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Original Article

Procalcitonin and C-Reactive Protein in Critically Ill Patients with Sepsis and Septic Shock Admitted in an ICU of a Tertiary Care Hospital in Bangladesh

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Abstract:

Background: *Early intervention and predicting outcome has become a cornerstone in the treatment of sepsis as this may ensure the difference between survival and mortality. Both C-reactive protein and Procalcitonin have long been identified as good diagnostic markers of sepsis but their prognostic value is still a matter of debate. This study aims to find this particular point out.*

Objectives: *Objective of this current study is to see the relationship of Procalcitonin and C-reactive protein respectively with the outcome of the patients with sepsis and septic shock and to compare their usefulness as predictors of outcome.*

Methods: *This study was carried out in Intensive Care Unit of BIRDEM General Hospital, Shahbag, Dhaka for a period of one year. All consecutive patients with sepsis and septic shock were enrolled as study subjects during this period according to selection criteria. At the time of diagnosis that is at zero hour of development of sepsis or septic shock both C-reactive protein and Procalcitonin were measured and it was repeated at 24 hours. Data were collected in preformed data collection sheet and analyzed by the SPSS.*

Results: *In this study, total 170 patients were enrolled as a case of sepsis or septic shock. The mean age was 59.5 ± 15.8 with a range between 20-96 years. Fifty seven (34%) patients had septic shock either during admission or during the first 24 hour of ICU stay and 46 (27.1%) patients did not survive their illness. The mean SOFA score was 6.30±2.18, mean duration of ICU stay 5.5.±2.98 days and mean MAP was 83.73±24.49 mmHg and 98 patients (57.65%) patients were ventilated during their admission. Diabetes mellitus had majority among co-morbidities with 147 (86.4%) patients having diabetes mellitus.*

Finally after calculating the cut off values from Youden's index C-reactive protein was found to be more sensitive and Procalcitonin more specific as predictors of outcome.

Conclusion: *This study concludes that both Procalcitonin and C-reactive protein can individually predict outcome in sepsis and septic shock and one is not inferiorto the other.The dynamic changes of both these biomarkers over first 24 hours were also strongly associated with outcome. It was noted that while C-reactive protein was more sensitive, Procalcitonin was more specific.*

Key words: *C-reactive protein, ICU, Procalcitonin, Sepsis, Septic shock.*

Introduction

Sepsis and its consequences are one of the leading causes of death in Intensive Care Units (ICUs) worldwide, with one in four patients dying of severe sepsis and septic shock[1]. It is vital to identify sepsis and septic shock patients with worsening prognosis or with increased risk of mortality to prevent consequent multi organ failures. Different initiatives have attempted to improve the survival of septic patients based on strategies designed to ensure the early diagnosis and treatment of these subjects[2]. But the disease process is often complicated by multi organ failure, polymicrobial infections of different sites or infections produced my multi drug resistant pathogens. Hence it is necessary to identify the patients with unfavorable outcome early on so that extensive measures can be taken to halt the progression of the disease process and decrease mortality and morbidity in doing so[3]. But to do that, it is necessary to identify these patients with a reliable biomarker as techniques such as cultures typically require long time intervals for obtaining results[4]. Still then only one third blood cultures are positive and in one third cases cultures from all sites are negative[1].

Procalcitonin (PCT) is a 116 amino acid long precursor of the hormone calcitonin and it is found in very low (<0.05ng/ml)

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or even undetectable concentration in healthy individuals. However in situations of infection, different body tissues release PCT into blood stream causing a rise above the normal level. Thus PCT is regarded as a biomarker for the diagnosis of sepsis and studies have suggested that dynamic changes of PCT could be predictive of outcome in patients with sepsis and septic shock[5].

C-Reactive protein (CRP) is another biomarker used to diagnose both chronic and acute inflammatory responses. It may be used to establish the severity of sepsis and septic shock and in the same time to establish prognosis[6].

