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Critical Care Unit

Rapid Detection of Early Sepsis in Intensive Care Unit: Comparison of Biomarkers - Procalcitonin, Serum Lactate and C - Reactive Protein

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Abstract **Original Research Article**

***Background*:** Intensivists would benefit from an accurate and easily accessible biomarker for identifying patients with different source of infections who require special attention in critical care units due to their higher risk of death. ***Objectives*:** The aim of the study was to determine the rapid detection of early sepsis in intensive care unit: comparison of biomarkers - procalcitonin, serum lactate and C - reactive protein. ***Methods*:** Prospective, observational study was carried out in the Department of Critical care unit, Evercare Hospital Dhaka, Dhaka, Bangladesh during January 2021 to June 2021. A total of 60 patients were participated in the study. Statistical analyses of the results were be obtained by using window-based Microsoft Excel and Statistical Packages for Social Sciences (SPSS-24), where required. ***Results*:** Patients admitted in Intensive Care Unit of different disciplines, of different adult ages 20-60 years. In this present series it was observed that 36.7% patients were blood culture positive among 60 cases, 21.7% were Urine culture positive among 60 cases, 28.0% were Tracheal Aspirate positive among 25 cases, and finally 25.0% were Wound Swab culture positive among 12 cases. ***Conclusion*:** Blood culture positivity was the most common, followed by urine culture positivity, tracheal aspirate positivity, and wound swab positivity. Procalcitonin had the highest sensitivity, accuracy, and positive predictive value for predicting sepsis, followed by C-Reactive protein and serum lactate.

Keywords: Early Sepsis, Intensive Care Unit, Procalcitonin, Serum Lactate.

INTRODUCTION

Despite the use of new treatment modalities, improvements in technology and increased experience, mortality of patients with sepsis, severe sepsis, septic shock and sepsis-induced multi-organ failure remains very high [1]. Such unfavorable prognosis of patients with sepsis is partly due to delayed diagnosis. Disclosure of severe infection is hampered by low sensitivity and specificity of the laboratory tests and by non-specificity of clinical signs [2]. Biomarkers offer a tool in facilitating early diagnosis, in identifying patient populations at high risk of complications, and in monitoring progression of the disease, which are critical assessments for appropriate therapy and improvement in patient outcome. More than 170 biomarkers have been identified as useful for evaluating sepsis as diagnostic, prognostic, monitoring, surveillance and stratification. The sensitivity, specificity and predictive values are the most important parameters that characterize the ideal biomarker. In these modern times, laboratory results are done on daily basis. Therefore, proper interpretation and wise use of biomarkers are necessary. Combination approaches of biomarkers with new techniques needs to be further evaluated.

The inflammatory variables appear early in response to sepsis, commonly used are Plasma C-Reactive Protein, Serum Procalcitonin, Serum lactate level, IL-6, IL-8, IL-10, TNF-α, IL-1β, LPS-Binding protein (LBP), proadrenomedullin, Angiopoietin etc.

Procalcitonin (PCT)

An elevated level of Procalcitonin (the precursor molecule to the hormone calcitonin) distinguishes sepsis from non-infectious SIRSs. A useful feature of Procalcitorin is that its blood levels are good reflections of the severity of a patient's sepsis. More than 2 SDs above the normal value is significant.

Among the potentially useful sepsis markers PCT has been proposed to be the most promising

candidates [3, 4]. Serum level of PCT is increased by 3 hrs with peak values between 6-24 hrs. Although progressively declining, serum levels remained above normal up to 7-14 days.

As a diagnostic marker, PCT has several advantages over other inflammatory markers, including CRP and serum lactate and white blood cell count. It shows:

i. An early and highly septic rise that can be observed 3-6 hours after exposure to an infection [5].
ii. Increased PCT concentrations were found even prior to the clinical manifestation of BSI (i.e., fever) illustrating the high sensitivity of PCT [6].
iii. More rapid decrease when the infection is controlled by the immune system supported by antibiotic therapy.
iv. It correlates with the extent and severity of infection.
v. Has prognostic implication, namely a) predicting the course of disease b) the risk for mortality in critically ill patients with infections and ventilator-associated pneumonia [7, 8].
vi. Unlike CRP, production is not attenuated by non-steroidal and steroidal anti-inflammatory drugs [8, 9].

