Original Article

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Serum Procalcitonin as a Diagnostic Marker for Systemic Inflammatory Response Syndrome in Intensive Care Unit Patients

Internal Medicine Section

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ABSTRACT

Introduction: Early assessment of Systemic Inflammatory Response Syndrome (SIRS) through various biomarkers like Procalcitonin (PCT), C-reactive Protein (CRP), Interleukin-1 (IL-1) etc., is crucial to manage the outcome of patients. Levels of PCT concerning its likelihood to distinguish patients with SIRS and non-SIRS and the possibility to predict mortality in patients with sepsis has been variable.

Aim: To investigate the role of PCT in early diagnosis of sepsis in patients admitted to Intensive Care Unit (ICU).

Materials and Methods: In this prospective observational study, 136 patients hospitalised in ICU at Vydehi Institute of Medical Sciences and Research Centre, Bangalore, Karnataka, India, between July 2019 to June 2020 were evaluated and PCT was analysed using Finecare™ PCT rapid test. Receiver Operating Characteristic (ROC) curve analysis and multiple logistic regression was carried out to detect the association of predictive PCT value with its outcomes.

Results: PCT showed the best predictive value in the diagnosis of SIRS at 1.68 ng/mL (Area Under Curve (AUC)-0.87; p<0.05) having Positive Predictive Value (PPV) and Negative Predictive Value (NPV) of 90.43% and 73.81%, respectively. Multiple logistic regression model adjusted for age, weight, and duration of stay to predict the outcome of SIRS, positive blood culture and fatality case rate derived a significant association of PCT with Odds Ratio (OR) being 1.23 (1.11-2.31), 1.06 (1.01-1.98) and 1.76 (1.08-2.14), respectively.

Conclusion: Early identification and treatment for sepsis significantly affects mortality. It appears that consecutive measurements of biomarkers could be valuable, but further prospective studies are important to characterise the role of PCT as a prognostic marker in sepsis and severe sepsis.

Keywords: Biomarkers, Prognosis, Sepsis

INTRODUCTION

Sepsis remains a major health problem in patients admitted to ICU [1]. Although the mortality rate of sepsis has declined in the last two decades, it is still unacceptably high and survival is frequently associated with long-term morbidity [2]. Few studies in India have reported frequent prevalence of sepsis with 28.3% contracting it during ICU stay and having a mortality rate of 34% [3].

Early assessment of SIRS to infection followed by prompt antimicrobial therapy is crucial to manage outcome of patients [4]. Regardless of the high sepsis recurrence, its diagnosis remains difficult, and clinical profile, identification of microbes, and inflammatory markers like leukocytosis, CRP and IL-1 are utilised for the same [5], however blood culture is considered as the gold standard which takes around 48-72 hours for reporting [6,7]. A marker which has good sensitivity and specificity would be exceptionally valuable for the diagnosis of SIRS and septic states which could assist to improve the outcome [8]. PCT has ended up being a marker for the identification of systemic infection which does not alter the presence of non-infectious inflammation or localised infection [8-11]. The plasma concentration rises rapidly after infection, which had caused systemic response [12] and is indirectly related to the severity of sepsis, and also PCT plasma elimination half-life indicates the course of the disease and the successful completion of therapy [13]. However, there is paucity of literature pertaining to this biomarker especially in Indian population and is not routinely used as a marker for early detection of infection in critically ill patients [5,14,15].

This study aimed to investigate the role of PCT in early diagnosis of sepsis in patients admitted to ICU, possibility to distinguish between patients with sepsis and those with non-infectious SIRS and the possibility to predict mortality in patients with sepsis.

MATERIALS AND METHODS

Study Design and Participants

In this prospective study done during the period between July 2019 to June 2020, 136 patients who were hospitalised in ICU aged 50 years or more under the Department of General Medicine and Endocrinology, Vydehi Institute of Medical Sciences and Research Centre, Bangalore, Karnataka, India, were enrolled consecutively. The research was carried out as per ethical standards of the Declaration of Helsinki and the study approval was obtained from the Ethics Committee of Vydehi Institute of Medical Sciences and Research Centre, Bangalore, Karnataka, India (ECR/747/Inst/KA/2019). The enrolled patients after getting informed consent were categorised on the basis of presence (n=96) or absence of SIRS (n=40). According to the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) [16], in all patients criteria for SIRS (body temperature >38 or <36°C, heart rate >90 beats/min, respiratory rate >20 breath/min or pCO_2 <4.3 kPa, white blood cell count >12.0×10^9/L or <4.0×10^9/L, or >10% immature forms) was evaluated and predictive value of PCT in sepsis was analysed.

Exclusion criteria: Patients with malignancy or haematological disorders, patients on anti-tumour drug therapy, patients with history of transplantation, and patients following a surgical treatment (less than 48 hours), were excluded).

