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A study on serum lactate levels as a prognostic marker of sepsis

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Abstract
Background: Sepsis and septic shock are a leading cause of mortality worldwide. An elevated serum lactate level is an early maker of sepsis induced hypoperfusion. This study evaluates the clinical utility of lactate clearance and serum lactate levels in sepsis as a prognostic marker in these patients.
Materials and Methods: An observational study was conducted over a period of 1 year and 109 ICU patients diagnosed with sepsis or septic shock were included. Mortality analysis was done using Chi-square test and unpaired t test. 'p' value < 0.05 was considered as statistically significant. Correlation coefficients were calculated for comparison of blood lactate levels with mean arterial pressure, serum creatinine and heart rate. The area under the receiver operating characteristic curve (AUROC) analysis was carried out for lactate levels at various time intervals, lactate/albumin ratio and lactate clearance to predict in house mortality; with AUROC closer to 1.0 being significant.
Results: Out of the 109 patieents studied, significant mortality was an associated with higher blood lactate levels on admission ($p<0.05$) as well as those taken at 6 hrs, 12hrs and 24 hrs after admission to intensive care unit ($p<0.05$). The decreased clearance of lactate and higher lactate/serum albumin ratio was associated with significant mortality ($p<0.05$). The blood lactate was found to have a positive correlation with heart rate, respiratory rate and serum creatinine and a negative correlation with mean arterial pressure. AUROC for lactate at 24 hrs post admission to ICU were superior as compared to those at 12hrs, 6 hrs post admission and that measured at the time of admission. AUC for lactate as tool for predicting mortality was found to be superior as compared to that of AUC (95%CI) of lactate clearance which was 0.68 (0.17-0.22) and lactate: albumin ratio 0.66 (1.9-2.48)
Conclusion: Successive lactate measurement serves as a better prognostic tool in patients with sepsis and septic shock as compared to initial lactate clearance and lactate: albumin ratio. Thus serum lactate levels could be used in patient assessment, for stratification of sepsis patients in intensive care units and in goal directed therapy for improving outcomes and for predicting prognosis.

Keywords: Serum lactate, lactate clearance, sepsis

Introduction
Sepsis is a clinical syndrome that has physiologic, biologic, and biochemical abnormalities caused by a dysregulated host response to infection. Sepsis and the ensuing inflammatory response leading to multiple organ dysfunction syndrome is the major cause of death in ICU patients. Severe sepsis and septic shock are a leading cause of mortality in the world [1]. It is therefore of utmost importance to recognize the patients who are at a risk of mortality to optimize clinical decision making in timely manner and thereby improve clinical outcomes.
Patients in sepsis suffer from low peripheral oxygenation leading to anaerobic glycolysis due to insufficient oxygen delivery, causing lactate production. An elevated serum lactate (eg, >2 mmol/L) can be a manifestation of organ hypo perfusion in the presence or absence of hypotension and is an important component of the initial evaluation, since elevated lactate is associated with poor prognosis. Lactate levels are a critical parameter indicating sepsis induced hypo perfusion and triggering guideline driven early goal directed therapy (EGDT) in the Surviving Sepsis Campaign [2]. In a multivariate analysis of over 20 hemodynamic and regional variables of organ dysfunction, lactate was the only parameter that could be attained in the emergency department that was predictive of outcome [3]. In a subset analysis of 28,150 subjects from the Surviving Sepsis Campaign database by Casserly B *et al.* [4], serum lactate measurements were commonly measured within 6 hours of presentation in the management of severe sepsis and septic shock. Patients who presented with lactate values

greater than 4 mmol/L, with and without hypotension, were significantly associated with in-hospital mortality and were associated with a significantly higher risk than intermediate levels (2-3 and 3-4 mmol/L).

In addition to serum lactate levels, lactate clearance and interval change in lactate over the first 12 hours of resuscitation has been evaluated as a potential marker for effective resuscitation. One meta-analysis of seven randomized control trials reported that lactate–guided resuscitation resulted in a reduction in mortality compared with resuscitation without lactate [5].

Very few studies have been done on this subject in the Indian ICU context. Therefore, in view of this limited data, we sought to study the role of lactate clearance and serum lactate levels in Sepsis, for guiding patient assessment and optimizing treatment as well as for predicting prognosis in these patients.

