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Original Article

Internal Medicine Section

Role of Arterial Serum Lactate as a Predictor of Undifferentiated Shock on Admission and its Outcome- A Cohort Study

AVADHESH KUMAR SHARMA[1], NANDAKUMAR BEKE[2], DATTATRAY PATKI[3], ARUN BAHULIKAR[4], DEEPAK SADASHIV PHALGUNE[5]

ABSTRACT

Introduction: Patients with elevated serum lactate levels may be at risk for considerable morbidity and mortality and require a prompt, thoughtful and systematic approach for diagnosis and treatment.

Aim: To find an association of on admission arterial serum lactate with outcome in Intensive Care Unit (ICU) patients.

Materials and Methods: This observational cohort study was conducted on 168 patients at Poona Hospital and Research Centre, Pune, India, between June 2018 to November 2019 after obtaining Institutional Ethical Clearance. The patients included were above 18 years of age who had Systolic Blood Pressure (SBP) <90 mmHg, Heart Rate (HR) >100/min and Respiratory Rate (RR) >20/min. The arterial serum lactate level were examined on the day of admission, 12 hours and 24 hours. The need of ionotropic support, duration of ICU stay and mortality in one month was noted. The primary outcome measures were to study the association of on admission arterial serum lactate level with a duration of ICU stay and in-hospital mortality, whereas the secondary outcome measure was to study the association of on admission arterial serum lactate with the requirement of ionotropic support. Analysis of data was done using Statistical Package for Social Sciences for Windows, version 20.0.

Results: The incidence in-hospital mortality was 20 (22.7%) out of 88 and 3 (3.8%) out of 80 in patients whose serum lactate levels on admission were >36 mg/dL and ≤36 mg/dL, respectively (p-value=0.002). The median duration of ICU stay was six and three days in patients whose serum lactate levels on admission were >36 mg/dL and ≤36 mg/dL, respectively (p-value=0.001). A 87 (98.9%) patients whose serum lactate levels >36 mg/dL on admission had the higher requirement of inotropes as compared to 35 (50.7%) patients whose serum lactate levels were ≤36 mg/dL. The percentage of patients whose serum lactate level >36 mg/dL, had a significantly higher Quick Sequential Organ Failure Assessment (qSOFA) scores and higher Shock Index (SI). There was a statistically significant positive correlation between serum lactate levels and qSOFA score (r=0.555) and SI (r=0.559).

Conclusion: Initial serum lactate level was associated with higher in-hospital mortality, the higher requirement of inotropic support and longer duration of ICU stay.

Keywords: Inotropes, Intensive care unit, Mortality, Quick sequential organ failure assessment score, Shock index

INTRODUCTION

Elevated serum lactate levels are not clearly and universally defined, but most studies use cut off values of 2-2.5 mmol/L, whereas high lactate levels have been defined as greater than 4 mmol/L in several studies [1-3]. The serum lactate level elevation may be caused by increased production, decreased clearance, or a combination of both. The aetiology of elevated serum lactate levels is best studied in shock states. Contributing factors are hypoperfusion due to macro-circulatory or microcirculatory dysfunction, mitochondrial dysfunction and the presence of a hypermetabolic state [4].

Shock is conceptualised as a clinical syndrome resulting from an imbalance between tissue oxygen demands and tissue oxygen supply. Impaired oxygen delivery is the primary problem in hypovolemic, cardiogenic, distributive (septic) and obstructive (pericardial tamponade, tension pneumothorax) forms of shock. The influence of elevated lactate levels on mortality mainly has been highlighted in septic shock. However, any form of shock with tissue hypoperfusion will result in elevated lactate [5].

Septic shock is defined as an unrecovered hypotension despite adequate fluid replacement. Sepsis-induced arterial hypotension is defined as SBP <90 mmHg or the Mean Arterial Pressure (MAP) <70 mmHg. Septic shock comprises of three components; arterial hypotension, tissue hypoperfusion associated with organ dysfunction and hyperlactatemia. The serum lactate levels have become a useful marker for tissue hypoperfusion and may also serve as an endpoint for resuscitation in patients with septic shock [6,7].

The utility of serum lactate in cardiogenic shock has not been established, but in patients with myocardial dysfunction resulting in shock after cardiac surgery, an elevated serum lactate levels were observed [8]. The serum lactate elevation is related to increased tissue lactate production rather than a decreased clearance [8]. In cardiogenic shock requiring extracorporeal membrane oxygenation, serum lactate has been found to be a useful variable for predicting mortality [9]. In cardiogenic shock after ST-Elevation Myocardial Infarction (STEMI), patients with ineffective lactate clearance (2 mmol/L) were associated with increased mortality rates independent of haemodynamic status and right ventricular dysfunction [10].

