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Protein C as an Early Indicator of Severe Coagulopathy and Mortality in Patients with Sepsis

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Abstract

Objective: To determine Protein C as a useful early predictor of severe coagulopathy and mortality.
Methodology: It was a prospective observational study conducted at Mayo Hospital and Chughtai Institute of Pathology, Lahore from January, 2023 till September, 2023. 87 Patients admitted in Intensive Care Unit (ICU) with sepsis according to Sequential Organ Failure Assessment Score (SOFA score >2 according to sepsis-3 criteria) and without overt DIC on ISTH criteria (ISTH score <5) were included in the study. Baseline levels of Protein C activity levels of 87 adult patients were taken at Day 0 of admission. Patients were followed till Day 3 for development of DIC and 28 days for mortality. According to the development of DIC at Day 3 patients were allocated into two groups: Overt-DIC Group (n=35) and Non-DIC Group (n=52).
Results: SOFA score and Protein C both showed positive correlation with DIC and mortality with p-value being <0.05. There was a significant difference in values of baseline Protein C activity in both groups p-value (0.00). The overall sensitivity of Protein C was 90.4% ,specificity 71.4% ,Positive Predictive Value (PPV) 73% and Negative Predictive Value (NPV) 95% (CI 88.54-90.52%). Cut-off level was established for Protein C which was 52.9%.
Conclusion: Low Protein C activity levels alone on admission in hospital can effectively predict the evolution of severe coagulopathy (over-DIC) and mortality in patients with sepsis.
Keywords: Protein C, Disseminated intravascular coagulopathy, Sepsis, Mortality.

Introduction

Sepsis is a life-threatening medical disorder caused by host's dysfunctional immune response to infection leading to multiorgan dysfunction. It is a leading cause of morbidity and mortality especially in intensive care and hospitalized patients.[1] In Pakistani population, the rate of hospital admissions due to sepsis is around 28% which is very high.[2] Mortality with sepsis is approximately 9.8% and much higher with septic shock (around 40%).[3]

Sepsis associated coagulopathy is the most commonly encountered complication in patients with sepsis. It ranges from subtle coagulation abnormalities, detected only by sensitive coagulation markers (slight prolongation of global clotting times and mild decrease in platelet count) to more severe disseminated intravascular coagulopathy (DIC).[4] DIC is an acquired thrombohemorrhagic syndrome which is characterized by the simultaneous endothelial injury, systemic activation of coagulation pathways, dysfunctional fibrinolysis resulting in microangiopathic thrombosis, and subsequent depletion of platelets and coagulation factors.[5] The main pathogenic event is the loss of localization of the coagulation cascade at the site of injury to the blood vessel and succeeding lack of natural inhibitors to control coagulation and blunt extreme thrombin generation.

The manifestations of DIC range from bleeding diathesis to hypercoagulable manifestations, all due to underlying pathophysiologic responses to sepsis, trauma or a malignant disease. It is sub-categorized as Non-overt DIC (compensated) and Overt DIC (decompensated) depending upon the severity of dysfunctional coagulopathy.[4] The mortality rate in patients with overt-DIC is as high as 28–43%. Consequently, early diagnosis of coagulation dysfunction and apt initiation of required treatment are critical to the prognosis of septic patients.[6] The clinical diagnosis of DIC is challenging so, multiple laboratory tests are fundamental to make the diagnosis. International guidelines recommend the use of DIC

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scoring systems to confirm the diagnosis.[7] International Society on Thrombosis and Haemostasis (ISTH) has recommended a criteria for 'overt-DIC' employing laboratory parameters such as Platelet Count (PC), Prothrombin Time (PT), Fibrinogen and D-dimers.[8]

The major drawback of DIC scoring systems is that it only helps in the confirmation of overt-DIC after it has developed. Currently, there are no functional laboratory parameters which can predict the evolution of overt-DIC in septic patients on admission. Protein C is a naturally occurring anticoagulant, when activated irreversibly inactivates factors Va and VIIIa.[9] Recently Protein C has been researched as a predictive marker of DIC in patients admitted with sepsis but have not yet developed overt DIC.[10] Use of such a marker can help predict the evolution of DIC at the time of admission. It would be more valuable for countries such as Pakistan where the rate of sepsis and sepsis related mortality is very high. The aim of this study was to establish a cut-off value for Protein C, so it can effectively predict evolution of DIC and mortality in septic patients.

