Original Article

Serum lactate and Procalcitonin as Biomarkers of Severe Sepsis

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ABSTRACT

Introduction: *Septicemia is a medical emergency that requires early diagnosis and proper treatment. Due to indiscriminate use of antibiotics in our country, in many cases of septicemia blood culture remains negative this creates a diagnostic challenge. These in turn affect management. Serum lactate as well as serum procalcitonin markers can be good options in this regard. This study will help us to find out the role of serum lactate and serum procalcitonin level as a marker of bacterial sepsis and will help to use antibiotic properly.* ***Objectives:*** *The main aim of this study was to find out serum lactate and serum procalcitonin as a biomarker of severe sepsis.* ***Methods & Materials:*** *It is an observational cross-sectional study was carried out the Medicine inpatient department and intensive care unit of Dhaka Medical College Hospital, Dhaka during September 2015 to February 2016. A total number of 40 patients were enrolled in this study. Statistical analyses of the results were be obtained by using window-based Microsoft Excel and Statistical Packages for Social Sciences (SPSS-24).* ***Results:*** *In this study, 52.5% of patients are between the ages of 51 – 65 years, with 25% falling between the ages of 36 – 50 years. The mean age was 49.67 ± 8.78 years. while, depending on gender, 32 (80%) were male while the remaining 8 (20%) were female. Among the 40 patients, 65% had diabetes mellitus as a co-morbidity. Other chronic diseases and immunosuppressive factors put the patients vulnerable to severe sepsis. The majority of the patients had a mix of disorders or risk*

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factors. ***Conclusion:*** *Serum procalcitonin (PCT) and lactate have been identified as two of the most promising indications of sepsis in critically sick patients. These markers can be used in conjunction with clinical signs and standard lab parameters that may indicate a severe infection at the time of ICU admission. serum PCT and lactate might be included to the routine work-up of critically sick patients who have a suspicion of sepsis, which could enhance patient treatment and enhancement diagnostic certainty.*

Keywords: *Septicemia, Serum lactate, Serum procalcitonin, Bacterial sepsis.*

INTRODUCTION

Sepsis is the immunological response of systemic inflammation to bacterial, fungal or viral infection. It is a heterogeneous clinical syndrome. The incidence of severe sepsis and the number of sepsis-related deaths are increasing day by day [1]. Of late, this growing healthcare problem has been recognized as a global health burden due to very high costs associated with its treatment and its relatively high mortality rate.

In developing countries, sepsis affects up to 30 of every 1000 live births and creates extreme pressure on healthcare budget [2]. Elderly people are at great risk for sepsis. So it is likely that sepsis will become an even greater problem as the population advance to the grey hairs. Sepsis is a very much burning issue as a public health nuisance as not only its early complications but also its grave late complication that is associated with its severity. The risk of death is higher within first year of severe sepsis [3].

The early diagnosis and stratification of sepsis patients is a difficult but essential task in that early intervention and appropriate antimicrobial therapy can reduce mortality and improve prognosis [4]. There has been a constant need for biomarkers which could indicate bacterial infection, sepsis or its severity, e.g. in the emergency room (ER) context [5].

Sepsis has some characteristic symptoms. It is frequently associated with fever or hypothermia, rapid breathing, elevated heart rate, confusion, and edema [6]. Early signs are elevated heart rate, decreased urination, and elevated blood sugar, while signs of established sepsis are confusion, metabolic acidosis with compensatory respiratory alkalosis (which can manifest as rapid breathing), decreased systemic vascular resistance, low blood pressure, high cardiac output, and dysfunctions of blood coagulation [7]. The most common primary sources of infection resulting in sepsis are urinary tract, lungs and abdomen. Typically, 50% of all sepsis start as an infection in the lungs. No source is found in one third of cases [8]. The infectious agents are usually bacteria but can also be fungi and viruses [9]. In the last decade, gram-positive bacteria, most commonly staphylococci, are thought to cause more than 50% of cases of sepsis, while gram-negative bacteria were previously the most common cause of sepsis [9].

