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Procalcitonin as A Diagnostic and Prognostic Marker of Sepsis in Critically Ill Patients in Intensive Care Unit

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ABSTRACT

Background: Sepsis is a leading cause of mortality in critically ill patients. However, differentiating sepsis from non-infectious triggers of the systemic inflammatory response syndrome (SIRS) is difficult. Procalcitonin is useful biomarker of systemic inflammatory response to infection. Its level rises in response to a proinflammatory stimulus, especially of bacterial origin and not rise significantly with viral or non infectious inflammation.
Objectives: The aim of this study was to determine the relation of procalcitonin (PCT) level with the development of organ failure and mortality in critically ill septic ICU patients
Patients and Methods: The current study was conducted on 60critically ill adult septic patients aged between 18-60 years old of both sex with anticipated stay of >48 hours. All patients were assessed clinically with haemodynamic and full laboratory monitoring, CRP, a PCT level and SOFA score were calculated in the1st and the 4th day of admission.**Results:** There was significant increase in PCT level between three groups and no significant difference between groups as regard CRP. According to SOFA score there was significant difference between three groups. There was a positive correlation between PCT level and SOFA Score (r = 0.924, P = 0.001) while there was no correlation between CRP and SOFA score (r = -0.233, P = 0.091).
Conclusion: PCT is a good diagnostic and prognostic marker of sepsis. PCT shows a closer correlation than that of CRP with the severity of infection and organ dysfunction.
Keywords: Procalcitonin, SOFA, sepsis.

INTRODUCTION

Sepsis is a leading cause of mortality in critically ill patients. Delay in diagnosis and initiation of antibiotics have been shown to increase mortality. However, differentiating sepsis from non-infectious triggers of the systemic inflammatory response syndrome (SIRS) is difficult, especially in critically ill patients who may have SIRS for other reasons[1].

Multiorgan dysfunction syndrome represents a continuum of organ dysfunction from very mildly altered function to total and, rarely, irreversible organ failure and is the major cause of death in the intensive care unit (ICU). Infections were initially thought to be the main cause of multiorgan dysfunction[2].

Procalcitonin (PCT), a 13 kDa protein has been studied as a useful biomarker of systemic inflammatory response to infection. It is the prohormone of calcitonin hormone and its production during inflammation is linked to the bacterial endotoxin and to inflammatory cytokines. The physiological PCT serum level is below 0.5 ng/ml, but the rise to a value higher than 2 ng/ml is indicative of sepsis[3]. The level of procalcitonin rises in response to a proinflammatory stimulus, especially of bacterial origin. It is produced mainly by the cells of the lung and the intestine. It does not rise significantly with viral or non-infectious inflammations. In serum, procalcitonin has a half-life of 25 to 30 hours[4].

C- Reactive protein (CRP) is a member of the class of acute-phase reactants, as its levels rise dramatically during inflammatory processes occurring in the body. This increment is due to a rise in the plasma concentration of IL-6, which is produced predominantly by macrophages as well as adipocytes. It is thought to assist in complement binding to foreign and damaged cells and enhances phagocytosis by macrophage It also play another important role in innate immunity, as an early defense system against infections[5].

The SOFA is a six-organ dysfunction/failure score measuring multiple organ failure daily providing a daily score of 0 to 24 points, each organ is graded from 0 (normal) to 4 (the most abnormal). SOFA was to create a simple, reliable, and continuous score easily obtained in every institution[6].

PATIENTS AND METHODS

The current study was carried out on 60 critically ill adult septic patients aged between 18-60 years old of both sex admitted to I C U of ALZahraa hospital, AL-Azhar University with anticipated stay of >48 hours..

After informed consent from patients or their relatives, patients were subjected to: full medical history,

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general examination including level of consciousness (GCS), pulse, BP. RR and temperature. Routine laboratory investigations (such as CBC, ESR, kidney and liver function), CRP, serum procalcitonin, SOFA (sequential organ failure assessment) were scored in 1^{ST} and 4^{th} day of admission.