When septic patients are admitted to the ICU, these biochemical markers are frequently evaluated to predict treatment response and infection severity but there is lack of evidence about the role of these two markers as predictors of outcome and the prognostic values of these biochemical markers are still debated. In this study both CRP and PCT were serially measured and the changes in their concentrations were investigated in critically ill patients with sepsis and septic shock to determine which biochemical marker better predicts outcome.

So, if it was proven in this study that CRP and PCT both had similar efficacy as predictor of outcome in these patients, then it might become the first step towards using these markers interchangeably. As CRP is much cheaper to carry out and this facility is more widely available than PCT, the cost benefit ratio will be immense.

Methods:

This prospective observational study was carried out in the Department of Critical Care Medicine, BIRDEM General Hospital, aiming at finding out the association between levels of Procalcitonin and CRP respectively with the outcome of the patients with sepsis and septic shock. The study period lasted for one year extending from January 2018 to December 2018.

Ethical approval was obtained prior to the commencement of the study. Informed written consent was taken from the participants or their guardians after explaining all the facts and potential dangers to the subjects in case of primary data collection. The patients' records/information was anonymized and de-indentified prior to analysis.

Patients

All adult patients with sepsis or septic shock were selected for the purpose of the study. All patients with other possible causes of shock and patients who were readmitted during the same hospitalization episode were excluded. All patients received standard supportive treatment as per the institution's protocol.

Definitions and Endpoints:

Patients were examined by Serum PCT level and Serum CRP level at 0 hour and 24 hour. Zero hour was denoted as the time of admission for patients with known sepsis or septic shock. For those patients who developed sepsis or septic shock during their ICU stay, zero hour was identified as the time of first recognition of sepsis or septic shock.

Patients were observed to see the outcome in relation with PCT and CRP from the time of admission. The patients were followed from the diagnosis of sepsis or septic shock, up until hospital day 28 and the outcome at the end of this period, i.e. transferred out of ICU, discharged from ICU or death, was defined as outcome related to sepsis or septic shock, whichever was earlier. The survivors were defined as those patients who were transferred out of ICU or discharged from ICU, or still staying at ICU maximally up to 28 days for some reason other than sepsis or septic shock.

Sepsis and septic shock were defined according to the third international consensus definitions for sepsis and septic shock (Sepsis-3)[7].On ICU admission, the illness severity of each patient was assessed by using the sequential organ failure assessment (SOFA) scores.

Sampling technique and statistical analyses:

Consecutive sampling was the method of choice for this study.

Collected data was processed and analyzed using Statistical Packages for Social Sciences (SPSS) software version 23 (SPSS,Chicago,IL,USA). The dynamic changes of PCT and CRP were analyzed by using the non-parametric Mann-Whitney U-test. The unpaired t test was used to find out statistical significance of categorical variables like SOFA score, MAP and duration of ICU stay. A receiver operator characteristic (ROC) curve analysis was used to determine the predictive performances of PCT (at 0hr and 24 hr) and CRP (at 0hr and 24 hr) for outcome. This provided the best cut-off value by using the Youden's index and the area under the ROC curve (AUC) values for mortality as well as sensitivity, specificity and accuracy values. Results are given with 95% confidence intervals (CI) and P values of <0.05 were considered as statistically significant. Comparison of prognostic accuracy of the biomarkers was made using ROC curve analysis which yielded the respective AUCs and standard error. The AUCs were then compared using the non-parametric test of Delong by the MedCalc software 18.11.6 version (Medcalc Software, Ostend, Belgium).