Sepsis can be difficult to distinguish from non-infectious conditions in critically ill or comatose patients in the early stages; and diagnosis, treatment and outcomes greatly differ between patients with and without sepsis [10]. Prompt diagnosis is crucial to the management of sepsis, as initiation of

early-goal-directed therapy is key to reducing mortality from severe sepsis. Within the first three hours of suspected sepsis, diagnostic studies include measurement of serum lactate, obtaining appropriate cultures before initiation of antimicrobial treatment, so long as this does not delay antimicrobial treatment by more than 45 minutes [11]. To identify the causative organism(s), at least two sets of blood cultures (aerobic and anaerobic bottles) should be obtained, with at least one drawn percutaneously and one drawn through each vascular access device (such as an IV catheter) in place more than 48 hours **[11]**. If other sources are suspected, cultures of these sources, such as urine, cerebrospinal fluid, wounds, or respiratory secretions, should be obtained as well, so long as this does not delay antimicrobial treatment.

Within six hours, if there is persistent hypotension despite initial fluid resuscitation of 30 ml/kg, or if initial lactate is ≥ 4 mmol/L (36 mg/dL), central venous pressure and central venous oxygen saturation should be measured. If the initial lactate was elevated, lactate should be re-measured.

Within twelve hours, it is essential to diagnose any source of infection such as necrotizing soft tissue infection, peritonitis, cholangitis, intestinal infarction that would require emergency source control [11].

Positive bacteriological cultures, including blood cultures, may not be available before 24 to 48 hours; interpretation of local colonization may be ambiguous; and traditional markers of infection, such as body temperature and white blood cell (WBC) count, may not be specific [12]. Furthermore, there are concerns about possible blood culture–negative clinical sepsis, particularly in the setting of increased prophylactic and empirical antibiotic use [13]. Conversely, differentiating true infection from contamination after growth of common skin commensals in blood cultures, poses a diagnostic problem [14]. Since early identification of infections and sepsis is crucial for patient management, an effective marker specific for bacterial infection is very useful in the critical care settings.

There are several markers of sepsis, like C-reactive protein, serum procalcitonin (PCT), IL-6, IL-8, serum lactate, etc., of which PCT has been found to be the most effective. PCT has been proposed as an indicator of the presence of infection and as a useful marker of the severity of sepsis [12]. Procalcitonin (PCT), a protein that consists of 116 amino acids, is the peptide precursor of calcitonin, a hormone that is synthesized by the parafollicular C cells of the thyroid and involved in calcium homeostasis. Procalcitonin arises from endopeptidase-cleaved preprocalcitonin. The reference value of procalcitonin in adults and children older than 72 hours is 0.15 ng/mL or less. Reference values have not been established in infants younger than 72 hours. In healthy adults, the reference range of procalcitonin is below the level of detection. The half-life of procalcitonin is 25-30 hours [15].

As a biomarker, serum lactate concentration has specific significance to distinguish sepsis from septic shock and predictor of the prognosis of the latter is serum lactate level. For decades, serum lactate level has been recognized and utilized as an indicator of tissue hypoxia,

which has immediate relevance to the fundamental pathophysiologic difference between sepsis and septic shock. Several studies support the use of serum lactate in both the diagnostic and treatment phases for septic shock. Lactate is generated from the anaerobic metabolism of pyruvate and signifies cellular hypoperfusion or impaired cellular oxygen utilization. In the Surviving Sepsis Campaign, a lactate level of greater than 4mmol/L is a resuscitation bundle element indicating sepsis induced hypoperfusion and triggers guideline driven early goal directed therapy (EGDT) [16].

There is no study regarding serum lactate and serum procalcitonin as a biomarker of sepsis in our country although in few centers in our country, serum procalcitonin estimation is done to diagnose septicemia.