Elevated serum lactate levels are encountered in a multitude of clinical presentations and disease states. There may be a considerable risk of morbidity and mortality in patients with elevated serum lactate levels. Therefore, a prompt, thoughtful and systematic approach for diagnosis and treatment is required for these patients. The present study was aimed to find out the association of on admission arterial serum lactate levels with outcomes in ICU patients.

MATERIALS AND METHODS

This observational cohort study was conducted between June 2018 and November 2019 in ICU of Poona Hospital and Research Centre, Pune, India. After approval from the Institutional Ethics Committee (Letter No. RECH/EC/2018-19/184), a written informed consent was obtained from all the patients prior to enrollment explaining the risks and benefits of the procedure.

Inclusion and Exclusion criteria: All patients admitted between 18-80 years of age who had SBP <90 mmHg, HR >100/min and RR >20/min were included. Patients who had a history of acute alcohol ingestion and ingestion of poison were excluded.

Sample size calculation: On the basis of a previously published study, a sample size of 168 patients was calculated by a formula $(Z\alpha)^2$ p(1-p)/d^2 with 80% power and 5% probability of Type I error to reject the null hypothesis [11].

Study Procedure

Detailed clinical history and examination findings were noted for each patient. Routine investigations, Arterial Blood Gas (ABG), haemogram, blood urea, serum creatinine, serum electrolytes, urine routine and chest X-ray were conducted. ABG and serum arterial lactate levels were measured at admission, 12 hours and 24 hours. The serum lactate levels were measured by machine ABL80SLEX by Indirect ion Selective Electrode (ISEs) method.

Data were collected on the need for ionotropic support, duration of ICU stay and mortality in one month.

Patients were divided into three groups.

Group 1: Patients with arterial serum lactate levels at the time of admission <2 mmol/L (<18 mg/dL).

Group 2: Patients with arterial serum lactate levels at the time of admission 2-4 mmol/L (18 mg/dL-36 mg/dL).

Group 3: Patients with arterial serum lactate levels at the time of admission >4 mmol/L (>36 mg/dL).

The Shock Index (SI) was calculated by measuring HR and SBP. SI is equal to HR/SBP [12]. qSOFA score was calculated by giving score 1 each for SBP ≤100 mmHg, RR ≥22 breaths/min and Glasgow coma scale ≤14 [13].

The primary outcome measures were to study the association of on admission arterial serum lactate level with a duration of ICU stay and in-hospital mortality, whereas the secondary outcome measure was to find the association of on admission arterial serum lactate with the requirement of ionotropic support.

STATISTICAL ANALYSIS

Data collected were entered in Excel 2007 and analysis of data was done using Statistical Package for Social Sciences for Windows, Version 20.0, from IBM Corporation, Armonk, NY, USA. The data on categorical variables are shown as n (% of cases) and the data on continuous variables are presented mean±Standard Deviation (SD). Non parametric data are shown as the median. The inter-group comparison of categorical variables and medians of continuous variables was done using Fisher's-exact test and Kruskal-Wallis-H, respectively. The confidence limit for significance was fixed at 95% level with p-value <0.05.

RESULTS

The study included 168 patients. The mean±SD of the age of the study population was 52.6±8.3 years. Out of 168 patients, 111 (66.1%) and 57 (33.9%) were males and females respectively and 118 (70.2%) had septic shock. The median serum lactate levels both at admission and at 12 hour were 38.50 mg/dL whereas the median serum lactate level was 36.00 mg/dL at 24 hour. Of 168 patients, 23 (13.7%) died in hospital. The median serum lactate levels at admission, 12 hours and 24 hours showed a statistically significant difference between different types of shock patients [Table/Fig-1].

A significantly higher proportion of patients whose serum lactate levels were >36 mg/dL on admission had a higher requirement of inotropes and a higher incidence of in-hospital mortality. The median duration of ICU stay was significantly higher in the group of patients who had serum lactate levels on admission >36 mg/dL [Table/Fig-2].

