Annals of Clinical and Analytical Medicine
Original Research

Serum Lactate as a predictor of in-hospital mortality in patients with sepsis

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Abstract
Aim: Sepsis is one of the leading causes of mortality and morbidity in health care setups. Various parameters have been investigated in sepsis. Non-invasive parameters such as serum albumin, serum lactate, and lactate to albumin ratio may be of clinical importance in predicting mortality in hospitalized patients.
Material and Methods: A descriptive prospective study was conducted at the medical wards of the Pakistan Institute of Medical Sciences. Baseline parameters including ESR, creatinine, TLC count, Percentage neutrophils, serum albumin, and lactate levels of patients who met inclusion criteria were taken and followed up until the outcome in hospital, i.e., discharge or mortality.
Results: One hundred fifty-six patients were enrolled; mortality was 24.4%. Mean TLC count and albumin levels were lower in the mortality group, while percentages of neutrophils, creatinine, lactate, and lactate to albumin ratio were higher among the mortality group. However, the difference was statistically significant only for lactate, lactate to albumin, creatinine, and percentage of neutrophils.
Discussion: High serum lactate to albumin ratio and serum lactate levels on admission in septic patients may be used as an independent predictor of in-hospital mortality.

Keywords
Lactate, Sepsis, Mortality, Prediction Models

DOI: 10.4328/ACAM.21068 Received: 2022-01-20 Accepted: 2022-02-23 Published Online: 2022-03-02
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Introduction

Sepsis is a common condition characterized by the body's overwhelming response to certain infective agents. Sepsis is a major cause of morbidity and mortality worldwide [1]. It is associated with high in-hospital mortality in adult patients, ranging from 23% to 39% [2]. Despite advances in its management, it is still the second most common reason for mortality in intensive care units (ICUs) [3].

Methods are needed to identify patients at risk of early death and to optimize management in order to improve clinical outcomes in these patients [1].

There are many clinical and laboratory parameters to diagnose sepsis including serum lactate levels, which are also used to guide the treatment. In critically sick patients, raised levels of serum lactate are strongly associated with significant morbidity and mortality [4].

Increased lactate production is caused by anaerobic metabolism due to tissue hypoxia caused by impaired circulation due to sepsis.

An elevated serum lactate level is directly proportional to the patients' need for mechanical ventilation, ICU care and need for inotropic support [5]. In patients presented to the emergency department with septic shock, elevated serum lactate level is associated with increased mortality, irrespective of the clinical evidence of organ dysfunction [4].

Therefore, it is a useful marker to identify patients at high risk for sepsis and septic shock, and hence timely intervention can decrease mortality and morbidity in these patients.

Multiple studies worldwide showed the association of serum lactate levels with the poor prognosis. Low serum lactate levels or even normal range have been shown to decrease the severity of sepsis [6].

Therefore, we prospectively collected clinical data on these patients to determine whether serum lactate level, independent of clinical evidence of organ dysfunction, reflects the severity of sepsis and serves as an independent predictor of the risk of death. This could help us in risk stratification of patients admitted with sepsis in developing countries where sophisticated predictors of mortality and morbidity cannot be applied.

Material and Methods

This was a prospective descriptive study conducted in the department of general medicine of Pakistan Institute of Medical Sciences, Islamabad from January 2019 to January 2020. Ethical approval was taken prior to enrollment of patients (No.F.1-1/2018/ERB/SZABMU/356). In this study, we evaluated the association of serum lactate levels and mortality in patients with sepsis. All patients between the ages of 12 and 75 years who were admitted with the provisional diagnosis of sepsis were enrolled in the study consecutively. Patients were evaluated within 24 hours and enrolled in the study if they fulfilled the inclusion and exclusion criteria and could provide written informed consent. Serum lactate levels along with baseline workup were determined within 24 hours and repeated within 7 days. All patients were given treatment as per the standard hospital protocol and were followed until discharge or death.

Data were analyzed using SPSS version 16. The association of baseline lactate and difference in lactate levels with treatment was calculated and analyzed for any association on mortality using Independent and paired T-test. A p-value of less than 0.05 was considered significant.

1. All patients with a confirmed diagnosis of infection (infective endocarditis, meningitis, encephalitis, pneumonia, cholecystitis, ascending cholangitis, hepatitis, pyelonephritis, cystitis, cellulitis or gastroenteritis etc.) for which the patient is on specific treatment
2. All patients with a temperature of >100.4F or less than 96F and bacteremia (positive blood culture)
3. All patients with no obvious source of infection but who met the following criteria and have been receiving treatment for an infective etiology

• ***At least three of the following***

a. Temperature of > 100.4F or less than 96 F
b. TLC of >12000/ul or <4000/ul or Percentage of Neutrophils > 80%
c. ESR > 50 mm/hr or CRP: positive
d. Systolic BP <90 or MAP <70

Results

A total of 156 patients were enrolled in the study, comprising 68 (43.6%) women and 88 (56.4%) men. The mean age of the patients in the study was 43.18 +/- 15.9 years. Death occurred in 38 (24.4%) of the study participants comprising 22 (32%) women and 16 (18.18) men. The mean TLC count of the patients was 14400/ul +/- 8.58, with a mean of 74.23% +/- 1.73 neutrophils. The mean values of ESR, albumin, creatinine, and lactate were 43.51 +/- 34.04, 3.0 +/- 0.69 gm/dl, 1.47 +/- 1.37 mg/dl, and 22.51 +/- 9.02 mmol/l respectively. The mean duration of hospital stay was 6.55 +/- 5.71 days.