Patients included in this study were fulfilling systemic inflammatory response syndrome criteria with two or more of the following:

1-temperature> 38ºC or < 36ºC.2-heart rate >90 beats/ minute.3-respiration >20/min or $paCO_2$ < 32mmHg.4-leukocyte count > 12,000/ mm³, < 4,000/mm³ or > 10٪ immature (band) cells. Patients with liver dysfunction, renal dysfunction or cardiac diseases, patients with history of malignancy, renal or hepatic impairment, trauma or recent surgery were excluded from this study.The treatment of all patients with severe sepsis or septic shock was performed including antimicrobial treatment, fluid resuscitation, vasopressor therapy and mechanical ventilation if needed.

Sampling

Ten milliliters of fasting venous blood samples were taken and divided into parts; 2 ml of venous blood was added to a tube containing EDTA for complete blood count and ESR. 8ml of blood was left to clot, then the serum was separated by centrifugation and stored at -20°C for determination of liver enzymes, blood urea and serum creatinine, , C-reactive protein (CRP), Procalcitonin (PCT).

Complete blood count was determined by cell counter sysmex KX21N (Siemens. Germany), liver enzymes, blood urea and serum creatinine were done using Cobas C311 (Roche .Germany). CRP was detected by turbidmetric technique supplied from Biosystem (spain) with Lot number 09285; using 8897 photometer 5010 ; Germany.

Serum Procalcitonin (PCT) was measured by quantitative sandwich enzyme immunoassay technique supplied from Thermo scientific with Catalog Number. EHPCT 233121216 ; using 1851 Das; Italy (reader) and 16041412 Bio Tek ; USA (washer).

The study was done after approval of ethical board of Al-Azhar University and an informed written consent was taken from each participant in the study.

Statistics

Statistical presentation and analysis of the present study was conducted, using the mean, SD, unpaired student t-test, paired student t-test, linear correlation coefficient, Analysis of variance [ANOVA], ROC curve by SPSS V17.

RESULTS

This study was carried out on 60 adult patients aged between 18-70 years old. The patients were divided equally into 3 groups (20 in each group) according to the level of PCT at day of admission. Group I: PCT level (0.5 to 2ng per ml),Group II:PCT level (2 to 5ng per ml), Group III:PCT level (more than 5 ng pre ml)

As regards the demographic data, there were no significant difference between the four groups as regards age and sex (P > 0.05) (Tab 1). Respiratory tract infection was the most common site of infection (45%) and urinary tract infection (30%) was the second most common followed by other sites (Tab 1).

There was no statistically significant difference in CRP between(1^{st}&4^{th}) day in each group and no significant difference between all groups at both days of observation(P > 0.05) (Tab 2).

There was statistically significant decrease in serum procalcitonin between(1^{st}& 4^{th}) day in all groups (group I (P<0.05) group II, III (P <00.1) respectively. Also there was significant difference between all groups at both days of observation (P < 0.001) (Tab 3).

There was statistically significant decrease in SOFA score between (1^{st}&4^{th}) day in each group (p<0.05). Also there was significant difference between all groups at both days of observation (P< 0.001) and there was no significant difference between group (I &II) but was higher in II more than I. There were highly significant increase between group (I& III), (I &IV), (II &III), (II &IV), (III & IV) and significant decrease atthe4^{th} day if compared tothe1^{st}day(Tab 4).

There was significant positive correlation between PCT level and SOFA Score (r = 0.924, P = 0.001) while there was no correlation between CRP and SOFA score (r = -0.233, P = 0.091) (Tab 5) (Fig 1,2).There was a significant difference between level of PCT in survivors and non survivors (P<0.001) while CRP did not reveal any significant difference between survivors and non survivors (P>0.05) (Tab 6).