Lactate

Lactate has been recognized and utilized as indicator of tissue hypoxia and anaerobic metabolism which has immediate relevance to the fundamental pathophysiologic difference between sepsis and septic shock, strongly predicts the prognosis. Half-life of lactate is around 20 minutes, even in septic patients. If the lactate level is persistently elevated, it's not because the body can't get rid of it, but because the body continues producing it, shifting to anaerobic metabolism. Serum Lactate levels >2 mmol/L on admission associated with a 1.94-10.89-fold increased mortality compared to levels below 2 mmol/L [10]. A lactate level of >4.0 mmol/L is concerning for end-organ dysfunction and adverse outcome, has a mortality rate of 87% and >3mmol/L or above upper limit of laboratory normal levels is significant.

C-Reactive protein

CRP is an acute phase reactant, synthesized by hepatocytes in response to cytokine stimulation. Normal plasma level of CRP is usually <0.35mg/dl. Plasma levels increase with within 4-6 hours after initial tissue injury and continue to increase several hundred folds within 24-48 hrs. CRP remains elevated during the acute phase response and returns to normal with resolution of tissue damage. Rapid decrease in CRP levels over the first 48 hrs. Of therapy has been shown to correlate with an effective response to the initial antimicrobial therapy in septic patients. CRP has also been shown to have a poor predictor of mortality compared to other biomarkers. CRP is useful in the detection of sepsis and that it is more sensitive than traditionally used markers such as body temperature and WBC [11].

METHODOLOGY

This Prospective, observational study was carried out in Department of Critical care unit, Evercare Hospital Dhaka, during January 2021 to June 2021. A total of 60 patients with clinical sign-symptoms of SIRS or Sepsis and laboratory suspicion who fulfilled the inclusion criteria were included in this study. Patients admitted in Intensive Care Unit of different disciplines, of different adult ages (20-60 years), both sexes and willing to take part in this study of Bangladesh Medical College and Hospital, Dhaka. After taking consent and matching eligibility criteria, data were collected from patients on variables of interest using the predesigned structured questionnaire by interview, observation. Statistical analyses of the results were be obtained by using window-based Microsoft Excel and Statistical Packages for Social Sciences (SPSS-22), where required.

RESULTS

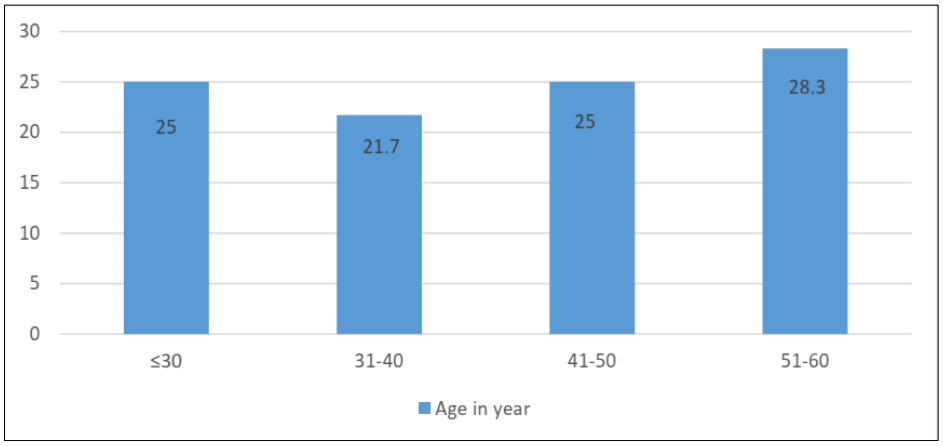

Figure 1: Bar diagram showing age distribution of the study patients

Figure 1 shows age distribution of the study patients. It was observed that more than one fourth (28.3%) patients belonged to age 51 – 60 years. The mean age was found 39.7±12.2 years with the range from 20 to 60 years.