Results

Patient characteristics

During the study period, in total 1397 patients were admitted at BIRDEM ICU. Among these patients, finally 170 patients were included in the study after consideration of all aspects. Majority patients were male (n=89) with 81 patients being female.The mean age was 59.5±15.8 with a range between 20-96 years. Fifty seven (34%) patients had septic shock either during admission or during the first 24 hour of ICU stay and 46(27.1%) patients did not survive their illness. The mean SOFA score was 6.30±2.18, mean duration of ICU stay 5.5.±2.98 days and mean MAP was 83.73±24.49 mmHg and 98 (57.65%) patients were ventilated during their admission (Table 1). Diabetes mellitus had overwhelming majority among co-morbidities with 147 (86.4%) patients being diabetic. It was followed by HTN (50.6%) and then chronic kidney disease (27.6%).

Table I: Baseline Characteristics of the patients (n=170)

Characteristics	Values
Age (yrs)	59.5 ± 15.8 (20 - 96)
Female	81 (47.65)
Male	89 (52.35)
DM	147(86.4)
HTN	86(50.6)
IHD	28(16.5)
CKD	47 (27.6)
SOFA	6.30±2.18
MAP (mmHg)	83.73±24.49
Mechanically ventilated	98(57.65)
Sepsis	113 (66.00)
Septic shock	57(34.00)

Outcomes of severe sepsis and septic shock in association with CRP and PCT:

It was found that 0 hour values of both CRP and PCT were associated with the outcome as were the 24 hour values. The dynamic changes of both CRP and PCT over this 24 hour period were also associated with outcome in the patients (Table II and Table III). The 0 hourvalues of PCT and CRP, although statistically significant might have been influenced by the time of presentation of the patient, i.e. not all patients presented at the same stage of disease process. Hence the 24 hr value of S. CRPO and S.PCT and the changes in their levels over this 24 hour period were further analyzed.

Table II: Outcome with serum procalcitonin at 0 hours and at 24 hours (n=170)

	Non survivor (n=46) n (%)	Survivor (n=124) n (%)	p-value
Serum Procalcitonin at 0 hour (pg/ml)	20701 ± 20769	13104 ± 13133	0.039
Serum Procalcitonin at 24 hour (pg/ml)	24297 ± 22069	9309 ± 10621	<0.001
Change in S. Procalcitonin	3596± 8246	- 3794 ± 5937	<0.001

Mann Whitney U test was done to measure the level of significance. Mean±Standard Deviation shown here.

p value <0.05 considered significant

Table III: Outcome with serum CRP at 0 hours and at 24 hours (n=170)

	Non survivor (n=46) n (%)	Survivor (n=124) n (%)	p-value
Serum CRP at 0 hour (mg/L)	152.18 ± 51.48	119.49 ± 62.53	0.002
Serum CRP at 24 hour (mg/L)	159.42 ± 68.12	92.78 ± 57.34	<0.001
Change in S. CRP	7.24 ± 51.61	- 26.71 ± 57.43	<0.001

Mann Whitney U test was done to measure the level of significance. . Mean±Standard Deviation shown here.

p value <0.05 was considered significant.

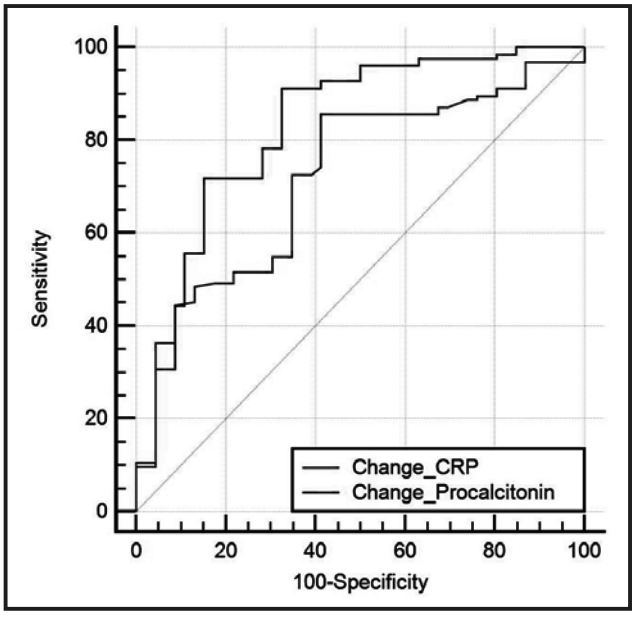

Fig 1: Comparison of AUCs of change in S.CRP and change in S. PCT

Table IV: Comparison of AUCs of changes in serum procalcitonin and serum CRP for prediction of outcome (n=170)