The cut off value of average PCT was 0.5 ng/mL which is significant (P=0.001), sensitivity 78.1, specificity 100% with high positive predicative value of 97.3 compared with average CRP, the cut off was 132.1 mg/mL which is not significant (P=0.917). (Tab 7)(Fig 3,4).

Table 1: Descriptive data in the studied groups.

parameters	Age		Sex	
	Range	Mean±SD	Female	Male
Group I	25-60	57.35±14.78	9	11
Group II	29-60	53.95±10.08	12	8
Group III	26-55	49.65±12.34	11	9
Respiratory tract infection patients no(%)	27 (45%)			
Urinary tract infection patients no(%)	18(30%)			
GIT infection patients no(%)	9 (15%)			
Infective endocarditis patients no(%)	6 (10%)			

Table (2): C-reactive protein (CRP) in the studied groups

Groups		CRP mg/l		Paired test
		1st day	4th day	
		Mean±SD	Mean±SD	
Group I		160.2±42.38	153.22±38.2	0.586
Group II		162.35±45.08	152.53±36.96	0.108
Group III		144.1±35.49	156.35±42.25	0.074
ANOVA	f	0.739	1.342	
	P-value	0.532	0.267	

Table (3): Level of procalcitonine (PCT) in the studied groups

Groups		Pctng/ml		Paired test
		1st day	4th day	
		Mean±SD	Mean±SD	
Group I		1.06±0.41	0.57±0.120	0.027*
Group II		5.01±2.30	2.30±0.64	0.003*
Group III		13.50±3.96	10.01±2.84	<0.001*
ANOVA	f	167.573	126.246	
	P-value	<0.001*	<0.001*	

Table (5): SOFA score in the studied groups

Groups		Pctng/ml		Paired test
		1st day	4th day	
		Mean±SD	Mean±SD	
Group I		5.05±1.36	2.71±0.63	0.038*
Group II		10.09±2.09	8.3±1.75	0.016*
Group III		14.4±3.46	10.7±2.01	0.005*
ANOVA	F	176.910	269.553	
	P-value	<0.001*	<0.001*	

Table (6): Correlation between PCT, CRP with four categories of SOFA Score:

SOFA	PCT		CRP	
	r	p-value	r	p-value
1-4	0.291	0.007*	-0.050	0.622
4-6	0.714	<0.001*	0.343	0.052
7-13	0.804	<0.001*	0.267	0.072
13-18	0.924	<0.001*	-0.233	0.091

Table (7): level of PCT and CRP in survival and non survival

	Mortality			
	Survival(n=42)	Non survival(n=18)	t-test	
	Mean±SD	Mean ±SD	t	P-value
PCT	4.54±1.91	8.20±2.17	2.938	0.004*
CRP	131.91±32.54	156.04±40.30	1.577	0.120

Table (8): Results of ROC curve during study period for PCT, CRP.

Results of ROC curve during study period for PCT and CRP								
		Cut off	**Sens.**	**Spec.**	**PPV**	**NPV**	**AUC**	**P-value**
Average	CRP	132.1	49.7	100.0	94.7	28.4	0.5	0.917
	PCT	0.5	78.1	100.0	97.3	63.7	0.9	0.001*