Materials and Methods

A prospective non interventional observational study was done over a period of 1 year conducted among patients admitted in the Intensive Care Unit in Krishna Hopital, Karad. The approval of the Ethics Committee of the Krishna Institute of Medical Sciences 'Deemed to be University' was obtained prior to the initiation of the study. Written informed consent was taken from all participants or their relatives before including them into the study.

Inclusion Criteria

- All patients with a diagnosis of Sepsis & Septic shock
- Age >18years

Exclusion Criteria

- Patients with other causes of Lactic Acidosis (Shock other than Septic Shock, Severe Anemia, and Patients on drugs and toxins causing Lactic Acidosis)

A detailed history was elicited from the patients enrolled in this study, and general physical examination and systemic examination of was done.

Serum lactate levels were obtained at the time of admission, after 6 hrs, 12hrs and 24hrs. Radiometer ABL FLEX837 blood gas analyzer was used to estimate these lactate levels using amperometric measuring principles. Lactate clearance which is defined as percentage of change in serum lactate levels measured over a period of time over the initial presentation, was calculated.

$$\text{Lactate clearance} = \frac{\text{Lactate at admission- Lactate at desired time}}{\text{Lactate at admission}} \times 100$$

Routine complete blood counts, routine urine analysis and microscopy, renal function tests, random blood sugar, liver function tests, serum electrolytes, prothrombin time and INR, chest X-ray, ECG were done for all patients and sputum Gram's stain/AFB, cultures-blood/sputum/urine etc. where ever indicated.

Statistical Analysis and Methods

Data was analyzed using Microsoft Exel 2010. Quantitative variables like age, heart rate, respiratory rate, mean arterial blood pressure, platelet count, serum creatinine level, serum albumin levels, blood lactate levels, lactate/ albumin ratio and lactate clearance were presented as mean ± SD and qualitative data was analyzed and presented as a percentage. Chi square test and unpaired student t test were used to evaluate the association of several characteristics like age, platelet count, serum albumin, serum creatinine, blood lactate levels, lactate clearance and lactate/albumin ratio with mortality. 'p' value < 0.05 was considered as statistically significant. Blood lactate levels were compared with parameters like heart rate, mean arterial pressure and serum creatinine by calculating correlation coefficients. The area under the receiver operating characteristic curve (AUROC) was calculated for predicting in-hospital mortality. AUROC analysis was carried out for lactate levels at 6hrs, 24hrs and admission, lactate/albumin ratio, lactate clearance; with AUROC closer to 1.0 being significant.

Results

A total of 109 patients diagnosed with sepsis in the intensive care unit of the Krishna Institute of Medical Sciences, Karad, Maharashtra were enrolled in this prospective non interventional observational cohort study. The basic characteristics have been included in the table no.1

Table 1: Basic characteristic of study population

Parameter	N(%) or Mean±SD
Male sex (%)	67 (61.4%)
Age (years)	58±16
Heart rate (beats per minute)	101±20
Mean arterial pressure (mm/Hg)	69±11.5
Respiratory rate (cycles per minute)	27±6
Platelet count (lakh/mm^3)	1.72±0.93
Serum creatinine (mg/dL)	2.49±1.54
Serum albumin (g/dL)	3.01±0.71
Lactate levels at admission in ICU (mmol/L)	5.79±4.27
Lactates 6hrs after admission to ICU (mmol/L)	4.59±3.58
Lactate level 24 hrs after admission to ICU (mmol/L)	3.81±3.48
Lactate clearance (%)	0.20±0.20
Lactate/serum albumin ratio	2.19±2.01

Mortality analysis

Association of mortality with selected parameters of the study population has been illustrated in Table no.2. Male and elderly populations were significantly associated with mortality. Lower platelet counts and higher serum creatinine levels were seen in non survivors as compared to survivors. Significant mortality was associated with higher blood lactate levels on admission as well as those taken at 6 hrs,

12hrs and 24 hrs after admission to intensive care unit. The decreased clearance of lactate was associated with significant mortality. It was observed in the study population that higher lactate/serum albumin ratio was associated significant mortality.