	AUC	SE	p-value	95% CI Min	95% CI Max
Change in S. CRP	0.720	0.043	<0.001	0.646	0.786
Change in S. PCT	0.832	0.037	<0.001	0.767	0.884
Difference of AUC[1]	0.112	0.054	0.039	0.005	0.218

[1]Non-parametric test of Delong was carried out.

p value <0.05 considered significant.

AUC = area under curve, SE= Standard error

Fig. 1 and Table IV shows that the AUC of change in S. CRP is 0.720 (95% CI 0.646-0.786) and AUC of Change in serum CRP is 0.832 (95%CI 0.767-0.884). This difference between two AUCs was not statistically significant (p= 0.039).

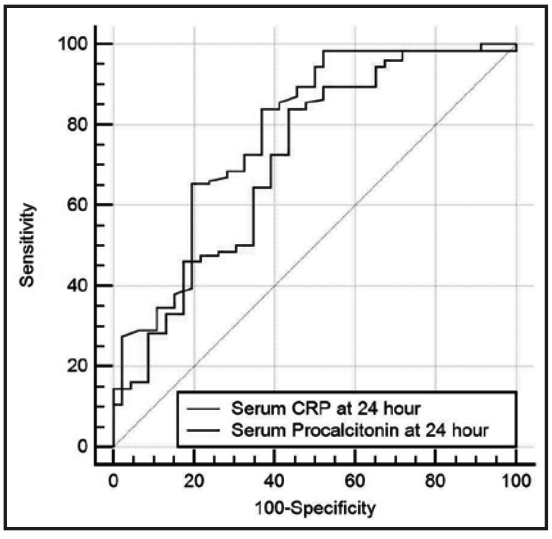

Fig 2: Comparison of AUCs of serum PCT and serum CRP levels at 24 hour

Table V: Comparison of AUCs of serum procalcitonin and serum CRP at 24 hours for prediction of outcome (n=170)

	AUC	SE	p-value	95% CI	
				Min	Max
Serum Procalcitonin	0.715	0.047	<0.001	0.624	0.807
Serum CRP	0.782	0.043	<0.001	0.698	0.865
Difference of AUC1	0.067	0.065	0.307	-0.061	0.194

[1]Non-parametric test of Delong was carried out.

p value <0.05 considered significant.

AUC = area under curve, SE= Standard error

Fig 2 and Table V shows that the AUC of serum PCT at 24 hour is 0.715(95% CI 0.624-0.807) and AUC of serum CRP at 24 hour is 0.782 (95%CI 0.698-0.865). This difference between two AUCs was not statistically significant (p= 0.307).

Table VI: Multivariate logistic regression to determine independent predictors of outcome (n=170)

Predictor	Coefficient	P Value	OR	95% CI of OR	Cox &Snell R^2	Nagelkerke R^2
CRP at 24 hour	0.15	**0.0001**	**1.19**	**1.07 to 1.23**		
PCT at 24 hour	0.67	**0.0012**	**1.12**	**1.09 to 1.56**		
Change in CRP	0.03	0.5296	0.99	0.98 to 1.07		
Change in PCT	0.02	**0.0017**	**1.02**	**1.01 to 1.04**		
Age	0.09	0.6611	1.09	0.97 to 1.05		
Gender	0.76	0.2790	0.47	0.12 to 1.85		
DM	0.92	0.2800	2.51	0.47 to 13.45	0.44	0.64
HTN	0.35	0.6749	1.42	0.27 to 7.35		
CKD	0.24	0.6592	1.27	0.43 to 3.73		
Ventilation status	0.03	0.0893	1.03	0.99 to 1.06		
SOFA	0.49	**0.0002**	**1.64**	**1.26 to 2.14**		
MAP	0.02	0.8429	1.01	0.98 to 1.02		
Duration of ICU Stay	0.19	0.1850	1.14	0.94 to 1.37		

OR= Odds Ratio ;CI = Confidence Interval.
p value <0.05 considered significant.