The association of mortality with age, TLC count, Percent Neutrophils, ESR, Albumin, and Creatinine is summarized in Table 1. The association of mortality with serum lactate levels is summarized in Table 2.

Discussion

This is a prospective study conducted on patients with sepsis at a tertiary care setup in Islamabad, Pakistan. Patients with sepsis were included, lactate levels were measured at admission within 24 hours and follow-up levels within 7 days along with other parameters. Patients were followed up until mortality or discharge. The study demonstrates significantly higher mean lactate levels in the mortality group versus the survival group. This difference was nearly similar in mean lactate levels at admission compared to follow-up levels. The study also demonstrated significantly higher mean lactate to albumin ratio in the mortality group compared to the survival group.

Higher mortality in septic patients with high lactate has been reported in multiple studies. An Australasian study has demonstrated high levels of lactate as an independent marker of severity in sepsis consistent with the current study. The study has also demonstrated an increased risk of 90-day mortality in patients with high serum lactate levels. High serum lactate levels were superior to refractory hypotension in predicting the

Table 1. Summary of results.

Group Statistics						
	outcome	Number	Mean	Std. Deviation	Std. Error Mean	P-value
age	Death	38	42.11	16.334	2.650	0.64
	Survived	118	43.53	15.819	1.456	
TLC count	Death	38	1.23E4	7.211.450	1.169.852	0.09
	Survived	118	1.50E4	8.899.866	819.299	
Percent Neutrophils	Death	36	652.944	2.418.657	403.110	0.0003
	Survived	116	770.000	1.343.951	124.783	
ESR	Death	34	53.18	38.735	6.643	0.57
	Survived	106	40.42	31.969	3.105	
Albumin	Death	36	27.833	.59833	0.09972	0.32
	Survived	116	30.655	.70859	.06579	
Creatinine	Death	38	20.405	215.976	0.35036	0.003
	Survived	118	12.900	.93933	.08647	

Table 2. Association of lactate with mortality

Lactate Levels	Outcome	Number	Mean	Std deviation	Std error of mean	P value
Lactate on Admission	Death	38	316.263	938.313	152.214	0.00003 x 10 -10
	Survived	118	193.661	664.867	0.61206	
Lactate levels within 7 days of treatment	Death	28	268.214	1.230.117	232.470	0.00003 x 10 -8
	Survived	100	148.480	438.216	.43822	
Lactate to Albumin ratio	Death	36	11.63	3.28	0.548	<0.001

outcome [7]. A Massachusetts-based study has assessed mean lactate levels on day 1, Sequential Organ Failure Assessment (SOFA) and the quick SOFA (qSOFA) and compared with patient outcomes. The lactate levels were shown to determine patients' outcomes as in the present study. However, this association was found to be associated with SOFA for outcome determination and superior to the use of qSOFA [8]. A single centred Korean study has compared serum lactate levels and lactate clearance for predicting patient outcomes. Both were found to have prognostic potential; however, serum lactate levels were superior to lactate clearance. Serum lactate levels of 2 mmol/L or greater had maximum sensitivity [9]. A US-based study on 3325 subjects demonstrated a greater risk of death in short run in those having high lactate levels. The study has also shown an increased risk of long-term mortality as well. However, the effect is not as pronounced as for poor outcome over a short run [10]. Serum lactate levels in sepsis for outcome were compared among elderly (defined as age equal to or greater than 65 years) and non-elderly patients. The sensitivity of serum lactate levels of greater than 2 mmol/L was found to be higher among the elderly as a predictor of poor outcome [11]. A US-based study over a large data has shown combination of high lactate and high glucose to be superior to either of parameters alone in predicting the outcome of septic patient [12].

Serum lactate to albumin ratio has also been associated with higher severity and mortality from sepsis. A US-based study retrospective single centred study over a large data has demonstrated lactate to albumin ratio to be superior to lactate alone in predicting the ICU mortality [13]. Another study aimed at comparing lactate, albumin and lactate to albumin ratio has shown the ratio to be a stronger predictor of ICU mortality as compared to either of the parameters alone [14]. A German single centred study followed patients and measured both in-hospital mortality as well as long-term mortality. The study showed both mortalities to be significantly higher in those showing higher lactate to albumin ratio in intensive care [15]. A Korean multicentre retrospective study aimed to investigate 28-day mortality in the ICU setting. The study demonstrates significantly higher levels of lactate to albumin ratio in the mortality group, which is quite consistent to the present study. The study has also shown the ratio to be superior to lactate alone as a predictor of 28-day mortality [16]. Another retrospective single centre study has demonstrated higher levels of lactate and lactate to albumin ratio in association with higher in-hospital mortality. The prognostic value of lactate to albumin ratio was better than lactate for in-hospital mortality in septic patients [17].

The limitations of study include the lack of evaluation of mean lactate values, peak lactate values that could have shown superiority as compared to lactate levels on admission. Mortality with different lactate levels was not studied, which could yield potentially useful information. Lactate clearance was not studied as it has been included in other studies. Risk ratio, area under the curve and sensitivity analysis with different values could be studied. Similarly, mortality was not categorized into the short and long term.

Conclusion:

Higher levels of serum lactate and lactate to albumin ratio are linked to in-hospital mortality in the septic patient. These markers may be utilized to predict the outcome of septic patients.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some

of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement
All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Funding: *None*

Conflict of interest
None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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How to cite this article:
Ahmed Farhan, Ali Sufyan, Muhammad Awais Tahir, Arslan Ahmad, *Sara Manzoor. Serum Lactate as a predictor of in-hospital mortality in patients with sepsis. Ann Clin Anal Med 2022; DOI: 10.4328/ACAM.21068*