Table 2: Distribution of the outcome in the study population and its correlation with parameters affecting the mortality

Parameter	Survivor	Non survivor	"P" value
Male gender (n)	37	30	'P'<0.05
Age (years)	51.7	65.6	'P'<0.05
Platelet count (lakh/cu.mm)	2.44	1.02	'P'<0.05
Serum creatinine (mg/dL)	1.89	3.52	'P'<0.05
Serum albumin (g/dL)	3.42	2.3	'P'<0.05
Lactate level at admission in ICU (mmol/L)	4.04	8.79	'P'<0.05
Lactate level after 6hrs (mmol/L)	2.96	7.36	'P'<0.05
Lactate level after 12 hrs (mmol/L)	2.16	6.61	'P'<0.05
Lactate level after 24 hrs (mmol/L)	1.49	6.6	'P'<0.05
Lactate/serum albumin ratio	1.9±1.63	2.6±2.49	'P'<0.05
Lactate clearance (%)	25±23	14±8	'P'<0.05

ROC curve analysis for lactate at various intervals, lactate clearance and lactate/albumin ratio

Analysis of the area under the receiver operating characteristic curve (AUROC) for lactate (Fig-01) at 24 hrs post admission to ICU were superior as compared to those at 12hrs, 6 hrs post admission as well as lactate measured at the time of admission. AUC (95% CI) for lactate at 24 hrs after admission was 0.97 (2.93-3.94) and 0.94 (3.81-4.32) for lactate 12hrs after admission. AUC (95%CI) for lactate were 0.91 (4.07- 5.11) and 0.87 (5.16-6.42) at 6 hrs post admission and at the time of admission respectively. AUC for lactate as tool for predicting mortality was found to be superior as compared to that of AUC (95%CI) of lactate clearance which was 0.68 (0.17-0.22) and lactate: albumin ratio 0.66 (1.9-2.48)

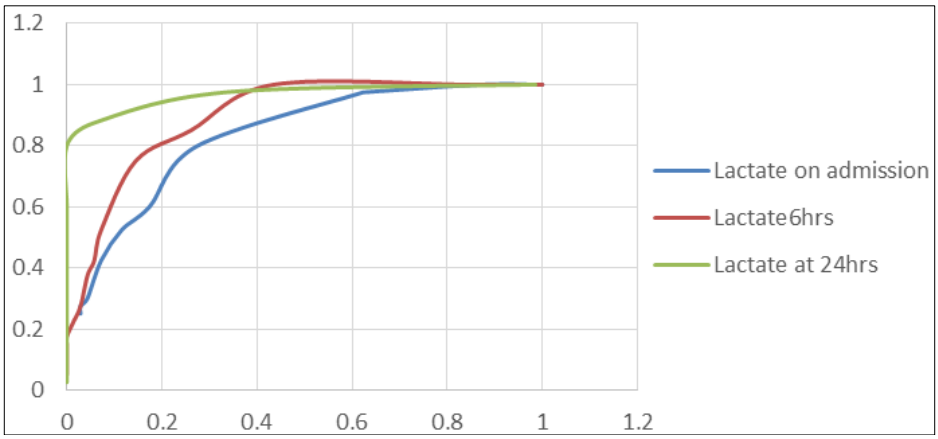

Fig 1: ROC curve for lactate levels at regular intervals and mortality

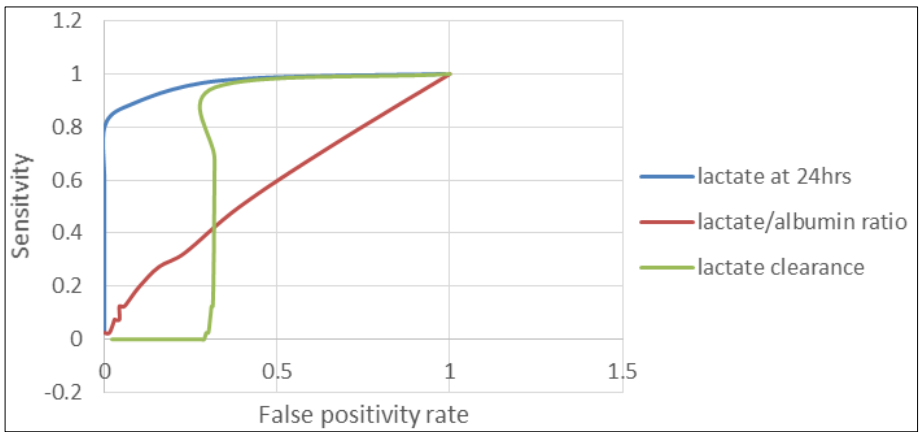

Fig 2: ROC curve of lactate at 24hrs post admission, lactate/ albumin ratio, lactate clearance as tool for predicting mortality