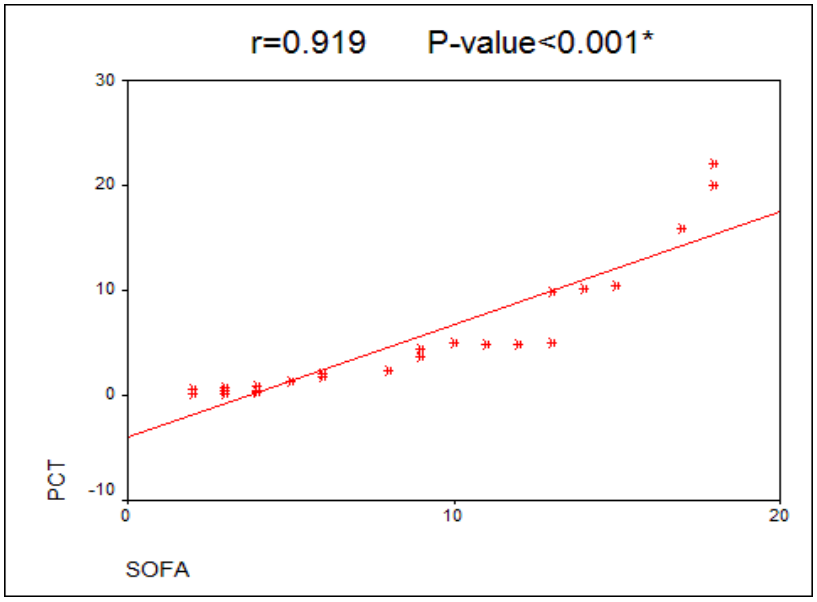

Fig. 1: Correlation between PCT and SOFA

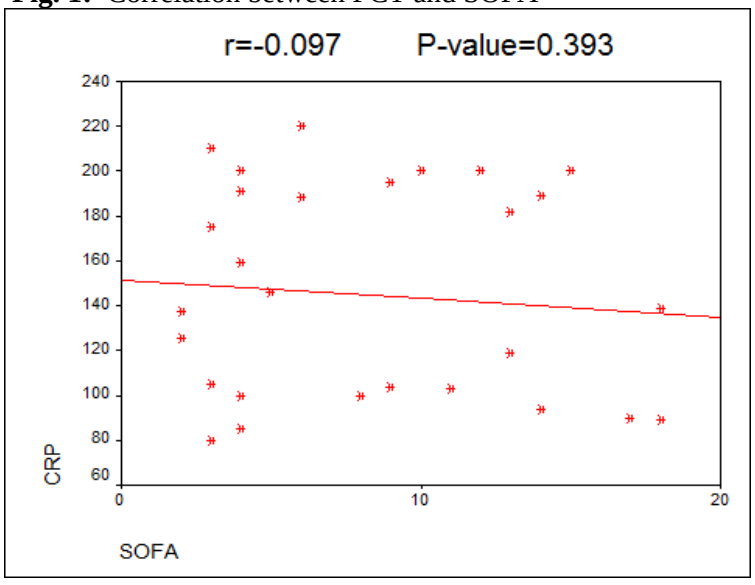

Fig. 2: Correlation between CRP and SOFA

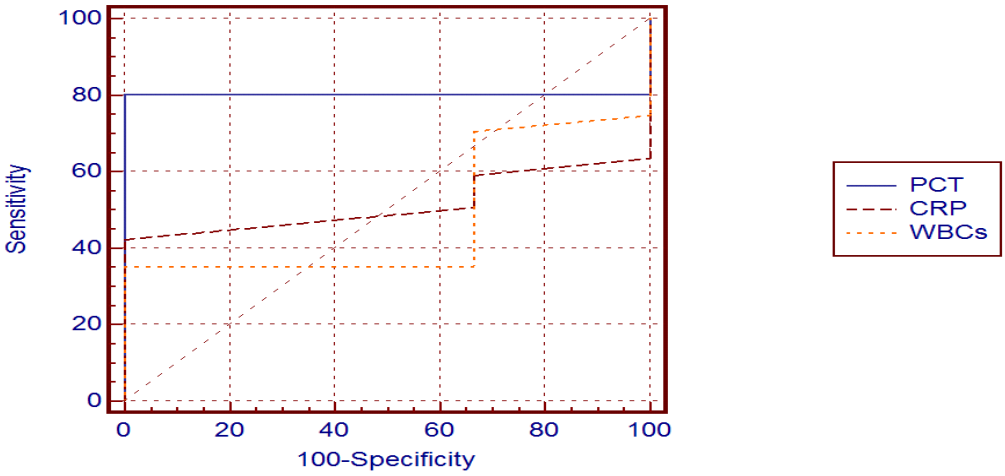

Fig. (3): ROC curve at the 1st day,

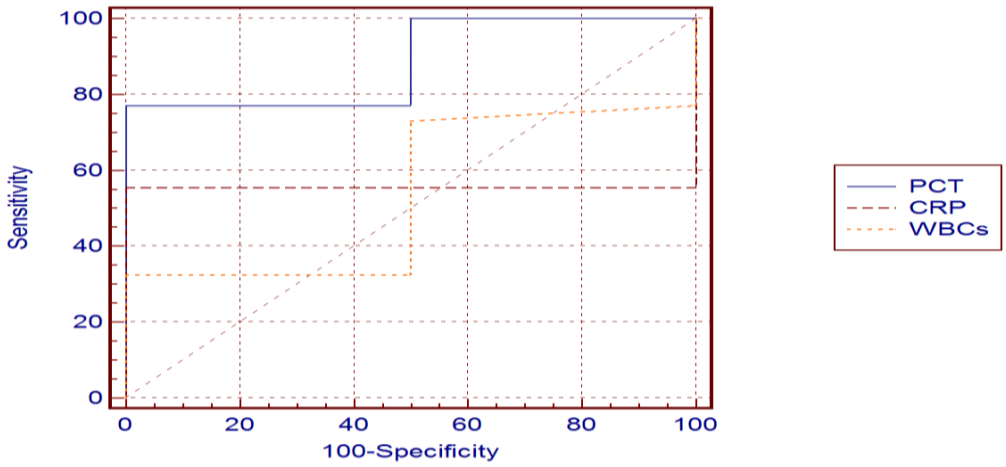

Fig. (4); ROC curve at the 4th day.

DISCUSSION

Sepsis is one of the most common causes of morbidity and mortality in ICU patients and multi organ dysfunction is one of the major complications of sepsis. Due to lack of specific symptoms and sensitive laboratory biomarkers, appropriate treatment is delayed or over utilizing antimicrobial in critically ill patients. Sepsis biomarker needs to provide information additional to that already available from established clinical assessments (e.g. history and examination) and investigations e.g. C-reactive protein (CRP) and white cell count (WCC).

PCT has been studied in critically ill patients both as a diagnostic and prognostic test and for its ability to aid antibiotic use by safely shortening antibiotic course length.

The current study aimed to evaluate the changes in the level of PCT and CRP over a period of time and was to explore if there is any correlation between PCT and SOFA, CRP and SOFA in sepsis patients.

Haemodynamic monitoring was used also in the comparison at the1st and4th day in this study.