Multivariate logistic regression analysis to determine the independent predictors of outcome shows that CRP at 24 hour, PCT at 24 hour and Change in PCT along with SOFA score has p values below 0.05. The odds ratio were as follows: CRP at 24 hr (OR: 1.19; 95% CI 1.07-1.23), PCT at 24 hr (OR 1.12; 95% CI 1.09-1.56), change in PCT (OR 1.02, 95% CI 1.02-1.04) and SOFA score (OR: 1.64; 95% CI 1.26- 2.14). The Cox & Snell R^2 value is 0.44 and the Nagelkerke R^2 value is 0.64.

To find out the specificity and sensitivity of CRP and PCT for this study, Youden's index was used to find out the specific cut of value. For serum procalcitonin at 24 hr, this value was 13250pg/ml and it showed the highest sensitivity of 60.9% and highest specificity of 72.6%.

Table VII: Sensitivity and specificity (at different cutoff values) of serum procalcitonin at 24 hours(n=170)

Serum Procalcitonin at 24 hrs	Sensitivity	Specificity
12850	60.9	70.2
13220	60.9	71.0
13250	**60.9**	**72.6**
13384	56.5	72.6
13517	56.5	74.2

*Values derived from Youden's Index

Similarly for CRP at 24 hours, this cut off value was 116.50 mg/L and it showed a sensitivity of 71.7% and specificity of 66.9%

Table VIII: Sensitivity and specificity (at different cutoff values) of serum CRP at 24 hours (n=170)

Serum CRP at 24 hr	Sensitivity	Specificity
112.50	76.1	65.3
114.00	76.1	66.1
116.50	**71.7**	**66.9**
119.00	71.7	68.5
120.50	67.4	68.5

*Values derived from Youden's Index

Discussion

Prognosis of sepsis and septic shock is a question, the answer to which is sought after by all health professionals, specially the intensivists. Although multiple studies[8,11] have irrevocably proven the usefulness of PCT over CRP in diagnosis of sepsis, same cannot be said about the prognostic value of these two very well known biomarkers. Moreover , studies where serial measurement of the two biomarkers were taken into consideration while evaluating their effectiveness as predictor of outcome are few and far between, specially in this sub continent. So, this study took a particular look at these variants.

Current study showed 147 (86.4%) patients had diabetes mellitus, 86 (50.6%) had hypertension, 28 (16.5%) patients had IHD 47(27.6%) had chronic kidney disease, 21(12.4%) had history of CVD and 8(4.7%) had COPD (Table I). In the study carried out by Ryuet al.[8] there were 73% patients with malignancy, 32% patient with Diabetes, 32 % with HTN, 11% patient had CKD,2% had IHD and 4% patient had COPD. This discrepancy emphasizes the importance of the centre where the study is being carried out on the comorbities of the study population. As BIRDEM is a tertiary care hospital and the topmost diabetes centre in the country, the overwhelming majority of the patients had DM. On the other hand, the Samsung Medical Centre in Seoul, Korea, where Ryu et al.[8] carried out their study, mainly included cancer patients with the majority patients having malignancy as the comorbidity.

In this study 98 (57.65%) patients needed the support of mechanical ventilator; the length of ICU stay was 5.51±2.98 days and SOFA score was 6.30±2.18 (Table I). The study by Ryu et al.[8] showed the SOFA score to be 11 (IQR 8-14) and 53% patients needed mechanical ventilation. This difference in SOFA score is due to the large number of febrile neutropenia patients, along with malignancy and immunocompromisation due to chemotherapy, in the latter study with more severe septic process and multiple organ dysfunctions.