Study Variables

Demographic characteristics such as age and sex were recorded. Whole blood samples were collected from the patients followed by serum separation. Serum PCT levels were quantitatively measured by Finecare™ PCT rapid test using Finecare™ Fluorescence Immuno Aassay (FIA) meter which is based on FIA technology. The

working range and the detection limit of the PCT test system are 0.1-100 ng/mL and 0.1 ng/mL, respectively. Each Finecare™ PCT rapid test cartridge contains internal control that satisfies routine quality control requirements. This internal control is performed each time a patient sample is tested. This control indicates that the test cartridge was inserted and read properly by Finecare™ FIA meter. An invalid result from the internal control causes an error message on Finecare™ FIA Meter indicating that the test should be repeated.

STATISTICAL ANALYSIS

Statistical Package for the Social Sciences (SPSS) version 21.0 was used for the analysis. The mean±Standard Deviation (SD) or median with interquartile range were applied in descriptive statistics depending on the normality of the data distribution. Mann-Whitney test or Student's t-test was used to compare continuous variables and the Fisher's exact test was used to compare categorical variables. The ROC curve was used to calculate the AUC for diagnostic value and accuracy of different used parameters with the best sensitivity and specificity for given cut-off values. PPV and NPV were calculated using recommended cut-off values. Multivariate logistic regression, stratified on the presence or absence of SIRS, positive blood culture and fatal outcome was performed adjusting for potential confounding variables (p<0.20), to assess independent relationship between PCT levels and outcomes. The p<0.05 was considered as statistically significant.

RESULTS

The characteristics of the participants enrolled are shown in [Table/Fig-1]. A significant difference was observed between the groups in terms of PCT levels, sex, blood culture and duration of stay.

Variables	Category	Total (n=136)	SIRS (n=96)	Non-SIRS (n=40)	p-value
Age (years)		54.12±18.98	54.70±18.69	52.87±17.65	0.72†
PCT	Median	1.45 (0.01-184.68)	1.95 (0.06-184.68)	0.78 (0.01-87.36)	<0.01*‡
Sex	Male	94 (69.12)	60 (62.50)	34 (85.00)	<0.01*§
	Female	42 (30.88)	36 (37.50)	6 (15.00)	
Blood culture	Positive	35 (25.74)	30 (31.25)	5 (12.50)	0.02*§
	Negative	101 (74.26)	66 (68.75)	35 (87.50)	
Death		16 (11.76)	15 (15.62)	1 (2.50)	0.03*§
Duration of stay (days)		8.12±7.76	10.23±4.34	5.34±3.54	<0.05*†

[Table/Fig-1]: Characteristics of study participants stratified by Systemic Inflammatory Response Syndrome (SIRS).
PCT: Procalcitonin; SIRS: Systemic inflammatory response syndrome
*-p<0.05; †-Student's t-test; ‡-Mann-Whitney test; §-Fischer Exact test

The best predictive value in the diagnosis of SIRS with the cut-off value of PCT at 1.68 ng/mL (AUC 0.87; p<0.05), with PPV of 90.43%, NPV of 73.81% and accuracy of 85.29%. Similarly, ROC analysis deciphered an optimal cut-off point of >67.89 ng/mL for the prediction of death, with an accuracy of 88.24%. With a prevalence of death being 16 (2 females and 14 males) out of 136 (11.76%), the PPV of PCT >67.89 ng/mL is 50.00% and the NPV is 94.83% [Table/Fig-2]. The major complications which arose among the deceased participants were acute kidney injury (68.75%) and metabolic acidosis (18.75%) and the cause of death was ascertained to septic shock (75.00%).

As outlined in [Table/Fig-3], the univariate relationship between demographic data, PCT and outcome showed that the levels of PCT were associated significantly with SIRS, positive blood culture and fatality case rate. A multiple logistic regression model adjusted for age (<50 years and ≥50 years), weight (<60 kg and ≥60 kg), and duration of stay in hospital (<7 days and ≥7 days) was then performed to predict the outcome which also derived a significant association.

Variables	SIRS	Blood Culture	Death
Cut-off	1.68 ng/mL	5.34 ng/mL	67.89 ng/mL
AUC	0.87±0.08	0.76±0.03	0.68±0.07
p-value	0.003*	0.02*	<0.001*
95% CI	0.80-0.94	0.69-0.83	0.55-0.82
Sensitivity (%)	88.54	57.14	62.50
Specificity (%)	77.50	90.10	91.67
PPV (%)	90.43	66.67	50.00
NPV (%)	73.81	85.85	94.83
Accuracy (%)	85.29	81.62	88.24

[Table/Fig-2]: Receiver Operating Characteristic (ROC) for procalcitonin for prediction of SIRS, positive blood culture and fatal outcome.
SIRS: Systemic inflammatory response syndrome; AUC: Area under curve; CI: Confidence interval; PPV: Positive predictive value; NPV: Negative predictive value; *-p<0.05