This study was carried out on 60 adult patients aged between 18-70 years old of both sexes who were admitted to intensive care unit with systemic inflammatory response syndrome (SIRS). The present study shows that respiratory tract infection was the most common site of infection (45%) and urinary tract infection was the second common site (30%). Also another two studies found that respiratory tract infection (50.1%) was the most common source of sepsis followed by urinary tract infection (26%), skin infection (4.9%) and gut infection (5.3%)[7,8].

Current study showed significant changes in PCT levels with sepsis with no significant change in CRP level. Study was done on seventy adult patients who were admitted to the intensive care unit for an expected stay >24 hrs. They found that PCT is a better marker of sepsis than CRP because of the course of

PCT shows a closer correlation than that of CRP with the severity of infection and organ dysfunction[9].

Also **Michael *et al***. results come in line with our results; PCT, CRP, (SOFA) score, Age, (APACHE) II score and survival were evaluated in 40 patients with systemic inflammation and consecutive MODS over a period of 15 days. They found that measurement of PCT concentrations during multiple organ dysfunction syndrome provides more information about the severity and the course of the disease than that of CRP[10].

In our study, PCT in septic patients was statistically decreased at D4 if compared to D1 ($p < 0.003$). Our results agreed with Charles et al., they found that there was a significant decrease of PCT levels in septic patients on day 2 and 3 of antibiotic therapy[11].

