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Association of Early-Rising Procalcitonin Level with Culture-Positive Bacterial Sepsis

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Abstract

Introduction: Diagnosis and treatment of sepsis poses a challenge for health care providers at clinical setup. Identifying sepsis and making rational decision regarding the treatment plan is crucial to the overall survival and recovery of the affected patients. Serum procalcitonin (PCT) is an emerging biomarker for diagnosing sepsis worldwide. But serum PCT data for diagnosing sepsis from our country perspective is scarce. Present study aims to evaluate the relation between serum PCT level and the clinical state of the sepsis among Bangladeshi patients. **Methods:** This was a cross-sectional study conducted among 61 clinically diagnosed patients with sepsis admitted at Dhaka Medical College Hospital and Apollo Hospital Dhaka aged 18 years or older. Data were collected from the respondents using a semi-structured questionnaire through a face to face interview. **Results:** Blood culture positive sepsis was found among 37.7% of the respondents. Escherichia Coli was the most commonly found organisms in blood culture. Meropenem was found to be sensitive antibiotics in most cases. Among the respondents around 2/3rd had serum PCT level ≥10 ng/ml and diagnosed as patients in septic shock. Mean serum procalcitonin level for respondents with culture positive bacterial sepsis was 22.60 ng/ml and for respondents without culture positive bacterial sepsis was 8.47 ng/ml and this difference was statistically significant ($p < 0.05$). **Conclusions:** The present study indicates that serum PCT level rises more among culture positive bacterial sepsis patients than patients without culture positive bacterial sepsis. In primary health care setup, serum PCT can be used as a tool for early diagnosing culture positive sepsis. A large scale, multicenter study should be under taken to

further evaluate the viability and feasibility of using serum PCT as a biomarker for diagnosing culture positive sepsis.

Keywords: Early Rising Procalcitonin, culture, positive bacterial, sepsis

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1.Introduction:

Systemic inflammatory response syndrome (SIRS) encompasses a variety of complex findings that result from systemic activation of the innate immune response. The clinical parameters include two or more the following: Fever (>38° C) or hypothermia (90 beats/min), tachypnea (>20 breaths/min) or hyperventilation ($PaCO_2$ < 32 mmHg), and altered white blood cell count (>12,000 cells/mm3 or 10% immature neutrophils. Sepsis is defined as SIRS resulting from infection, whether of bacterial, viral, fungal, or parasitic origin. Severe sepsis is associated with at least one acute organ dysfunction, hypoperfusion, or hypotension. [1,2] Despite the enormous investment in critical care resources, severe sepsis mortality ranges from 28% to 50% or greater. Moreover, cases of severe sepsis are expected to rise in the future for several reasons, including: increased awareness and sensitivity for the diagnosis; increasing numbers of immunocompromised patients; wider use of invasive procedures; more resistant microorganisms; and an aging population. [3] Definitions for the terms of "SIRS", "sepsis", "severe sepsis" or "septic shock" have been proposed by the ACCP/SCCM Consensus Conference in 1992, and are now widely used. Traditional markers of systemic inflammation, such as CRP, erythrocyte sedimentation rate (ESR) and white blood cell count (WBC), also have proven to be of limited utility in such patients due to their poor sensitivity and specificity for bacterial infection. Moreover, microbiological cultures; the conventional gold standard diagnostic method for sepsis, are often time consuming do not reflect the host response of systemic inflammation or the onset of organ dysfunction, and sometimes misleading with false positive or false negative reports. These shortcomings in both culture and available blood tests have driven researchers to find other more sensitive and specific markers. In recentyears, PCT has been the focus of much attention as a specific and early marker for systemic inflammation, infection, and sepsis, both in children and adults [2,4] Procalcitonin is the prohormone of calcitonin, secreted by different types of cells from numerous organs in response to proinflammatory stimulation, particularly bacterial stimulation; whereas calcitonin is only produced in the C cells of the thyroid gland as a result of hormonal stimulus.[5] Depending on the clinical background, a PCT concentration above 0.1 ng/mL indicate clinically relevant bacterial infection, requiring antibiotic treatment.[6] At a PCT concentration > 0.5 ng/mL, a patient should be considered at risk of developing severe sepsis or septic shock.[7,8] A number of studies have shown that the systematic use of PCT for sepsis diagnosis and monitoring may also have a positive impact on the reduction of antibiotic (AB) treatment, therefore allowing a shorter stay in the ICU and lower costs per case. This will also be beneficial in combating the increase of antibiotic-resistant micro-organisms which is mainly related to the excess use of antibiotics.[9-12] Additionally, researchers found a ≥30% decrease in PCT levels between days 2 and 3 to be an independent predictor of survival in ICU patients.[13] Thus, procalcitonin has been identified as a promising biomarker that may provide added value to the clinical decision process, i.e. assist in diagnosis, assess prognosis, and assist in treatment selection and monitoring. This biomarker is now widely used in Europe and recently it was approved by the FDA in USA for the diagnosis and monitoring of sepsis and evaluation of the systemic inflammatory response in the clinical arena. [14]