In this study both CRP and PCT levels were taken at 0 hr and 24 hrs to see both the dynamic relationship and absolute value of the levels with outcome. This was done because multiple studies[9,10,11] showed that CRP and PCT have different kinetics over the period of 5-7 days. But due to resource constraints and the academic nature of this study only 2 samples (one at 0 hr and another at 24 hours) were taken. Hence it became important to consider both the dynamic change and the absolute values.

While the baseline, i.e. 0 hour value of CRP was significantly related with outcome (p value 0.002) same could be said about the PCT value (p value = 0.039) (Table II and Table III). While considering the 24 hour value of CRP and PCT among survivors and non survivors, the difference was found significant for both biomarkers with a p value of <0.001 in both cases. Multiple studies have found that baseline values of PCT fail to predict outcome[12,13]. These studies also show that the baseline CRP value is not a good predictor of outcome but our study findings show otherwise. This discrepancy may be due to the fact the majority patients in this study had multiple comorbidities, specially DM. Suberviola et al.[12] had different methods of measuring both S. PCT (based on time resolved amplified cryptate emission) and S.CRP (COBAS INTEGRA 400 analyzer) and the study population consisted solely of septic shock patients. This might have been the attributing reasons behind the dissimilarity of findings.

In case of PCT, the survivors showed a fall in the level (9309±10621 pg/ml from 13104±13133 pg/ml) but in the non survivors the level increased from 20,701±20,769 pg/ml to 24,297±22069 pg/ml (Table II). This dynamic change was statistically significant (p <0.005). Similarly in case of CRP, the survivors showed a fall in the level (92.78±57.34 to 19.49±62.53) while the non survivors showed an increase (152.18±51.48 to 159.42±68.12). This change in parameters was statistically significant as well (p<0.005) (Table III).

Receiver operating characteristic (ROC) curve of change in S. CRP (CRP 24 hr value minus CRP 0 hr value) and change in S. PCT (PCT 24 hr value minus PCT 0 hr value) were considered. It showed that the area under curve (AUC) for change in CRP was 0.720 and AUC for change in S. PCT was 0.832. This difference was significant (p value < 0.05) (Table IV and Fig. 01). Ryu et al. (2015)[8] found in their study that in survivors, both CRP clearance and PCT clearance levels fall significantly within the first 24 hours in comparison with the non survivors. But in their study the difference between the respective AUROC for CRP clearance and PCT clearance over 24 hour were not significant (both values were 0.77).

This discordance may be due to the difference in study design and demographics as theirs were a retrospective study and contained significant patients with febrile neutropenia and malignancy while in this study, majority patient had DM and CKD. On the other hand the study by Suberviol et al.[12] showed that the difference of clearance of PCT between survivors and deceased was significant (p value <0.01) but same could not be said about CRP clearance (p value 0.80). This difference in clearance of biomarkers from the current study may once again be attributed to the difference of measurement procedure and different patient population as all these patients had septic shock. Hoeboer et al. (2013)[14] showed that both clearance of PCT and CRP were significantly associated with outcome.

Finally, the 24 hour value of both CRP and PCT were considered in survivors and non survivors (Table V). In cases of PCT at 24 hour, these values were 24297±22069 pg/ml and 9309±10621 pg/ml for survivors and non survivors, respectively. The difference between these values were significant (p<0.001). Similarly for CRP at 24 hour, these values were 159.42±68.12 mg/L and 92.78±57.34 mg/L respectively for survivors and non survivors and the difference was statistically significant (p <0.001). Garnacho-Montero et al. [15] showed that the day 2 value of both CRP (p value 0.003) and PCT (p value <0.001) were significantly associate with outcome. These findings also agreed with the findings of Hoeboer et al. (2013)[14] where the absolute values of both CRP and PCT at day 7 in comparison to the baseline value were significantly associated with the outcome of the critically ill febrile patients. On the other hand, Tanriverdi et al. (2015)[16] showed that the D3 and D7 value of PCT, but not CRP, was associated with outcome in VAP patients. This difference may be due to the reason that they only considered ventilator associated pneumonia patients and all the patients needed assisted ventilation and with a very different co-morbidity profile in comparison to this study.