METHODS AND MATERIALS

This observational cross-sectional study was carried out the Medicine inpatient department and intensive care unit of Dhaka Medical College Hospital, Dhaka during September 2015 to February 2016. Admitted patient of both sexes and age more than 18 years in Medicine department & ICU of DMCH. 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-24).

RESULTS

Table I: Age distribution of the study patients (n=40)

Age distribution	Male (n=32)	Female (n=8)	Total (n=40)
18 – 35 years	2 (3.25%)	0 (0%)	2 (5%)
36 – 50 years	9 (28.12%)	1 (12.5%)	10 (25%)
51 – 65 years	16 (50%)	5 (62.5%)	21 (52.5%)
>65 years	5 (15.62%)	2 (25%)	7 (17.5%)
Mean age (in years)	52.46±9.25	48.13±6.39	49.67±8.78
Age range (in years)	27 – 79	38 – 76	27 - 79

Table I shows that 52.5% patients belong to 51-65 years age group whereas 25% patients belong to 36-50 years age group. The mean age was 49.67±8.78 years. The age range was 27 to 79 years.

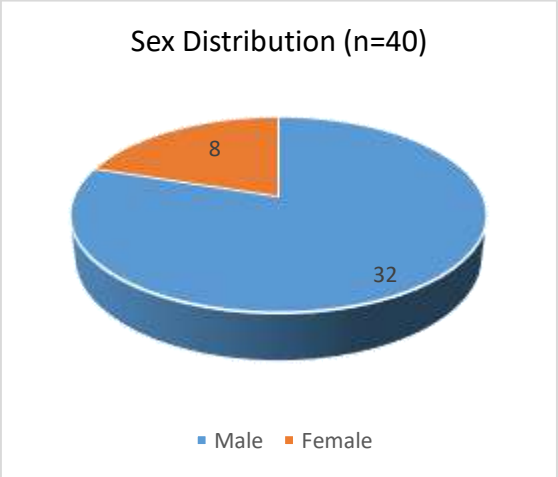

Figure 1: Age distribution of the study patients (n=40)

Figure 1 show that among 40 patients 32 (80%) were male and rest 8(20%) were female. The male to female ratio was 4:1.

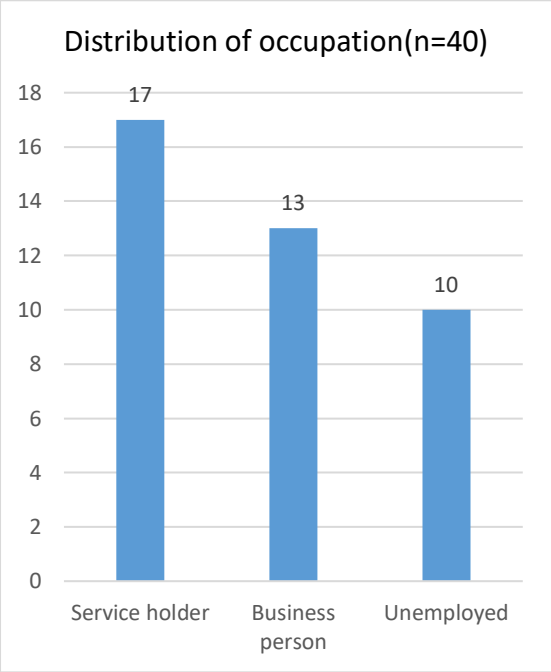

Figure 2: Distribution of occupation (n=40)

Figure 2 shows that among 40 patients 17(42.5%) patients were service holder, 13 (32.5%) patients were business person and rest 10 (25%) patients were unemployed. Here the unemployed group includes housewives, retired persons or unemployed as physically handicapped.