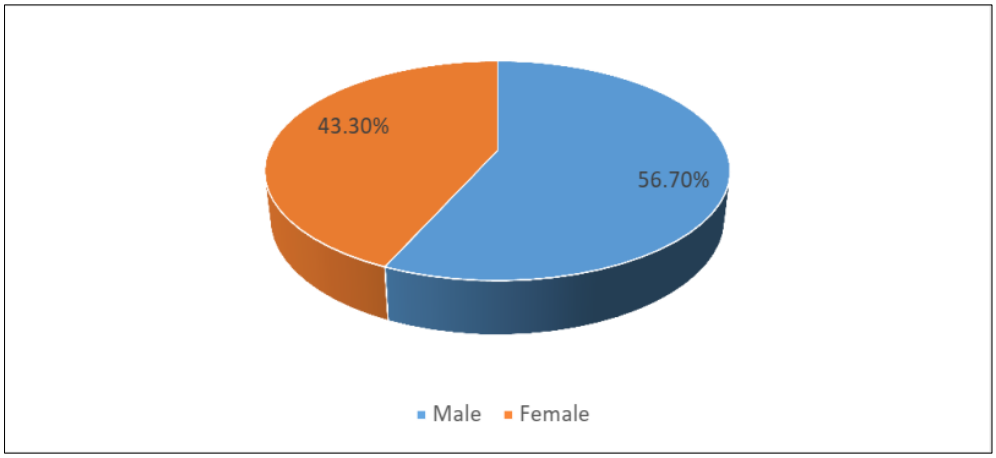

Figure 2: Distribution of the study patients by sex (n=60)

Figure 2 shows sex of the study patients. It was observed that majority i.e., 56.7% patients were male and 43.3% patients were female.

Table 1: Distribution of the study patients by culture positive

Name of culture	Culture positive	Percentages
Blood (n=60)	22	36.7
Urine (n=60)	13	21.7
Tracheal Aspirate (n=25)	7	28.0
Wound Swab (n=12)	3	25.0

Table 1 shows Blood, Urine, Tracheal Aspirate and Wound Swab of the study patients. It was observed that 22 (36.7%) patients were blood culture positive among 60, 13 (21.7%) patients were Urine culture positive among 60, and 7 (28.0%) patients were Tracheal Aspirate culture positive among 25 cases and finally 3 (25.0%) patients were Wound Swab culture positive among 12 cases.

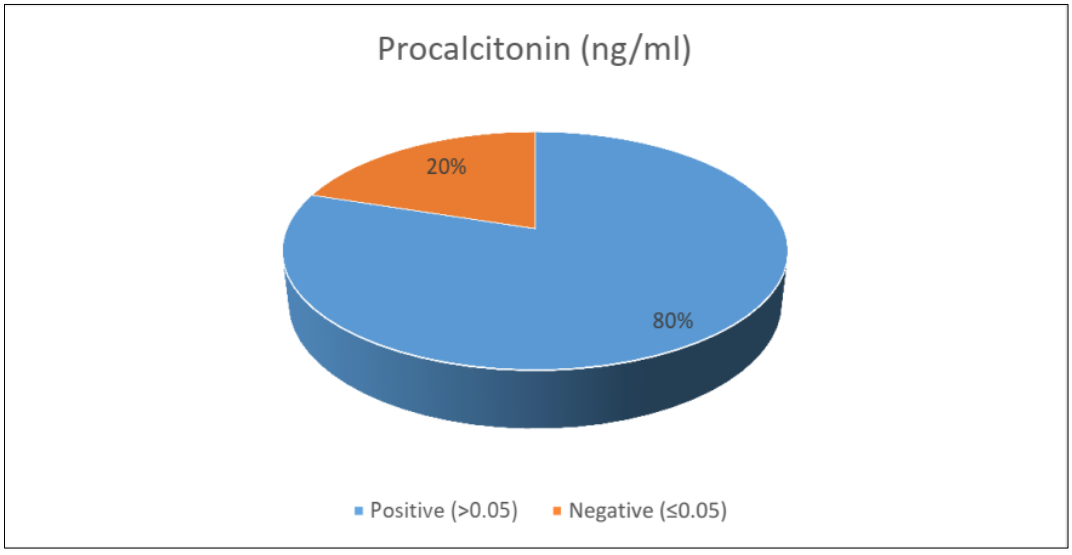

Figure 3: Pie diagram showing distribution of the study patients by Serum Procalcitonin.

Figure 3 shows Procalcitonin of the study patients. It was observed that more than three fourth (80.0%) patients had Procalcitonin level > 0.05 ng/ml.