Median serum lactate levels (mg/dL)	Types of shock				p-value
	Septic shock n=118	Cardiogenic shock n=14	Hypovolemic shock n=29	Neurogenic shock n=7	
Admission	44.50	35.00	26.00	40.00	0.001
12 hours	46.00	38.00	27.00	45.00	0.001
24 hours	40.00	38.50	21.00	46.00	0.001

[Table/Fig-1]: Median serum lactate levels on admission, 12 hours and 24 hours according to types of shock.
Kruskal-Wallis-H test was used

Variacles	Serum lactate levels on admission (mg/dL)			Total (n=168)	p-value
	<18 (n=11)	18-36 (n=69)	>36 (n=88)		
Inotropes required (%)	0 (0.0)	35 (50.7)	87 (98.9)	122 (72.6)	0.001*
Median duration of ICU stay in days	0	3	6		0.001**
Mortality (%)	0 (0.0)	3 (4.3)	20 (22.7)	23 (13.7)	0.002*

[Table/Fig-2]: Association of serum lactate levels on admission with requirement of inotropes, duration of ICU stay and mortality.
*Fisher's-exact test was used; **Kruskal-wallis-H test was used; ICU: Intensive care unit

The incidence of in-hospital mortality differed based on the lactate levels. The incidence of mortality was significantly higher in patients who had ≤20% fall in serum lactate levels at 24 hours of admission [Table/Fig-3].

Variables	Mortality		Total	p-value
Fall in serum lactate levels at the time of admission	Died (n=23)	Survived (n=145)		
At 12 hours				
≤20%	22 (95.7)	117 (80.7)	139	0.133
>20%	1 (4.3)	28 (19.3)	29	
At 24 hours				
≤20%	22 (95.7)	84 (57.9)	106	<0.001
>20%	1 (4.3)	61 (42.1)	62	

[Table/Fig-3]: Association of fall in serum lactate levels on admission with mortality (Fisher's-exact test was used).

There was a statistically significant difference between the qSOFA score and serum lactate levels. The percentage of patients whose serum lactate level >36 mg/dL, had significantly higher qSOFA score as compared to the patients whose serum lactate levels were <18 mg/dL and 18-36 mg/dL [Table/Fig-4].

qSOFA score	Serum lactate levels on admission mg/dL			Total n (%)	p-value
	<18, n (%)	18-36, n (%)	>36, n (%)		
1	2 (25.0)	5 (62.5)	1 (12.5)	8	<0.0001
2	9 (6.5)	61 (44.2)	68 (49.3)	138	
3	0 (0.0)	2 (9.1)	20 (90.9)	22	
Total	11 (6.5)	68 (40.5)	89 (53)	168	

[Table/Fig-4]: Distribution of serum lactate levels on admission based on qSOFA score.
Fisher's-exact test was used; qSOFA: Quick sequential organ failure assessment

There was a statistically significant difference between patients with SI and serum lactate levels. The percentage of patients' whose serum lactate levels >36 mg/dL had significantly higher SI as compared to patients whose serum lactate levels were <18 mg/dL and 18-36 mg/dL [Table/Fig-5].

There was a statistically significant positive correlation between serum lactate levels and qSOFA score (r=0.555, p-value <0.001) and SI (r=0.559, p-value <0.001). There was a statistically significant difference between patient's SI, qSOFA score and in-hospital mortality. The percentage of patients whose SI was IV and qSOFA score was 3 had a significantly higher in-hospital mortality rate [Table/Fig-6]. It was observed that 0/14 (0.0%), 2/29 (6.9%), 1/7 (14.3%) and

20/118 (16.9%) patients died who had cardiogenic, hypovolemic, neurogenic and septic shock, respectively.

Shock index	Serum lactate levels on admission mg/dL			Total n (%)	p-value
	<18 n (%)	18-36 n (%)	>36 n (%)		
I (<0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0	<0.0001
II (≥0.6 to <1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0	
III (≥1.0 to <1.4)	11 (10.9)	58 (57.4)	32 (31.7)	101	
IV (≥1.4)	0 (0.0)	10 (14.9)	57 (85.1)	67	
Total	11 (6.5)	68 (40.5)	89 (53)	168	

[Table/Fig-5]: Distribution of serum lactate levels on-admission based on Shock Index (SI).
Fisher's-exact test was used

Shock index	Discharged n (%)	Died n (%)	Total n (%)	p-value
I (<0.6)	0 (0.0)	0 (0.0)	0	<0.0001
II (≥0.6 to <1.0)	0 (0.0)	0 (0.0)	0	
III (≥1.0 to <1.4)	97 (96.1)	4 (3.9)	101	
IV (≥1.4)	48 (71.6)	19 (28.4)	67	
Total	145 (86.3)	23 (13.7)	168	
qSOFA score				
1	8 (100.0)	0 (0.0)	8	<0.0001
2	137 (99.3)	1 (0.7)	138	
3	0 (0.0)	22 (100.0)	22	
Total	145 (86.3)	23 (13.7)	168	

[Table/Fig-6]: Distribution of incidence of mortality based on Shock Index (SI) and qSOFA.
Fisher's-exact test was used; qSOFA: Quick sequential organ failure assessment

DISCUSSION

The present study was conducted in order to find out the role of on admission arterial serum lactate as a predictor of undifferentiated shock and its outcome. The association of on admission arterial serum lactate level with the duration of ICU stay, ionotropic support required for patients and in-hospital mortality was also determined. It was observed that patients whose serum lactate levels were >36 mg/dL on admission needed longer ICU stay, inotropic support and had a higher incidence of in-hospital mortality.

