

Study of early lactate clearance as an independent predictor of survival in patients with presumed sepsis

ABSTRACT

Aim- Measurement of serial serum lactate levels in patients presenting with sepsis and correlating with 1. early lactate clearance with mortality. 2. Early lactate clearance vs. first (baseline) lactate level in mortality prediction. 3. Early lactate clearance vs. ACUTE PHYSIOLOGY AND CHRONIC HEALTH EVALUATION II score in mortality prediction. 4. Early lactate clearance vs. non lactate clearance in mortality prediction.

Place and Duration of Study: Department of General Medicine, SMIMER, Surat, Gujarat between December 1st 2017 and November 25th 2019.

Methodology: 50 patients (36 male, 14 females; age more than 18 years) Patient with sepsis were selected from Medicine ICU by using ACUTE PHYSIOLOGY AND CHRONIC HEALTH EVALUATION II score ≥ 12 points. Lactate levels at 0, 6, 12, 24 and 48 hours were measured by using ABG done by ABL 800 basic analyzer. ACUTE PHYSIOLOGY AND CHRONIC HEALTH EVALUATION II score was calculated on admission. Lactate clearance was calculated ($<10\%$ OR $>10\%$) and was correlated with mortality (< 7 days or > 7 days).

Results: Among 50 patients studied, 39 patients were in lactate clearance group and 11 patients were in lactate non-clearance group. In lactate clearance group 35 (89%) patients survived and 4 (11%) patients expired. In lactate non-clearance group 9 (81%) patients expired and 2 (19%) patients survived. On observing the lactate trend, Serial serum lactate

levels were decreasing in survived patients while serial serum lactate levels were static or increasing in expired patients. There was no correlation between serum lactate at 0 hour and mortality in the study group (p value > 0.05). There was correlation between serum lactate at 6, 12, and 24 hours with mortality (p value <0.05). There was strong correlation between serum lactate clearance and mortality (p value < 0.01).

Conclusion: Study confirmed the prognostic value of serial serum lactate monitoring and its clearance for prediction of mortality. We concluded that early lactate clearance could be used as an independent predictor of survival in patients with presumed sepsis.

Keywords: lactate clearance, mortality, serum lactate, sepsis.

1. Introduction

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. Clinical organ dysfunction [presumed sepsis] can be represented by an increase in the Sequential [Sepsis-related] ACUTE PHYSIOLOGY AND CHRONIC HEALTH EVALUATION II score of 12 points or more, which is associated with in-hospital mortality greater than 10%. Sepsis is the most common cause of lactic acidosis, and septic patients with lactic acidosis show a higher mortality rate [2,3].

Lactic acidosis is a medical condition characterized by the buildup of lactate (especially L-lactate) in the body, with formation of an excessively low pH in the bloodstream. It is a form of metabolic acidosis, in which excessive acid accumulates due to a problem with the body's oxidative metabolism. Lactic acidosis is typically the result of an underlying acute or chronic medical condition, medication, or poisoning. The symptoms are generally attributable to these underlying causes, but may include nausea, vomiting, Kussmaul breathing (labored and deep), and generalized weakness. The etiology of lactic acidosis in sepsis is complex. It may result from either impaired lactate clearance or increased lactate production [4].

Therefore, increased or sustained lactate levels represent severe sepsis or septic shock. Lactate level has also been used as a prognostic indicator for mortality. In particular, the patients with an initial lactate level ≥ 3.0 mmol/L had higher mortality risks, and the probability of death was substantially increased with a high initial lactate level [5]. Some of the studies reported that lactate

clearance, derived from calculating the change in lactate levels at different times, may have potential prognostic value [6,7,2].

These studies have proved that a decrease in these markers within the first several hours may be predictive of a favorable outcome. However, no study has yet examined which factor is the most important mortality risk factor among initial lactate, lactate clearance, or inflammatory markers in severe sepsis patients with lactic acidosis. Lactate elevation is an important marker of impaired tissue perfusion in patients with sepsis and is often elevated even in the absence of arterial hypotension [8]. Blood lactate concentrations ≥ 3 mmol/L are unusual in normal and non-critically ill hospitalized patients, regardless of their underlying comorbidities [9].