Some specialized & tertiary care hospitals in Bangladesh has been using procalcitonin as a diagnostic tool of sepsis. A number of studies has been carried out in different parts of the world to determine the usefulness of procalcitonin in the diagonosis of sepsis. But due to the scarcity of literature the exact number of such study in Bangladesh is unknown. Information obtained from this study may help in early diagnosis of infectious state (sepsis) and monitoring to the researcher for further study.

2.Materials and methods:

The present study was cross-sectional observational study. The study was carried out at Dhaka Medical College Hospital and Apollo Hospital in Dhaka city from July 2019 to December 2019 among the patients with clinical manifestation of sepsis. 61 cases aged 18 years or older were selected for the study. The study subjects were screened by history and clinical examination and were selected consecutively from the study population. Data were collected using a structured questionnaire containing all the variables of interest. Data were processed and analyzed using computer software SPSS (Statistical Package for Social Sciences), version 21. The test statistics to be used are descriptive statistics and Chi-square or Student’s t-Test as and where applicable. Level of significance was set at p-value < 0.05 were considered significant.

3.Results:

Table1: Distribution of study population according to signs and symptoms present at the time of data collection

Signs and symptoms	Frequency	Percentage
Anaemia	39	63.9
Jaundice	5	8.2
Skin rash	3	4.9
Clubbing	1	1.6
Leukonychia	2	3.3
Ascites	2	3.3
Oedema	4	6.6
Dehydration	48	78.7
Pleural effusion	6	9.8

Among the respondents, 63.9% were anaemic, 78.7% were dehydrated and 9.8% had pleural effusion. Also, 8.2% had jaundice, 6.6% had oedema and 4.9% had skin rash.

Table2: Distribution of study population according to history of patients

Criteria	History of patient	Percentage
Habit	Smoking	36.1
	Alcohol consumption	21.30
Present history	H/O recent infection	13.1
	No H/O recent infection	86.90

Past history	H/O fever	77
	H/O infection	8.20
Co-morbidities	Diabetes Mellitus	52.5
	HTN	42.6
	Dyslipidaemia	29.5

Among the study population 36.1% had H/O smoking and 23.0% had H/O alcohol consumption. 13.1% had H/O recent infection and 77.0% had recent H/O fever and 8.2% had resent H/O infection. Among the respondents, 52.5% had Diabetes Mellitus, 42.6% had HTN and 29.5% had Dyslipidemia.