Outcomes	Univariate analysis	Multivariate analysis		Confounding factors‡		
	OR	aOR†	p-value†	Age	Weight	Duration of stay
SIRS	1.78 (1.26-2.76)	1.23 (1.11-2.31)	0.02*	0.23	0.04*	<0.01*
Positive blood culture	1.44 (1.21-2.13)	1.06 (1.01-1.98)	<0.01*	0.36	0.43	0.04*
Death	1.82 (1.12-2.45)	1.76 (1.08-2.14)	<0.01*	0.21	0.02*	<0.01*

[Table/Fig-3]: Univariate and multivariate logistic regression for the outcome predictors from procalcitonin levels.
aOR: adjusted Odds ratio; SIRS: Systemic inflammatory response syndrome; *-p<0.05; †-Multivariate logistic regression analysis adjusted for confounding factors with p<0.20; ‡-p values derived from multiple regression analysis

DISCUSSION

The capacity to diagnose or exclude suspected sepsis is basic for patients' outcomes. It has been demonstrated that earlier diagnosis of sepsis and satisfactory and early initiated treatment prompts better results and diminishes mortality brought about by sepsis [17].

Procalcitonin was first depicted in the plasma of patients with sepsis and infection in the early 1990s as a protein induced by sepsis [9]. From that point onwards, it has been assessed in clinical settings as an apparatus to differentiate bacterial infection from other inflammatory states and infections [18]. The diagnostic capacity of PCT was superior to that of other parameters of infection and inflammation in certain indications due to its preferential induction during inflammation of bacterial origin and its high concentration during the severe stages of sepsis and systemic inflammation as depicted by Meisner M [19]. It is viewed as a decent biomarker of sepsis that has a correlation with severity of infection [20] and also rules out or anticipate bacteraemia in patients with acute fever [21]. The predictive value of PCT in diagnosis of sepsis [22-24] and bacteraemia [15,23,25-27] has been examined in different studies to acquire best sensitivity and specificity. In present study also significant differences in the values of PCT between SIRS and non-SIRS patients, and between blood culture positive and negative sepsis was evaluated. The differences observed in the median absolute value for PCT in present study, and among some other studies by Robriquet L et al., (3.6 ng/mL), Tsalik EL et al., (2.3 ng/mL), Charles PE et al., (0.44 ng/mL) and Hangai S et al., (0.38 ng/mL) could have been due to variation in the composition of study population owing to genetic make-up and geography [24-27].

Other than the fact that PCT is a marker of sepsis, it tends to be a useful determinant for rational administration of antibiotics and its usage may safely lead to significant decrease of pointless antibiotic abuse. The levels of PCT in healthy people are extremely low and often difficult to detect. At the time of infection, a continuous release of PCT is activated by an expression of the calcitonin-I gene which in turn is induced by bacterial component such as

lipopolysaccharide or a cytokine such as Tumour Necrosis Factor-α (TNF-α) or IL-6 [28].

Procalcitonin and sepsis showed a positive correlation with increased risk of mortality in a meta-analysis comprising 12 studies conducted by Liu D et al., [29]. In present study also there was a correlation between PCT levels and mortality. Becker KL et al., cited that the toxic proinflammatory effects of PCT on leukocytes along with cytokine production might be the reason of decreased survival in cases of patients with sepsis. The researchers have conducted experiments on animals who have shown significant improvement in survival with experimental sepsis with antibodies against PCT [30].

The data obtained from this study will contribute in increasing the knowledge of the importance of diagnosis of SIRS earlier since PCT test can be performed within 30 minutes and gives important data well before culture results are accessible. This also is a pioneer study in Indian population as the estimated levels of PCT have always been derived from studies conducted in western countries. As there is still no particular biomarker for recognising sepsis, it appears that consecutive measurements of various biomarkers could be valuable, but further prospective studies in the initial phases of sepsis are important to characterise the function of PCT as a prognostic marker in sepsis and severe sepsis, and to investigate its effect on therapeutic techniques, for example, in early initiation of intensified antibiotic therapies.

Limitation(s)

The study is however not without limitations. One limitation is that the inclusion of participants was done via convenience sampling from patients admitted only in the ICU by the attending physician. In addition, other confounding variables which could affect the development of SIRS were not taken into consideration and that could have increased the probability of deriving further correlation among the study variables. Also, an account of the baseline diseases was not taken when patients were selected for inclusion into the study. There is likewise a controversy with respect to whether there is any impact of immune condition on the estimation of diagnostic value of PCT in disease [27,31-33].

CONCLUSION(S)

Rapid identification and early treatment of sepsis have a significant impact on mortality reduction. An ideal biomarker for infections should be able to diagnose early and predict the course and prognosis of the disease and also aid in course of treatment. In the present study, PCT showed the best predictive value in the diagnosis of SIRS at 1.68 ng/mL (AUC-0.87; $p<0.05$) having PPV and NPV of 90.43% and 73.81%, respectively and also a significant association was established with predictive levels of PCT and outcomes such as SIRS, positive blood culture and death.

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