The blood lactate was found to have a positive correlation with heart rate, respiratory rate and serum creatinine and a negative correlation with mean arterial pressure

Table 3: Correlation between Blood lactate levels and parameters such as heart rate, mean arterial pressure and serum creatinine.

Correlation of lactate with	*'rho'* value	'p'value
Serum creatinine	0.97	'P'<0.0001
Mean arterial pressure	-0.81	'P'<0.0001
Heart rate	0.71	'P'<0.0001

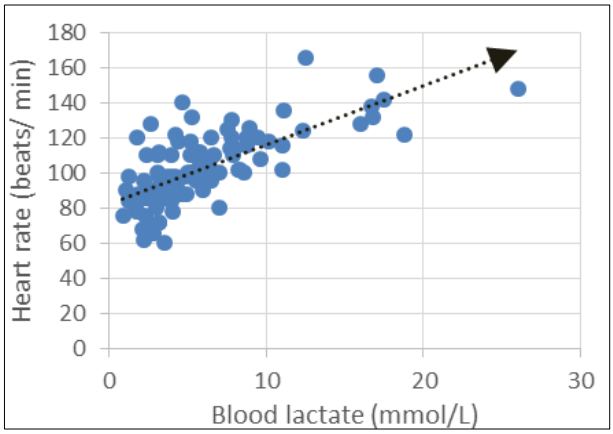

Fig 3: Graph showing a positive correlation between Blood lactate and heart rate

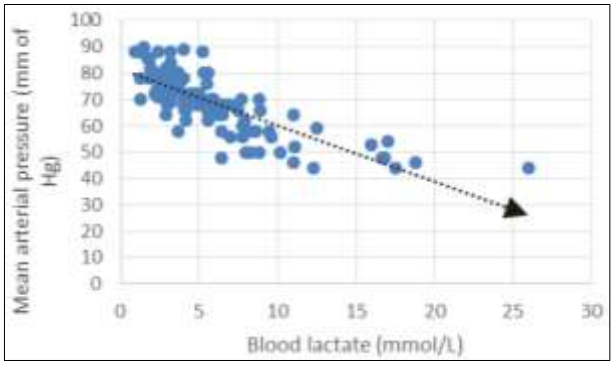

Fig 4: Graph showing a negative between Blood lactate and mean arterial pressure

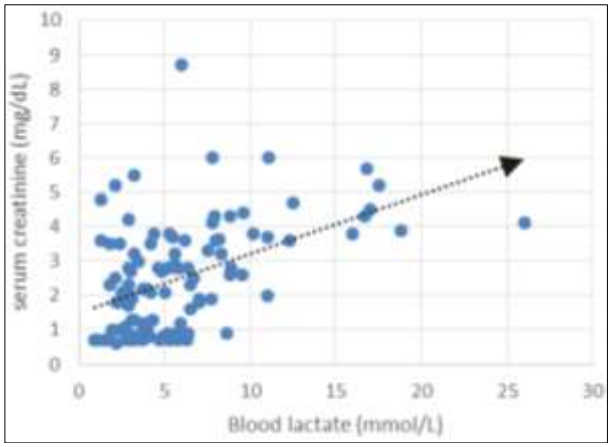

Fig 5: Correlation between Blood lactate and serum creatinine

Discussion

Sepsis contributes to a considerable amount of mortality and morbidity worldwide. Lower respiratory tract infections have been observed to be a major cause of sepsis in several studies, followed by diarrheal diseases. Similar observations were noticed in the present study, in which patients with pneumonia and ARDS constituted majority of the cases while those with gastrointestinal involvement were second most common [1].