Table 3: Distribution of respondents according to blood culture findings

Blood Culture	Frequency	Percentage
Culture Positive	23	37.7
Escherichia Coli	5	8.2
Acinetobacter	4	6.6
Streptococcus Pneumoniae	3	4.9
Staphylococcus Aureus	3	4.9
Salmonella Typhi	3	4.9
Pseudomonas Aeruginosa	2	3.3
Klebsiella Pneumoniae	1	1.6
Clostridium Difficile	1	1.6
Staphylococcus Epidermidis	1	1.6
Culture Negative	38	62.3

Among the respondents, Blood Culture was done and 37.7% were found to be culture positive and 62.3% were culture negative. Escherichia Coli was found among 8.2% respondents and Acinetobacter was found among 6.6% respondents. Streptococcus Pneumoniae, Staphylococcus Aureus and Salmonella Typhi were present in 4.9% respondents each, Pseudomonas Aeruginosa was found in 3.3% respondents and Klebsiella Pneumoniae, Clostridium Difficile and Staphylococcus Epidermidis were found among 1.6% respondents each.

Table 4: Distribution of study population according to antibiotic sensitivity for blood culture

Antibiotics	**Frequency**	**Percentage**
Meropenem	12	19.7
Tigecycline	2	3.3
Colistin	2	3.3
Ceftazidime	2	3.3
Ceftriaxone	2	3.3
Metronidazole	1	1.6
Vancomycin	1	1.6
Tazobactam	1	1.6
Total	23	37.7

Among the study population 37.7% were found to be culture positive for blood. When sensitivity for antibiotics were done, 19.7% of the study population were found to be sensitive to Meropenem. Tigecycline, Colistin, Ceftazidime and Ceftriaxone were found to be sensitive among 3.3% of the study population each. Metronidazole, Vancomycin and Tazobactam were found to be sensitive among 1.6% of the study population.

Table 5: Distribution of study population according to Serum Procalcitonin

Serum Procalcitonin Level (in ng/ml)	Frequency	Percentage

<0.5 (Systemic infection not likely)	10	16.4
≥0.5 – <2 (Moderate systemic inflammatory response)	2	3.3
≥2 – <10 (Severe sepsis)	8	13.1
≥10 (Septic shock)	41	67.2

Among the respondents, serum procalcitonin level was <0.5 ng/ml for 16.4% of the respondents. Serum procalcitonin level was ≥0.5 – <2 ng/ml for 3.3% respondents. Serum procalcitonin level was ≥2 -<10 ng/ml for 13.1% respondents and ≥10 ng/ml was for 67.2% respondents.

Table6: Distribution of study population according to association between early rising procalcitonin level with culture positive bacterial sepsis.

Criteria	Serum Procalcitonin level raised	Serum Procalcitonin level normal	Total	Odds ratio	P value
Respondents with culture positive bacterial sepsis	27 (90.0%)	3(10.0%)	30 (49.2%)	2.63	0.33
Respondents without culture positive bacterial sepsis	24 (77.4%)	7(22.6%)	31 (50.8%)		
Total	51 (83.6%)	10 (16.4%)	61 (100%)		

Pearson Chi-Square was done to assess the association between early rising procalcitonin level with culture positive bacterial sepsis. But one cell had expected count less than 5, so Yates's correction was done. P value was non-significant (p = 0.33). odds ratio was found to be 2.63, meaning although there is no statistically significant association between early rising procalcitonin level with culture positive bacterial sepsis, Respondents with culture positive bacterial sepsis are 2.63 times more likely to have raised serum procalcitonin level than respondents without culture positive bacterial sepsis.

Table7: Distribution of study population according to difference in serum procalcitonin levels among respondents with type of sepsis

Criteria	Serum procalcitonin levels		Indpendent sample t-test
	Mean	**SD**	
Respondents with culture positive bacterial sepsis	22.60	36.57	p = 0.045
Respondents without culture positive bacterial sepsis	8.47	6.32	

Independent sample t-test was performed to assess the difference in serum procalcitonin levels among respondents. Mean serum procalcitonin level for respondents with culture positive bacterial sepsis was 22.60 ng/ml and for respondents without culture positive bacterial sepsis was

8.47 ng/ml. Statistically significant ($p<0.05$) difference between the mean serum procalcitonin level was found between the respondents with and without culture positive bacterial sepsis.

