0.001$), length of stay in ICU ($P = 0.001$), ventilator days ($P = 0.018$) showed high significant elevation in non survivors when compared to survivors' groups. In addition, need for vasopressors ($P < 0.001$), two or more causes of sepsis ($P = 0.004$) and septic shock as admitting diagnosis ($P < 0.001$) were highly increased in non-survivors' group.

Our results were supported by study of **Ryoo et al.(13**) reported that the severity scores, including maximum SOFA and Acute Physiology and Chronic Health evaluation (APACHE) II scores were higher in the non-survivor group (10.0 [8.0–13.0] vs. 7.0 [5.0–10.0], $p < 0.001$; 24.0 [18.0–34.0] vs. 18.0 [13.0–24.0], $p < 0.001$; respectively).

In the study of **Cerceo et al. (14)** reported that septic shock was found in 1,064,790 (1.6%) of the patients included in the study. The average age was 68 years, and there were 49.3% females, Female gender was associated with a lower risk of septic shock (OR 0.76 [0.76–0.77]) as well as acute kidney injury (OR 0.72 [0.72–0.73]), and mortality (OR 0.78 [0.77–0.78]) in hospitalized patients. The reference group for comparison is male gender, also advancing age increased risk of septic shock, acute kidney injury and mortality, and was associated with lower risk of dialysis. For patients with septic shock who underwent dialysis for acute kidney injury, there was a slight increased risk of death.

Furthermore, **Huang et al. (15**) revealed that the significant factors associated with survival in patients with sepsis included APACHE II scores, and the length of ICU stay. Regarding the severity of illness, APACHE II and SOFA scores were compared in the two groups. Both scores were higher in the non-survivors, but only APACHE II scores showed a significant difference. In addition, survivors tended to have shorter ICU stays but longer overall hospital stays than non-survivors. A shorter duration of ICU stay was also a significant factor associated with survival in patients with sepsis in the ICU.

Our results were supported by study of **Cui et al. (8)** reported that on the 2nd, 3rd, and 5th days, the CRP level was higher in the non-survivor group than in the survivor group, the levels of PCT were significantly different between non-survivor and survivor groups, whereas they did not differ between patients in the sepsis and septic shock groups.

Nargis et al.(16) revealed that both serum PCT and CRP showed significant raise of the mean values along with increased severity of the clinical presentations in the study subjects. Significantly higher mean PCT and CRP values were observed in sepsis and septic shock patients. However, a number of studies not able to demonstrate significant relations of PCT or CRP with severity of diseases raised controversies regarding their utility as prognostic markers.

Furthermore, **Jain et al. (17)** demonstrated that procalcitonin value was a better predictor of all-cause short-term mortality than C-reactive protein. Those patients with Procalcitonin levels <7 ng/ml showed higher cumulative survival than those with level greater than or equal to 7 ng/ml (69.1% vs. 39.5%, $p = 0.02$). No such effect was observed in relation to C-reactive protein. Procalcitonin levels greater than or equal to 7 ng/ml predicted mortality with a hazard ratio of 2.6(1.1-6.3).

In the study of **Azevedo et al. (11)** revealed twenty-eight PCT determinations were performed at diagnosis of sepsis, 27 after 24 hours and 26 after 48 hours. The initial concentration was not

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significantly different between survivors' and non-survivors' groups, but the differences between the two groups after 24 and 48 hours were expressively statistically significant. The 24-hour procalcitonin clearance proved to be significantly higher in the survivors' group (3.0 versus 300.0, p = 0.028). Although the 48-hour procalcitonin clearance has shown higher results in the survivors' group when compared to the non-survivors', the difference did not reach statistical significance.

In the study of **Ryoo et al. (13)** stated in univariate logistic regression, CRP increased the 28-day mortality rate it was not an independent predictor of 28-day mortality in multivariate logistic regression analysis. The optimal cut-off values of CRP and PCT in receiver operating characteristic (ROC) curve were 14 mg/dL and 17 ng/dL, respectively. The sensitivity, specificity, positive predictive value, and negative predictive value of CRP were 52.5%, 56.4%, 23.9%, and 82.0%, respectively, and those of PCT were 39.1%, 65.7%, 22.8%, and 80.5, respectively.

CONCLUSION

Kinetic studies of PCT and CRP can improve sensitivity and accuracy when evaluating the prognosis of patients with sepsis and septic shock in addition PCT was found to be better than CRP for prediction of mortality especially in the 5th day PCT value**.**

No Conflict of interest.

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