In **Karlsson's** study the effect on hospital survival was connected with a decrease in PCT concentrations of greater than 50% between the 1st and 3rd study day[12].**Małgorzata** who studied on 50 critically ill patients found significant PCT level decrease on the5th day of admission with cut-off value (1.13 µg/l and AUC = 0.582) which represents the best prognostic properties resulting in a good outcome[13].**Hochreiter *et al***. found that PCT-guided patients also received a significantly shorter duration of antibiotic therapy (5.9±1.7 days versus 7.9±0.5 days) in their randomized controlled trial of surgical intensive care patients with confirmed or highly suspected infections[14].

The present study shows that there was also significant difference between level of PCT in survivors and non survivors while CRP did not reveal any difference between survivors and non survivors. Our results are in agreement with the results of another study conducted on 40 patients with systemic inflammation and consecutive MODS over a period of 15 days[15].

The study by **Christophe*et al***. approved that PCT may be a valuable early diagnostic and prognostic marker in patients with septic shock.PCT concentrations were significantly higher in those who died than in the survivors while C-reactive protein was not helpful for predicting mortality[16].Our results are similar to **Sakran** who demonstrated higher PCT values in the non-survivors group[17].

Multicenter randomized study was done on 1575 critically ill patients treated with antibiotic with median duration of treatmentof5 days, they found decrease in duration of treatment and mortality rate (20%) for procalcitonin guided groups compared with more treatment duration and (27%) mortality in patient standard care[18].In **Seligman's** study the decrease of PCT on the 5th day vs. 1st day predicts favorable outcome[19].

Another study was done on 72 critically ill patients with new-onset fever, CRP and PCT were measured on day 0, 1, 2 and 7 and their clinical course was documented over 1 week with follow-up to day 28, They found that PCT is better than CRP in indicating the risk of complications, such as blood stream infection, septic shock, organ failure and mortality, and therefore might help deciding on safe discontinuation of antibiotics[20].

As regards SOFA score, the present study showed that there was no significant difference between group (I **&**II) but higher in II more than I. There were highly significant increase between group (I**&** III), (I **&**IV), (II **&**III), (II **&**IV), (III**&** IV) and significant decrease at the4th day if compared to the1stday which agree with a study that revealed a much higher scores denoting a higher severity of sepsis[21] and the study on 103 intensive care patients with suspected sepsis found that PCT (AUC=0.81) and the sequential organ failure assessment (SOFA) score (AUC=0.82), but not CRP, which were the only independent predictors of infection[22]. Another study found that the kinetics of PCT achieved prognostic significance earlier than the changes of the patient's clinical condition reflected by SOFA score[13].

Also study on three hundred fifty-two consecutive patients (mean age, 59 years) admitted to the ICU for more than 24 hours for whom the SOFA score was calculated on admission and every 48 hours until discharge, they found that the initial and highest scores of more than 11 or mean scores of more than 5 corresponded to mortality of more than 80%[23].

Also **Acharya *et al* .**in their study on fifty patients admitted to ICU with SIRS,SOFA scores were calculated at zero hour, after 48, and after 96 hours and till discharge from hospital. They found that the SOFA scoring system is useful in predicting outcomes in ICU. The initial SOFA score > 11 predicted a mortality of 90%. Similarly, mean SOFA score of > 7 predicted a mortality of 73.9% and high SOFA score > 11 predicted a mortality of 87.5%[24].

The study by **Charan*et al***, found that SOFA score at 48 h of admission was a better predictor of mortality ($P < 0.001$) than the score at admission. Both the mean and highest SOFA scores were particularly useful predictors of outcome[25].But Sean studyon1, 449 patients from 40 intensive care units throughout the world found that unlike other ICU mortality systems, SOFA was not designed to accurately predict mortality, and was originally developed examining

ICU mortality (not hospital mortality) which disagree with our results[26].

CONCLUSION

PCT is a good diagnostic and prognostic marker of sepsis. PCT shows a closer correlation than that of CRP with the severity of infection and organ dysfunction.

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