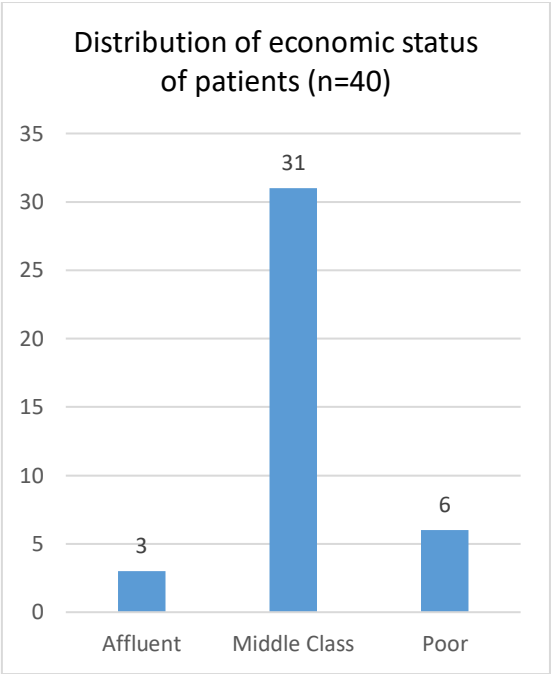

Figure 3: Distribution of economic status of patients (n=40)

Figure 3 shows that among 40 patients 31 (77.5%) patients come from middle income level (10,000-30,000 taka/monthly income) followed by 6(15%) patients from poor class (<10,000 taka/monthly income). Only 3(75%) patients were from affluent society (>30,000/monthly income).

Table II: Distribution of co-morbidities (n=40)

Co-morbidities	Frequency
Diabetes mellitus (type I & II)	26 (65%)
Cardiovascular disease[a]	19 (47.5%)
Bronchial asthma or COPD[b]	13 (32.5%)

Malignancy (Hematological)	5 (12.5%)
Immunosuppressive drug intake[c]	7 (17.5%)
Rheumatic disease	2 (5%)

Table II shows that among 40 patients 65% beared diabetes mellitus as co-morbidity other chronic diseases and immunosuppressive conditions made the patients vulnerable for the severe sepsis. Here most of the patients beared combination of diseases or risk factors.

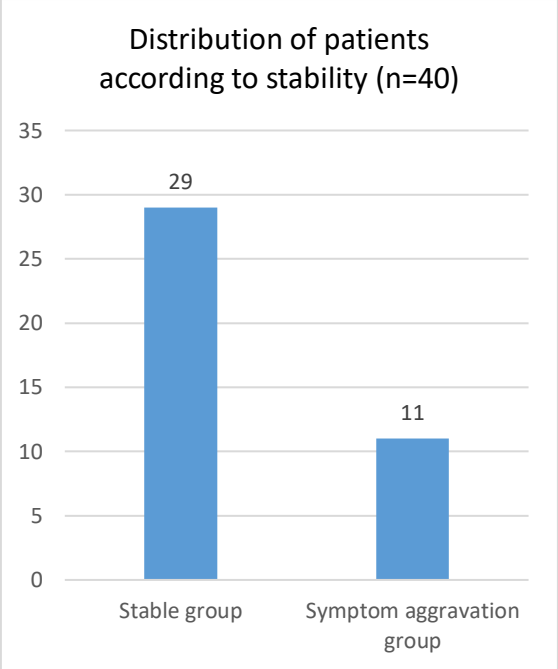

Figure 4: Distribution of patients according to stability (n=40)

Figure 4 shows that out of 40 patients, 29 (72.5%) belonged to stable group and 11 (27.5%) belonged to symptom aggravation group.