4.Discussion:

In present study, among the study population men had a mean age of 44.21 years and women had a mean age of 48.47 years. Combined mean age of study population was 45.54 years. Highest proportion (41.0%) of respondents were from age group "30 to 44 years" followed by 27.9% from age group "60 years and above". Former study showed the mean age in men to be 49.3 ± 12.5 years, and in women 42.4 ± 13.7 years from similar study. [15] These results are consistent with current study findings. In this study among the study population 77.0% had recent H/O fever and 8.2% had resent H/O infection. Among the respondents, 52.5% had Diabetes Mellitus, 42.6% had HTN and 29.5% had Dyslipidaemia. A study conducted by Snjezana Mehanic and Rusmir Baljic in 2013, 30 – 40% of the patients with infection was found to have febrile illness. [16] These results are slightly lower than what we have found in present study. The study found 65.6% had at least one of the co-morbid conditions, 37.7% had 2 co-morbid conditions and 21.3% had 3 co-morbid conditions. Study shows comorbidity is present in over 25% of adults in the Dutch population, with four or more conditions together in 55% of patients over the age of 75 years [17, 18] and in Canada two or more distinct conditions are present in over 90% of the population aged over 65 years. [19] These results while differ from present study, are consistent with present study findings. The study also revealed 63.9% were anaemic, 78.7% were dehydrated and 9.8% had pleural effusion. Also, 8.2% had jaundice, 6.6% had oedema and 4.9% had skin rash. From study [20] the overall prevalence of anaemia was seen to be 41.1% which is while slightly lower than present study finding, is consistent with present study findings. It was found among the study population, 85.7% of the men were found to be anaemic and 63.2% women were found to be anaemic. Combinedly 78.7% of the study population were found to have lower blood Hb level than normal. Statistically significant relation ($p < 0.05$) was seen between gender and total blood Hb level. Other studies have shown similar results. In a study adult men and adult women were shown to have different blood haemoglobin levels. [21] In the study it was observed that among respondent's similar proportion of culture positive ((49.2%)) bacterial sepsis and culture negative (50.8%) bacterial sepsis. The study found no association between early rising procalcitonin level with culture positive 52 bacterial sepsis ($p = 0.33$). Two widely quoted reviews and meta-analyses have come to differing conclusions. [22,23] The study by Tang et al. suggested that PCT could not reliably differentiate sepsis from other noninfectious causes of SIRS in critically ill adult patients. [22] Uzzan and colleagues concluded that PCT represented a good biological diagnostic marker for sepsis, severe sepsis, or septic shock, which are difficult diagnoses in critically ill patients. It was superior to CRP and should be included in diagnostic guidelines for sepsis and in clinical practice in intensive care units. [23] Present study after assessing the difference in serum procalcitonin levels among respondents, found statistically significant ($p<0.05$) difference between the mean serum procalcitonin level between the respondents with and without culture positive bacterial sepsis. In previous studies it was shown that the procalcitonin levels are strongly related to a positive bacterial culture from body fluids and blood. Furthermore, it has also been shown that other inflammatory markers like WCC and neutrophil count do not clearly show a relationship with a positive culture. [24]

This study was conducted in only two centres. Due to sample sample size and short study period, the sample in this study may not be representative of whole population. So that large scale, multicentre study should be under taken.

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.

5.Conclusion:

There is a significant difference of mean serum procalcitonin levels among respondents between with and without culture positive bacterial sepsis. So in primary health care settings as procalcitonin can be detected earlier and easier than blood culture in respect of duration and cost so we can use procalcitonin levels to decide the treatment protocol to be established without any delay.

RECOMMENDATION

This study can serve as a pilot to a 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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DECLARATION

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