2. Material and Method

2.1 Inclusion and Exclusion Criteria

The inclusions criteria were Patients admitted in Medicine ICU. Patients had sepsis ≥ 12 ACUTE PHYSIOLOGY AND CHRONIC HEALTH EVALUATION II score and lactate level in ABG ≥ 3 mmol/L. Patients of sepsis had normal lactate level were excluded. Also, patients had hyperlactatemia due to any other causes apart from sepsis like Ethanol poisoning, Aluminum Phosphide, Cardiogenic shock, Hemorrhagic shock, Severe liver dysfunction, Diabetic ketoacidosis, Trauma, Burns, Seizures and Drugs were excluded.

2.2 Study Design

Patient with sepsis were selected from Medicine ICU by using ACUTE PHYSIOLOGY AND CHRONIC HEALTH EVALUATION II score ≥ 12 points. Lactate levels at 0, 6, 12, 24 and 48 hours were measured by using ABG done by ABL 800 basic analyzer. ACUTE PHYSIOLOGY AND CHRONIC HEALTH EVALUATION II score was calculated on admission. Lactate clearance was calculated ($<10\%$ OR $>10\%$) and was correlated with mortality (< 7 days or > 7 days).

2.3 Statistical analysis

Data was entered in MS EXCEL Spread sheet and analyzed with the help of Openepi & spss software version 2.0. The statistical analysis was done by appropriate Statistical method. Descriptive statistic was explained by frequency and percentage. Chi-Square test was applied.

3. Results and Discussion

3.1 Results

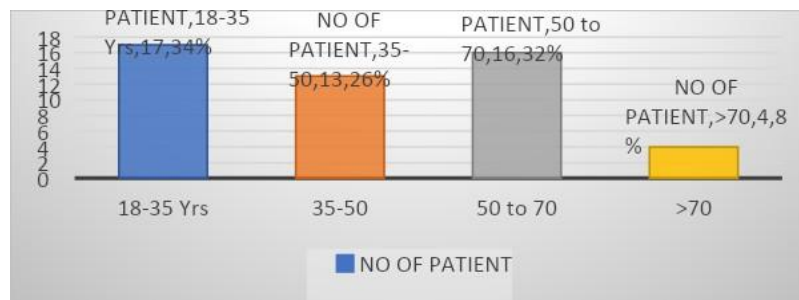


Figure 1 Age Distribution

Out of 50 patients 17 (34%) patients were between 25 to 35 years, 13 (26%) were 35 to 50 years and 16 (32%) patients were between 50 to 70 and 4 (8%) patients were more than 70 years (Figure 1) Out of total 50 patients 36 (72%) were male and 14 (28%) were female (Table 1).

Sex	No of patients	Percentage
Male	36	72%
Female	14	28%

Table 1: distribution of patients according to gender.

Out of total 50 patients, 13(26%) patients were having Acute respiratory distress syndrome (ARDS), 12(24%) were having community acquired pneumonia (CAP), 13(26%) were having septicemia, 4(8%) were having pyelonephritis, 2(4%) were having inflammatory bowel disease (IBD), 4(8%) were having spontaneous bacterial peritonitis (SBP), 2(4%) were having meningitis. ARDS, CAP, and septicemia were diagnosis in 38(76%) patients (Figure 2).