Table-III: Distribution of common organisms (n=40)

Organisms	Symptom aggravating group (n=11)	Stable group (n=29)
Common organisms causing UTI		
E. coli	8 (72.72%)	15 (51.72%)
Enterococcus fecalis	5 (45.45%)	11 (37.93%)
Pseudomonas	7 (63.63%)	14 (48.27%)
Staphylococcus	3 (27.27%)	9 (31.03%)
Common organisms causing RTI		
Klebsiella	7 (63.63%)	16 (55.17%)
Staphylococus	2 (18.18%)	11 (37.93%)
E. coli	1 (9.09%)	8 (27.58%)
Pseudomonas	4 (36.36%)	10 (34.48%)
Actinobacter	1 (9.09%)	2 (6.89%)

Table III shows the Distribution of common organisms. Here, according to Symptom aggravating group the E. coli, Enterococcus fecalis, Pseudomonas, Staphylococcus were 72.72%, 45.45%, 63.63%, 27.27% and according to stable group the E. coli, Enterococcus fecalis, Pseudomonas, Staphylococcus were 51.72%, 37.93%, 48.27%, 31.03% respectively.

Table IV: Distribution of initial vital sign (n=40)

Initial vital sign	Symptom aggravating group (n=11)	Stable group (n=29)	P-value
Systolic blood pressure	112.39±27.98	135.69±18.19	0.02^{S}
Diastolic blood pressure	71.76±17.87	76.89±12.1	0.16^{NS}
Heart rate	88.99±17.79	89.88±15.21	0.79^{NS}
Respiratory rate	20.36±1.96	20.47±1.93	0.88^{NS}
Body temperature	38.29±0.97	37.53±0.99	0.37^{NS}
Fever (>38^{0}C)	2 (18.18%)	16 (55.17%)	0.85^{NS}

Table IV shows that among the 40 patients with severe sepsis, symptom aggravating group systolic blood pressure was significantly lower than that of stable group (P=0.02). But other vital signs showed no significant differences between the groups.

Table V: Distribution of blood biochemistry level (n=40)

Initial vital sign	Symptom aggravating group (n=11)	Stable group (n=29)	P-value
WBC (10^{3}/mL)	13.11±5.69	11.69±4.69	0.225^{NS}
Hemoglobin (g/dL)	12.82±1.59	13.29±1.65	0.497^{NS}
Platelet (10^{9}/L	183.29±91.76	195.39±81.65	0.497^{NS}
Glucose (mg/dL)	144.34±63.39	145.78±73.56	0.987^{NS}
BUN (mg/dL)	24.49±21.69	14.59±6.59	0.001^{S}
Creatinine (mg/dL)	1.51±1.16	1.08±0.73	0.038^{S}
AST (IU/L)	170.72±196.73	259.55±498.77	0.39^{NS}
ALT (IU/L)	131.02±110.45	181.84±233.85	0.27^{NS}
Total bilirubin (mg/dL)	2.29±1.93	2.58±2.36	0.58^{NS}

Table V shows that out of 40 patients, blood urea nitrogen and serum creatinine of symptom aggravating group are significantly higher than that of stable group (P=0.001 and 0.038) rest of the biochemical parameters showed no significant differences.

Table VI: Distribution of serum lactate and procalcitonin (n=40)

Biomarker	Symptom aggravating group (n=11)	Stable group (n=29)	P-value
Procalcitonin (ng/mL)	6.09±1.5	0.99±0.13	0.031[S]
Lactate (mmol/L)	2.1±0.91	1.1±0.05	0.049[S]

Table VI shows that both the study biomarker lactate and procalcitonin are significantly higher in symptom aggravating group than stable group (P=0.031 and 0.049).

DISCUSSION

The study population in this study was large and diverse critically ill adult patients with sepsis admitted to ICU of Dhaka Medical College Hospital. This study was designed as a real-life study, to closely resemble clinical practice. We evaluated the combined role of serum PCT and Lactate as predictors of sepsis in which we explored that the level of these biomarkers raised in sepsis. So, these can be good predictors of severity of sepsis from a clinical perspective.

Incidence was more in patients aged over 50 years (70%). The age distribution is similar to studies done around the world. A western study reported a higher incidence of sepsis in patients aged above 57 years [17]. The mean age in an epidemiological study of sepsis in India was 54.9 years [18]. which is very nearer to the mean age of this study and here the mean age was 51.67±8.78 years.