Methodology

It was a prospective observational study conducted at Mayo Hospital and Chughtai Institute of Pathology, Lahore from January, 2023 till September, 2023, after the approval from Ethical and Research committee. Informed consent was obtained from all the patients or the attendants. Patients admitted in Intensive Care Unit (ICU) with sepsis according to Sequential Organ Failure Assessment Score (SOFA score >2 according to sepsis-3 criteria) and without overt DIC on ISTH criteria (ISTH score <5) were included in the study using consecutive convenient sampling.[8,11] Baseline levels of global coagulation markers (Platelet count, PT-INR, Fibrinogen levels and D-Dimers) and Protein C activity levels of 87 adult patients above 18 years, both male and female were taken at Day 0 of admission. Protein C activity was measured using Siemens Berichrome Protein C kits. Patients with decompensated cirrhosis, chronic renal failure on hemodialysis, inherited platelet disorders, hematological malignancies, recent major surgery and history of therapeutic anticoagulation or recent blood transfusion were excluded from the study. Patients were followed till Day 3 for development of DIC and 28 days for mortality. Global coagulation markers were used to determine the ISTH score of DIC. According to the development of DIC at Day 3 patients were allocated into two groups: Overt-DIC Group (n=35) and Non-DIC Group (n=52). Protein C activity levels, SOFA scores and mortality in both groups was analyzed and correlated.

Statistical differences between both groups were analyzed using Wilcoxon rank-sum test for non-normally distributed variables, Chi-square or Fisher's exact test for categorical variables as applicable. Mann-Whiteny U test was applied to check the significance of difference in Protein C in both groups. Receiver Operator Curve (ROC) analysis was conducted to evaluate the ability of the Protein C to discriminate among patients who developed Overt-DIC verses Non-DIC. The results of the ROC curve analysis along Area Under the Curve (AUC), Cut-off values, sensitivity, specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) were calculated. P-value of <0.05 was considered statistically significant. Data were analyzed using Statistical Package for Social Sciences (SPSS) version 21.0.

Results

Total of 87 septic patients were included in the study, of which 35 were included in the Overt-DIC Group and 52 in Non-DIC Group. Baseline characteristics and 28 Day mortality of both groups is shown in Table I. SOFA score and Protein C both showed positive correlation with DIC and mortality with p-value being <0.05. There was a significant difference in values of baseline Protein C activity in both groups p-value (0.00).

The Protein C produced an area under the curve, by ROC analysis, at 0.89 (P < .001) (Figure 1). The overall sensitivity was 90.4%, specificity 71.4%, Positive Predictive Value (PPV) 73% and Negative Predictive Value (NPV) 95% (CI 88.54-90.52%). Cut-off level was established for Protein C which was 52.9% as shown in Table II.

Discussion

In patients with overt-DIC Protein C activity levels are low due to downregulation of thrombomodulin and Endothelial Protein C Receptor (EPCR). Its levels are also affected by vascular leakage, liver dysfunction and increased consumption.[12,13] In light of these facts clinical trials have been conducted to determine whether the administration of recombinant thrombomodulin and Activated Protein C (APC) results in lower mortality in patients with overt-DIC.