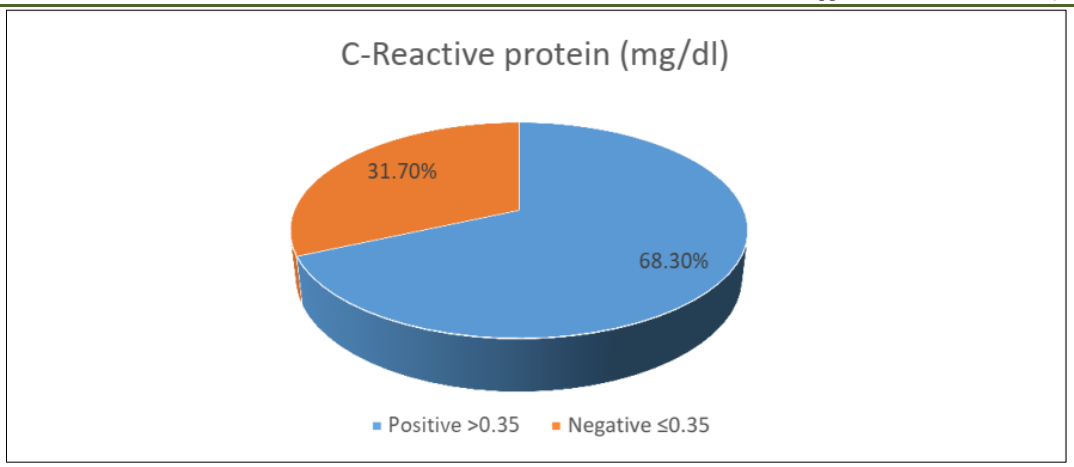

Figure 4: Pie diagram showing distribution of the study patients by C-Reactive protein.

Figure 4 shows C-Reactive protein of the study patients. It was observed that more than two third (68.3%) patients had C-Reactive protein level > 0.35 mg/dl.

Table 2: Comparison between Culture positive (any culture) and Procalcitonin evaluation for sepsis (n=60)

Procalcitonin	**Culture**	
	Positive (n=45)	**Negative (n=15)**
Positive (n=48)	40 (True positive)	8 (False positive)
Negative (n=12)	5 (False negative)	7 (True negative)

Table 2 shows Procalcitonin evaluation for sepsis. True positive 40 cases, false positive 8 cases, false negative 5 cases and true negative 7 cases identified by Culture positive (any culture).

Table 3: Comparison between Culture positive (any culture) and C-Reactive protein evaluation for sepsis (n=60)

C-Reactive protein	**Culture**	
	Positive (n=45)	**Negative (n=15)**
Positive (n=41)	34 (True positive)	7 (False positive)
Negative (n=19)	11 (False negative)	8 (True negative)

Table 3 shows C-Reactive protein evaluation for sepsis. True positive 34 cases, false positive 7 cases, false negative 11 cases and true negative 8 cases identified by Culture positive (any culture).

Table 4: Comparison between Culture positive (any culture) and Serum Lactate evaluation for sepsis (n=60)

Serum lactate	**Culture**	
	Positive (n=45)	**Negative (n=15)**
Positive (n=39)	31 (True positive)	8 (False positive)
Negative (n=21)	14 (False negative)	7 (True negative)

Table 4 shows Serum Lactate evaluation for sepsis. True positive 31 cases, false positive 8 cases, false negative 14 cases and true negative 7 cases identified by Culture positive (any culture).

Table 5: Sensitivity, specificity, accuracy, positive and negative predictive values of the Procalcitonin, C-Reactive protein and Serum Lactate for prediction of sepsis.

Validity test	Procalcitonin (%)	C - Reactive protein (%)	Serum Lactate (%)
Sensitivity	88.9	75.6	68.9
Specificity	46.7	53.3	46.7
Accuracy	78.3	70.0	63.3
Positive predictive value	83.3	82.9	79.5
Negative predictive value	58.3	42.1	33.3

Table 5 shows the validity of the Procalcitonin. C-Reactive protein and Serum Lactate evaluation for prediction of sepsis was correlated by calculating sensitivity, specificity, accuracy, positive and negative predictive values.

DISCUSSION

In this present study it was observed that more than one fourth (28.3%) patients belonged to age 51 – 60 years. The mean age was found 39.7±12.2 years with the range from 20 to 60 years. Miglietta *et al*., (2015) found the mean age values were 64.4±11.8 years for patients with SIRS, 60.1±16.5 years for patients with bacterial sepsis and 65.8±16.2 years for patients with systemic candidiasis. Rica and Suberviola found the mean age were 65.6±16.9 years and 64.8 ± 18.7 years respectively [12, 13].

In this current study it was observed that majority i.e., 56.7% patients were male and 43.3% patients were female. Male to female ratio was 1.3:1, which is closely resembled with Rica and Miglietta studies, where they found male 59.5% and 59.3% respectively [12-14].