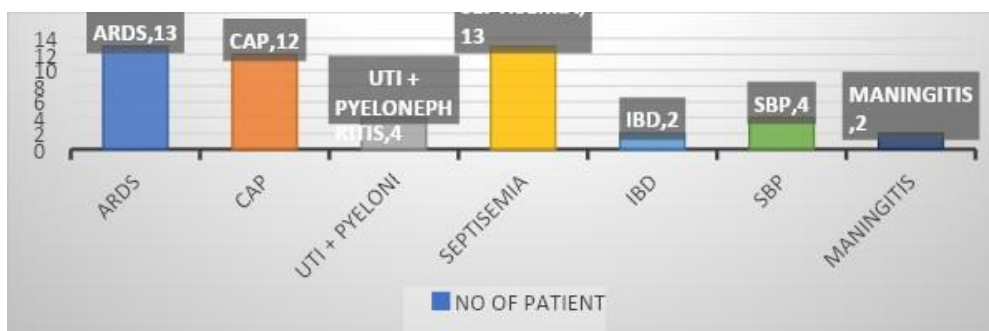


Figure 2- Dignosis

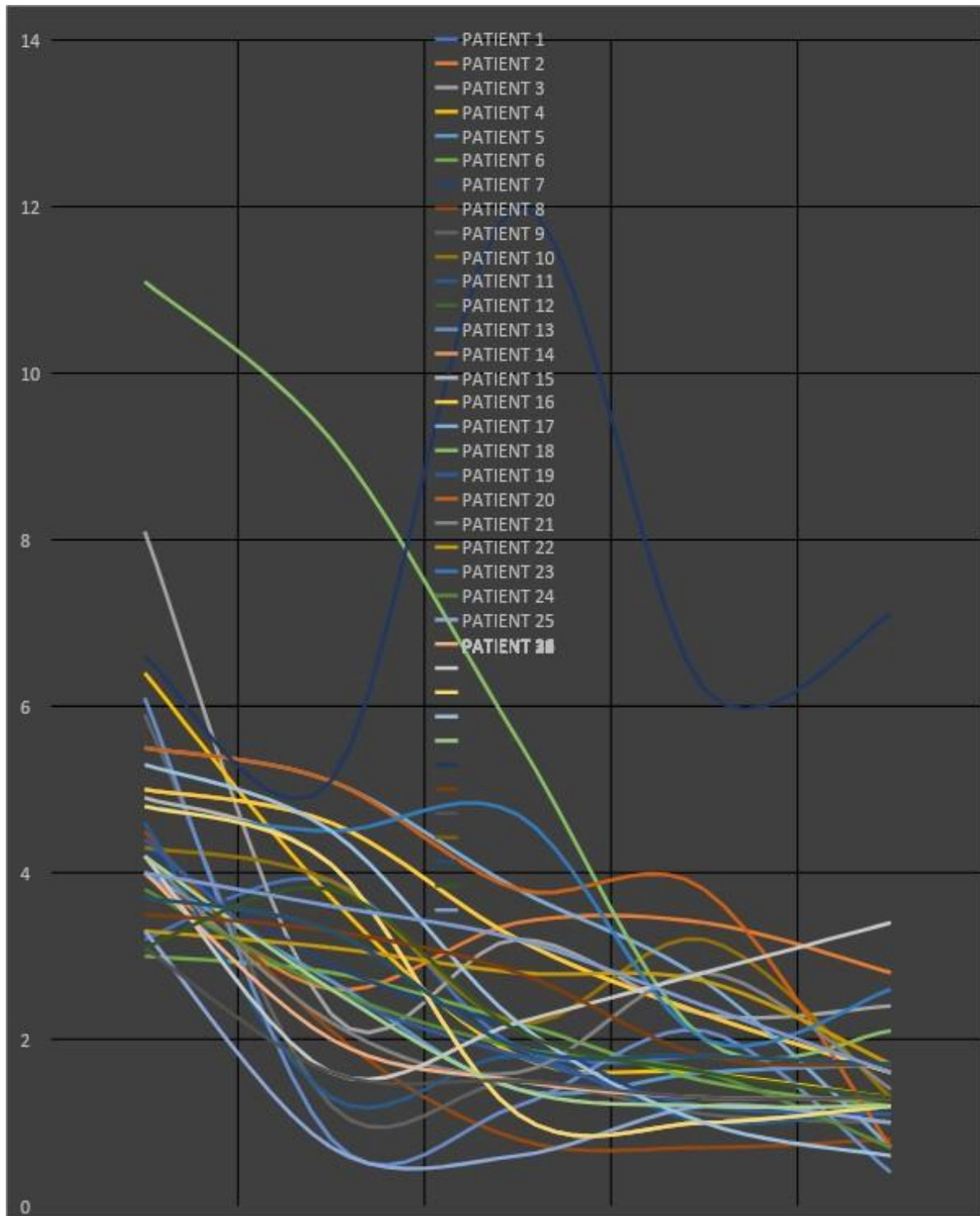
Out of 50 patients 37 (74%) patients survived and 13 (26%) patients did not survive more than 7 days.