Sadly the results of these trials have been unsatisfactory, emphasizing the need for establishing a good predictive marker for overt-DIC.[14,15]

Table I: Demographic characteristics of septic patients.				
Demographics	All patients (n=87)	Overt-DIC (n=35)	Non-DIC (n=52)	p-value
	Mean±SD			
Age	58.82±18.2	60.51±19.51	57.7±17.47	
Gender Male Female	 45 (51.7%) 42 (48.3%)	 21 (60%) 14 (40%)	 24 (46.2%) 28 (53.8%)	
Source: Pulmonary Urinary Abdominal Gynaecological Others	 38 (43.7%) 18 (20.7%) 5 (5.7%) 2 (2.3%) 24 (27.6%)			
SOFA score	4.32±1.47	4.6±1.4	4±1.4	0.027*
Protein C (low)	45	33 (73.3%)	12 (26.6%)	0.00* 0.00**
28 Day Mortality	37	31 (83.7%)	6 (16.2%)	0.00*
** Pearsons correlation/ Chi-Square Test. ** Mann-Whitney U test.*				

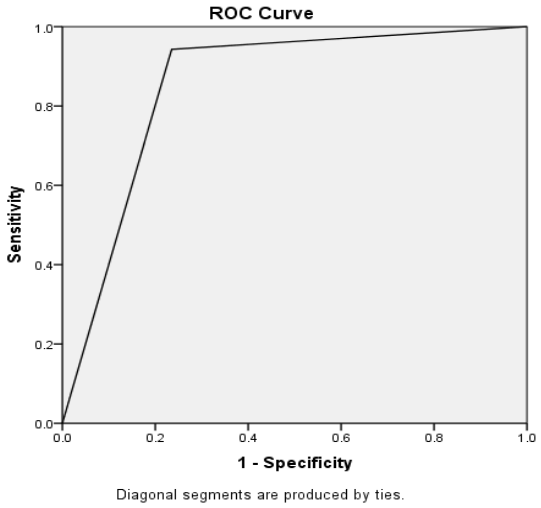

Figure 1: ROC analysis of the Protein C

Table II: AUC and ROC analysis of protein C.	
Statistics	Value
AUC	0.89
Sensitivity	90.4%
Specificity	(100-28.6) 71.4%
Positive predictive value	73%
Negative predictive value	95%
Cut-off value	52.9%

Our study showed significant differences in baseline Protein C activity levels on admission in both groups. Levels were significantly lower in those patients who later on developed overt-DIC. There are very few studies conducted around the world to determine whether Protein C or any other biomarker can predict the development of overt-DIC in patients with sepsis. These previous studies showed a positive correlation of Protein C with overt-DIC.[10,16,17] Similar results were found in our study which showed a strong correlation between baseline Protein C levels and evolution of DIC. Sensitivity and specificty of Protein C were impressive in predicting DIC i.e 90.4% and 71.4% respectively. A similar study conducted by Koyama et al. showed sensitivity and specificity of Protein C as predictive marker to be 81% and 79% which is similar to ours.[16]

We determined the cut-off level for Protein C which can easily predict the evolution of a septic patient to overt-DIC. Our study showed that patients with Protein C activity levels of 52.9% and lower have increased chances of developing overt-DIC during their hospital stay. A similar cut-off was established by Koyama et al. of 46%.[16] Daily Protein C activity levels were not performed in our study due the use of anticoagulants or infusion of Fresh Frozen Plasma (FFP) in patients with sepsis.

Our study showed a strong correlation between Protein C, SOFA score and 28-Day mortality. We used SOFA score to determine organ dysfunction in patients with sepsis. There was a significant difference in scores of both groups as well a strong association of SOFA score with mortality. Previous studies have shown it to be a useful tool in predicting mortality of hospital admitted patients.[18] SOFA score and Protein C can be very useful in predicting mortality in septic patients.

The limitations of our study were that firstly, it was a single center study with a small population of patients meeting the criteria, so the results are difficult to be applied to

whole population. Secondly, due to budget issues we could not compare Protein C with other such biomarkers, which are hypothesized to predict overt-DIC. But despite these shortcomings our study has showed that baseline Protein C activity levels alone are amazingly effective in predicting overt DIC and mortality in patients with sepsis. Such a marker can be very helpful in a country like Pakistan where sepsis and DIC related mortalities are very high and not many treatment and management options are available.

Conclusion

Low Protein C activity levels alone on admission in hospital can effectively predict the evolution of severe coagulopathy (over-DIC) and mortality in patients with sepsis. Such a marker can be very helpful in prediction and timely management of patients evolving into DIC.

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