Howell MD et al., reported that the serum lactate level was strongly associated with 28 days in-hospital mortality in univariate analysis and that patients with either septic shock or lactate ≥4.0 mmol/L had a mortality rate of 28.3% [1]. Oedorf K et al., reported that the mortality was the highest in the patients whose serum lactate level was >4.0 mmol/L [11]. Villar J et al., reported that three days, 30 days, and one year mortality were 2.5%, 10% and 24% respectively [14]. Mikkelsen ME et al., studied the association between serum lactate levels and mortality. The study further stated that in the non-shock subgroup, the initial median serum lactate level was significantly higher in non survivors as compared with survivors at 28 days (3.4 mmol/L vs 2.6 mmol/L, p-value <0.001), whereas in the shock subgroup, non survivors also had significantly higher initial median serum lactate levels as compared with survivors (5.2 mmol/L vs 3.3 mmol/L, p-value <0.001) [12]. Blum A et al., reported that the patients who died within 24 hour of admission had higher lactate levels (8 mmol/L) as compared to patients who survived (2.1 mmol/L) (p-value <0.001) [13]. In the present study, patients whose serum lactate levels on admission were >36 mg/dL (>4 mmol/L) had a mortality rate of 22.7% (p-value=0.002).

Karen B categorised 87 (70.2%) out of 124 patients as responders to shock treatment as their serum lactate levels dropped by >20% within six hours after treatment initiation, 37 (29.8%) out of 124 patients were categorised as non responders to shock treatment within six hours [15]. It was further reported that the 30 days mortality rate was 17.2% and 35.1% in responders and in non responders respectively (p-value=0.036). In the present study, the incidence of mortality was 20.8% and 1.6% in patients who had ≤20% and >20% fall in serum lactate levels respectively at 24 hour of admission (p-value=0.0003).

Karen B reported that the septic shock was observed in 51% patients [15]. In a study conducted by Vitek V and Cowley RA on serum lactate levels in different types of shock, the majority of cases were presented with septic shock [16]. In the present study, 70.2% patients had septic shock.

Limitation(s)

This study has potential limitations. Other co-morbidities (i.e., liver disease) and medications (i.e., metformin) can affect the lactate level, yet may not be related to the acute illness treated in the ICU. The present study does not account for these alternative factors influencing lactate levels. The treating clinicians were not blinded to the results of lactate analysis and we do not know how this information may have affected clinical care, and thereby possibly the outcome parameters (i.e., use of vasopressors). This could have an impact on the ability to investigate lactate as a predictor of this outcome. However, within our ICU the decision to use vasopressors is based on blood pressure parameters, not guided by lactate levels. The study was conducted in a single centre with a small sample size. Multi-centric studies with a large sample size are recommended to substantiate the research findings described in this paper.

CONCLUSION(S)

A significantly higher proportion of patients with on admission serum lactate levels >36 mg/dL had the higher requirement of inotropes, longer duration of ICU stay and higher incidence of in-hospital mortality. Patients with fall in serum lactate ≤20% within 24 hour of admission had higher in-hospital mortality rate. The serum lactate levels at admission were highest in septic shock patients followed by neurogenic shock and lowest in hypovolemic shock. The percentage of patients whose serum lactate level >36 mg/dL, had a significantly higher qSOFA score and higher SI as compared to the patients whose serum lactate levels were <18 mg/dL and 18-36 mg/dL. There was a statistically significant positive association between serum lactate levels, qSOFA score and SI. The percentage of patients whose SI was higher (III and IV) and qSOFA score 3 had a significantly higher in-hospital mortality rates.

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PARTICULARS OF CONTRIBUTORS:
1. Senior Resident, Department of Medicine, Poona Hospital and Research Centre, Pune, Maharashtra, India.
2. Consultant Physician, Department of Medicine, Poona Hospital and Research Centre, Pune, Maharashtra, India.
3. Consultant Physician, Department of Medicine, Poona Hospital and Research Centre, Pune, Maharashtra, India.
4. Head and Consultant Physician, Department of Medicine, Poona Hospital and Research Centre, Pune, Maharashtra, India.
5. Research Consultant, Department of Research, Poona Hospital and Research Centre, Pune, Maharashtra, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Deepak Sadashiv Phalgune,
18/27, Bharat Kunj-1, Lane #4, Laxmi Bungalow, Erandawane,
Pune-411038, Maharashtra, India.
E-mail: dphalgune@gmail.com

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