As both the 24 hour values showed significant difference between survivor and non-survivors, these particular values were given further evaluation. A ROC curve was drawn (Table V and Fig. 02) that showed that S. PCT at 24 hour had an AUC of 0.715 and for S.CRP at 24 hour this value was 0.782. The difference between these two AUROC were not significant (p value = 0.307). Extensive literature review failed to yield any other study where the absolute value at 24 hour or day 2 was evaluated by a ROC curve. But Daniels found that D10 value of the AUROCs for predicting outcome were similar for CRP and PCT (0.712 and 0.670 for PCT and CRP, respectively, p value = 0.43). The difference in value from this study may be attributed to the difference in time of estimation of the serial measurement.

Noticing the number of co-morbidities and multiple factors that might affect the outcome in sepsis and septic shock patients, a multivariate regression analysis was done including demographic variables, major co-morbidities and CRP and PCT values (both changes over 24 hour and absolute value at 24 hour were considered)along with SOFA score, ventilation status, MAP and duration of ICU stay. After adjusting all these factors only the absolute values of both CRP and PCT at 24 hours and the change in serum PCT and SOFA score were identified as independent predictors of outcome (Table VI). Ryu et al.[8] also found that both CRP clearance and PCT clearance along with SOFA score came out as independent predictors of outcome in sepsis and septic shock patients. They did not consider absolute values of CRP or PCT at 24 hours, so these findings could not be compared. Tanriverdi et al.[16], in their multivariate regression analysis found that only PCT levels at D3 and PCT kinetics from D0 to D3 remained independent risk factors for mortality. This discrepancy may be due to the much smaller number of patients having only VAP as the sepsis source (45 patients in comparison to 170 in this study) enrolled in the study.

After this, using the Youden's index the cut-off value of CRP and PCT were calculated for this study. For PCT, this value was 13,250 pg/ml(Table VII) and for CRP it was 116.50 mg/L (Table VIII). With regards to the prognostic performance of CRP and PCT it was found that, both these biomarkers showed moderate efficiency with PCT being more specific and CRP more sensitive. Garnacho-Montero et al. (2014)[15] also found that CRP is more sensitive that PCT (93.91%vs. 81.03%), although PCT was more specific than CRP (67.44% vs. 30.95%).

Limitations:

Like any other scientific study, the present study is not without limitations. The following limitations deserve mentioning:

– As the sample size was small, so the findings derived from this study could not be generalized to reference population.

Conclusions

This study concludes that both Procalcitonin and CRP can individually predict outcome in sepsis and septic shock. Comparison between these biomarkers also showed that, CRP was not inferior to PCT in this regard. The dynamic changes of both these biomarkers over first 24 hours were also strongly associated with outcome. So this research suggests that CRP may be considered as effective as PCT in predicting outcome in critically ill sepsis and septic shock patients. While comparing the sensitivity and specificity, it was noted that while CRP was more sensitive while Procalcitonin was more specific.

References:

1. Angus DC, Van der Poll T. Severe sepsis and septic shock. New England Journal of Medicine. 2013 Aug 29;369(9):840-51.

2. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive care medicine. 2013 Feb;39:165-228.

3. Alberti C, Brun-Buisson C, Goodman SV, Guidici D, Granton J, Moreno R, Smithies M, Thomas O, Artigas A, Le Gall JR. Influence of systemic inflammatory response syndrome and sepsis on outcome of critically ill infected patients. American journal of respiratory and critical care medicine. 2003 Jul 1;168(1):77-84.