In general, indicators such as APACH II, MEDS, SOFA, and SAPS II are used to predict the possibility of death or the prognosis in patients with severe sepsis. These indicators have been reported to be useful for severely ill patients [19]. However, there are no reports about indicators that may be used to predict symptom aggravation in patients in the early stages after presentation to an emergency care center. This also applies to patients with infections which might progress to sepsis. We therefore examined whether procalcitonin would be useful as an indicator for prognosis and predicting future clinical deterioration in the early stages when patients present to an emergency care center.

Procalcitonin, a precursor hormone of calcitonin is a protein complex that is composed of 116 amino acids of 13-kDa in molecular weight. Nijsten et al. reported that procalcitonin responded to bacterial or viral infections, which led to increased serum levels of procalcitonin in the early stage of infection [20]. Many studies have reported that procalcitonin is a marker for systemic infection, which can be utilized to predict the prognosis in patients with severe infection [21]. Park et al. reported that it is a useful indicator for the prediction of severe clinical deterioration and potentially death in patients with community-acquired pneumonia. In addition, Clec'h et al. reported that serum levels of procalcitonin were significantly higher in the intensive-care-unit (ICU) patients who were receiving medical or surgical treatments for sepsis or septic shock [22].

In addition, Deis et al. also reported that procalcitonin level is a useful marker for

severe bacterial infection in pediatric patients in an emergency care setting. In addition, these authors noted that serum levels of procalcitonin were significantly increased in patients with different infections like respiratory tract infections, urinary tract infections or appendicitis [23]. Consistent with previous reports, our results also demonstrated that serum levels of procalcitonin were relatively higher in patients with a sepsis. Moreover, serum levels of procalcitonin became significantly higher in patients with symptom detoriation, compared with the stable group.

This indicates that the serum levels of procalcitonin would be a useful indicator for the prediction of symptom exacerbation in patients with severe sepsis that present to an emergency care center. By contrast, consistent with previous reports concerning infectious diseases, [24] mean WBC count was 13.11±5.69 /10^3 cm-m was higher symptom aggtavating group than stable group. But the difference was not statistically significant (p=0.225). Clec'h et al. measured serum procalcitonin within 24 hours following the diagnosis of sepsis because it is an indicator for mortality in septic patients and concluded that a cut-off value of 6 ng/ml should be used. Moreover, other studies have also reported that the cut off value of serum procalcitonin was 9.70 ng/ml and 6.00 ng/ml for the prediction of death in the survival group and the death group respectively, following a comparison in patients with sepsis who were receiving medical and surgical treatments [22]. The above studies have also been conducted in patients who were diagnosed with sepsis.

Initially serum lactate level is accepted as a prognostic marker and as a method for evaluating tissue perfusion in several populations of critically ill patients [25, 26]. In both retrospective and prospective studies performed with patients with suspected infection, lactate levels exhibited prognostic value irrespective of the number of organ dysfunctions [26]. Moreover, the initial lactate values are often used for screening, as they are the trigger for the beginning of sepsis resuscitation measures.

In the present study, the symptom aggravating group showed more lactate level than the stable group which was found statistically significant (p= 0.049).

Lactate and procalcitonin levels usually manifest their multidimensional role in septic and cryptic shock. But as this study only limited in severe sepsis patients; so, shock patients were not categorized here. This study only observed the stable patients and symptom aggravating patients separately to observe the rising trend of procalcitonin and lactate level with deterioration of the patients' condition.

CONCLUSION

The present study demonstrates serum PCT and Lactate to be among the most promising sepsis markers in critically ill patients, capable of complementing clinical signs and routine lab parameters suggestive of severe infection at the time of ICU admission. Serum PCT and Lactate measurement appears to be a better predictor to distinguish patients with stable and unstable patients with severe sepsis. Thus, our data raise the possibility that the addition of serum PCT and Lactate to the standard work-up of critically ill patients with suspected sepsis would increase diagnostic certainty

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