The blood culture still represents the gold standard for sepsis diagnosis; however, treatments are usually delayed while waiting for lab results [15, 16]. In this present series it was observed that 36.7% patients were blood culture positive among 60 cases, 21.7% were Urine culture positive among 60 cases, 28.0% were Tracheal Aspirate positive among 25 cases, and finally 25.0% were Wound Swab culture positive among 12 cases. Miglietta observed a total of 145 patients and based on the blood culture results, diagnosis was SIRS 29.0% bacterial sepsis 48.3%, systemic candidiasis 22.8% [14]. Mariappan found that 42.0% of patients had a positive urine culture, whereas only 5.6% had a positive urine culture from the bladder [17]. According to the study of Margel, positive detection of urine culture is accepted as a relative risk for SIRS [18].

In this current series it was observed that more than three fourth (80.0%) patients had Procalcitonin > 0.05 ng/ml. Riedel *et al*., (2011) observed 295 patients and classified according to the presence or absence of pathogenic organisms isolated in BCs and the level of Procalcitonin detected in their serum samples [19]. Various markers of sepsis, including C-Reactive protein (CRP), tumour necrosis factor (TNF)-α, IL-1β, IL-6 and IL-8, have all been studied for their ability to differentiate SIRS from sepsis [9-21]. Several investigators have questioned the diagnostic accuracy of procalcitonin (PCT) measurement, results with which have been inconsistent and variable [22, 23].

In this present study it was observed that majority (65.0%) patients had Serum Lactate > 2.0 mmol/L. Lactate has been incorporated into definitions for sepsis and normalization of serum lactate levels has been used as part of goal-directed care [24]. There is a broad consensus that an association between elevated lactate concentrations and poorer outcome is seen; however, a recent review that included 28 studies found no ability to recommend a threshold value because of the extensive overlap of levels among patients with different outcomes [25]. Serum Lactate concentration at the time of admission has been recommended by the surviving sepsis campaign guidelines as a marker of hypoperfusion [26], and a trial looked at using serum lactate to monitor resuscitation efforts [27]. Severe sepsis is sepsis induced tissue hypoperfusion or organ dysfunction sepsis with, at least, one acute organ dysfunction (sepsis-induced), evidence of tissue hypoperfusion or hypotension or abnormal serum lactate level or oliguria.

Procalcitonin and C-Reactive protein are probably the most widely used biochemical parameters for diagnosis and management of patients with sepsis, together with lactate. TNF, IL-1β and IL-6 are cytokines that act as mediators of the immunological response to infection and could be potentially useful as biomarkers of sepsis [28]. Among the common biomarkers used, C-Reactive protein (CRP) is a useful marker of systemic inflammation without discriminating infection from other inflammatory processes [29]. In this present series it was observed that C-Reactive protein evaluation for sepsis, true positive 34 cases, false positive 7 cases, false negative 11 cases and true negative 8 cases identified by culture evidence.

In 2003, elevations of both CRP and PCT were added to the updated definition of sepsis. During the last decade, serum lactate has been used for guiding therapy of severe sepsis and septic shock [30]. No single biomarker of sepsis is ideal, but many of them have proven the utility in identifying critically ill patients who are at high risk and who need to be diagnosed as soon as possible [28]. In this current study it was observed that Serum Lactate evaluation for sepsis, true positive 31

cases, false positive 8 cases, false negative 14 cases and true negative 7 cases identified by Culture evidence.

In this present study it was observed that the validity of the C-Reactive in the prediction of sepsis was 75.6% sensitive, 53.3% specific, 70.0% accurate, 82.9% positive predictive values and 42.1% negative predictive values. On the other hand, the validity of the Serum Lactate evaluation for prediction of sepsis was 68.9% sensitive, 46.7% specific, 63.3% accurate, 79.5% positive predictive values and 33.3% negative predictive values.

Limitations of the Study

The present study was conducted in a very short period due to time constraints and funding limitations. The small sample size was also a limitation of the present study.

CONCLUSION

This study was undertaken to initiate early and appropriate management of sepsis and to reduce the hospital stay and overall cost of the patient. Most of the patients were in 5th decade and male predominant. Blood culture positive was more common followed by urine culture positive, tracheal Aspirate culture positive and Wound Swab culture positive. Procalcitonin level positive was more frequent followed by C-Reactive protein and Serum Lactate. The Sensitivity, Accuracy and Positive predictive value of Procalcitonin was higher followed by C-Reactive and Serum Lactate for prediction of sepsis.

RECOMMENDATION

This study can serve as a pilot to much larger research involving multiple centers that can provide a nationwide picture, validate regression models proposed in this study for future use and emphasize points to ensure better management and adherence.

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