4. Esteban A, Frutos-Vivar F, Ferguson ND, Peñuelas O, Lorente JÁ, Gordo F, Honrubia T, Algora A, Bustos A, García G, Diaz-Regañón IR. Sepsis incidence and outcome: contrasting the intensive care unit with the hospital ward. Critical care medicine. 2007 May 1;35(5):1284-9.

5. Schröder J, Staubach KH, Zabel P, Stüber F, Kremer B. Procalcitonin as a marker of severity in septic shock. Langenbeck's archives of surgery. 1999 Feb;384:33-8

6. Castellanos-Ortega Á, Suberviola B, García-Astudillo LA, Holanda MS, Ortiz F, Llorca J, Delgado-Rodríguez M. Impact of the Surviving Sepsis Campaign protocols on hospital length of stay and mortality in septic shock patients: results of a three-year follow-up quasi-experimental study. Critical care medicine. 2010 Apr 1;38(4):1036-43.

7. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS. The third international consensus definitions for sepsis and septic shock (Sepsis-3). Jama. 2016 Feb 23;315(8):801-10.

8. Ryu JA, Yang JH, Lee D, Park CM, Suh GY, Jeon K, Cho J, Baek SY, C. Carriere K, Chung CR. Clinical usefulness of procalcitonin and C-reactive protein as outcome predictors in critically ill patients with severe sepsis and septic shock. PloS one. 2015 Sep 14;10(9):e0138150.

9. Meisner M, Tschaikowsky K, Palmaers T, Schmidt J. Comparison of procalcitonin (PCT) and C-reactive protein (CRP) plasma concentrations at different SOFA scores during the course of sepsis and MODS. Critical Care. 1999 Feb;3:1-6.

10. Castelli GP, Pognani C, Meisner M, Stuani A, Bellomi D, Sgarbi L. Procalcitonin and C-reactive protein during systemic inflammatory response syndrome, sepsis and organ dysfunction. Critical care. 2004 Aug;8(4):1-9.

11. Rau BM, Frigerio I, Büchler MW, Wegscheider K, Bassi C, Puolakkainen PA, Beger HG, Schilling MK. Evaluation of procalcitonin for predicting septic multiorgan failure and overall prognosis in secondary peritonitis: a prospective, international multicenter study. Archives of Surgery. 2007 Feb 1;142(2):134-42.

12. Suberviola B, Castellanos-Ortega A, González-Castro A, García-Astudillo LA, Fernández-Miret B. Prognostic value of procalcitonin, C-reactive protein and leukocytes in septic shock. MedicinaIntensiva (English Edition). 2012 Apr 1;36(3):177-84.

13. Claeys R, Vinken S, Spapen H, verElst K, Huyghens L, Gorus FK. Plasma procalcitonin and C-reactive protein in acute septic shock: clinical and biological correlates. InAdvances in Critical Care Testing: The 2002 IFCC-Roche Diagnostics Award 2004 (pp. 17-31). Springer Berlin Heidelberg.

14. Hoeboer SH, Groeneveld AJ. Changes in circulating procalcitonin versus C-reactive protein in predicting evolution of infectious disease in febrile, critically ill patients. PloS one. 2013 Jun 6;8(6):e65564.

15. Garnacho-Montero J, Huici-Moreno MJ, Gutiérrez-Pizarraya A, López I, Márquez-Vácaro JA, Macher H, Guerrero JM, Puppo-Moreno A. Prognostic and diagnostic value of eosinopenia, C-reactive protein, procalcitonin, and circulating cell-free DNA in critically ill patients admitted with suspicion of sepsis. Critical care. 2014 Jun;18(3):1-9.

16. Tanrıverdi H, Tor MM, Kart L, Altın R, Atalay F, SumbSümbüloğlu V. Prognostic value of serum procalcitonin and C-reactive protein levels in critically ill patients who developed ventilator-associated pneumonia. Annals of thoracic medicine. 2015 Apr;10(2):137.