The lactic acidosis in the states of sepsis and septic shock is frequently attributed to oxygen deficit developing at the cellular level. This oxygen deficit subsequently results into anaerobic glycolysis which is considered as a compensatory response to maintain adenosine triphosphate (ATP) production. However recent literature has revealed the pathogenesis of lactic acid excess in the states of sepsis and septic shock to have several other contributory factors. In the stressful state of sepsis, body increases rate of tissue oxygenation and ATP production. Thus factors such as glycolytic acceleration, inhibition of pyruvate dehydrogenase and changes in the intermediary metabolism may be responsible for lactic acid excess. Major factions of patients with sepsis subsequently develop multiorgan dysfunction with kidneys and liver being prominently involved. It is a well-studied fact that aforementioned organs serve as a major path for lactate clearance. Consequently due to organ dysfunction, the process of lactate clearance in these patients gets compromised. Thus inability to eliminate excess lactate is an important pathogenic factor which also contributes to lactic acidosis [6, 7].

Varpula *et al.* in their research work observed initial lactate levels to be lower in survivors as compared to non-survivors (2.1 mmol vs 3.4 mmol respectively) [8]. A research article by Marecaux *et al.* mentioned initial lactate levels to be higher than the lactate levels in blood samples taken later during the hospital stay. This observation was in contrast to those made in certain cases in the current study. It could be explained by the differences in the severity of inflammation and stages of organ dysfunction which would decrease the lactate clearance and lead to higher lactate in later stages of the disease. However irrespective of the intervals at which measured, lactate levels were considerably higher in non-survivors than survivors. This finding was supported by observations noted in existing literature [9, 10, 11]. Trzeciak *et al.* observed lactate level of 4 mmol/L to possess an appropriate prognostic potential. Sixfold mortality was observed in patients with lactate level > 4mmol/L [12]. In the current study, successive lactate measurements done at scheduled intervals were observed to have more statistically significant discriminative prowess as far as predicting prognosis was concerned. Similar observations were reported by Marty *et al.* in their research [13]. Existing studies have reported association between higher sequential organ failure assessment (SOFA) score, APACHE III and mortality. A positive correlation has been observed between the inflammation severity scores and blood lactate levels which further support the association with mortality [14].

Lactate clearance has been studied as a prognostic tool in critically ill patients. The lactate clearance was defined by the equation $[(\text{lactate}_{initial} - \text{lactate}_{delayed})/ \text{lactate}_{initial}] \times 100\%$. Ryoo *et al.* observed higher lactate clearance in survivors as compared to non-survivors. [10] Marty *et al.* too reported an association between decreased lactate clearance and mortality. They also observed that lactate clearance calculated in later stages of the disease had better prognostic significance [13]. The observations were supported by those made in the current study wherein lactate clearance amongst the survivors (25±23%) was higher as compared to non survivors(14±8%). It was observed that both lactate and lactate clearance had an association with mortality. However

lactate proved to be a better prognostic tool when compared to lactate clearance (AUC 0.87 vs 0.67; $p<0.01$).

Serum albumin level is a proven indicator of severity of inflammation. It is a negative acute phase reactant. Inflammatory states such as sepsis are associated with acute decrease in albumin levels. Chronic inflammatory states are associated with hypoalbuminemia, which is an independent indicator of mortality and is known to increase susceptibility to infections. Lactate and serum albumin both are independent indicators of mortality and morbidity. Their combination in the form of lactate: serum albumin ratio has been investigated as a prognostic tool in patients with sepsis and has been reported to be associated with mortality. In present study the lactate: serum albumin ratio was associated with mortality (AUC 0.68) and supports the findings of previous research studies [14, 15].

Lactate could be considered as a marker for predicting multiorgan dysfunction in patients with sepsis. As a prognostic tool its role has positively discussed in existing literature and similar observations are noticed in the current study. It was observed that lactate was superior to lactate clearance and lactate: serum albumin ratio as far as predicting mortality was concerned. This observation was similar to those reported by existing literature· [10] Thus lactate levels within first 24 hrs could be used for the purpose of risk stratification in intensive care units and treat patients accordingly.

Conclusion

In conclusion, we can assert that successive lactate measurement supersedes initial lactate clearance and lactate: albumin ratio as prognostic tool in sepsis. Blood lactate levels could be used stratification of patients in intensive care units and efficacy for lactate clearance-directed therapy should be evaluated in patients for better outcome.

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