The data showed in Table 2 for survival patients and Table 3 for expired patients.

PATIENT NO	0 hour	6 hours	12 hours	24 hours	48 hours
PATIENT 1	3.2	3.9	1.9	1.8	1
PATIENT 2	4	2.6	3.4	3.4	2.8
PATIENT 3	8.1	2.3	3.2	2.3	2.4
PATIENT 4	6.4	3.7	1.8	1.6	1.3
PATIENT 5	4	2.7	1.4	1.6	1.7
PATIENT 6	3	2.8	2.2	1.5	1.2
PATIENT 7	4.3	2.9	2.1	1.1	1.2
PATIENT 8	4.5	2.1	0.8	0.7	0.8
PATIENT 9	5.9	1.2	1.5	1.1	1
PATIENT 10	4.3	3.9	2.2	3.2	1.3
PATIENT 11	4.6	1.3	1.8	1	1.2
PATIENT 12	4.9	4.1	1.1	1	1.2
PATIENT 13	6.1	0.8	1.2	2.1	0.4
PATIENT 14	5	4.6	3.2	2.3	1.6
PATIENT 15	4.9	4.1	1.1	1	1.2
PATIENT 16	5	4.6	3.2	2.3	1.6
PATIENT 17	5.5	5.1	3.8	2.7	0.7
PATIENT 18	11.1	9.2	5.6	2	2.1
PATIENT 19	4.4	2.6	1.8	1.2	1.1
PATIENT 20	5.5	5.1	3.8	3.8	0.7
PATIENT 21	4.2	2.2	1.6	2.8	1.4
PATIENT 22	3.3	3.1	2.8	2.7	1.7
PATIENT 23	4.8	4.5	4.7	2	2.6
PATIENT 24	3.8	2.6	1.9	1.6	0.7
PATIENT 25	3.3	0.7	0.6	1.2	1
PATIENT 26	4	2	1.5	1.3	1.3
PATIENT 27	4.2	1.6	2.2	2.8	3.4
PATIENT 28	4.8	4.1	1.1	1	1.2
PATIENT 29	5.3	4.5	2.2	1	0.6
PATIENT 30	4.2	2.6	1.4	1.2	1.2
PATIENT 31	6.6	5.1	12	6.2	7.1
PATIENT 32	3.5	3.3	2.8	1.8	1.7
PATIENT 33	3.1	1.6	1.5	1.3	1.3
PATIENT 34	3.7	3.3	1.9	1.8	1.7
PATIENT 35	3.7	3.3	1.9	1.8	1.7
PATIENT 36	3.1	3.8	2.1	1.6	1.3
PATIENT 37	4	3.6	3.2	2.4	1.6

Table 2: This Table shows serum lactate level at 0, 6, 12, 24 and 48 hours in survived patients

Figure 3: This graph shows serum lactate level at 0, 6, 12, 24 and 48 hours in survived patients



Patient No	0 hours	6 hours	12 hours	24 hours	48 hours
PATIENT 1	6.4	2.3	2.4	4.5	-
PATIENT 2	3.1	6	9.2	7.2	-
PATIENT 3	4.3	3.1	2.3	1.4	1.2
PATIENT 4	6.9	7.3	7.3	8.8	-

PATIENT 5	3.9	7.7	5.5	7.6	4.8
PATIENT 6	4.7	5.3	5.8	6	7.6
PATIENT 7	5.3	5.2	2.7	2	3.3
PATIENT 8	3.1	2.6	1.3	1.5	-
PATIENT 9	5.3	4.3	4	6.8	-
PATIENT 10	4.8	1.9	5	7.7	3
PATIENT 11	3.6	8.9	8.2	10	-
PATIENT 12	6.3	8.2	9.4	9	12.6
PATIENT 13	20	19	21	21	20

Table 3: serum lactate level at 0, 6, 12, 24, and 48 hours in expired patients.

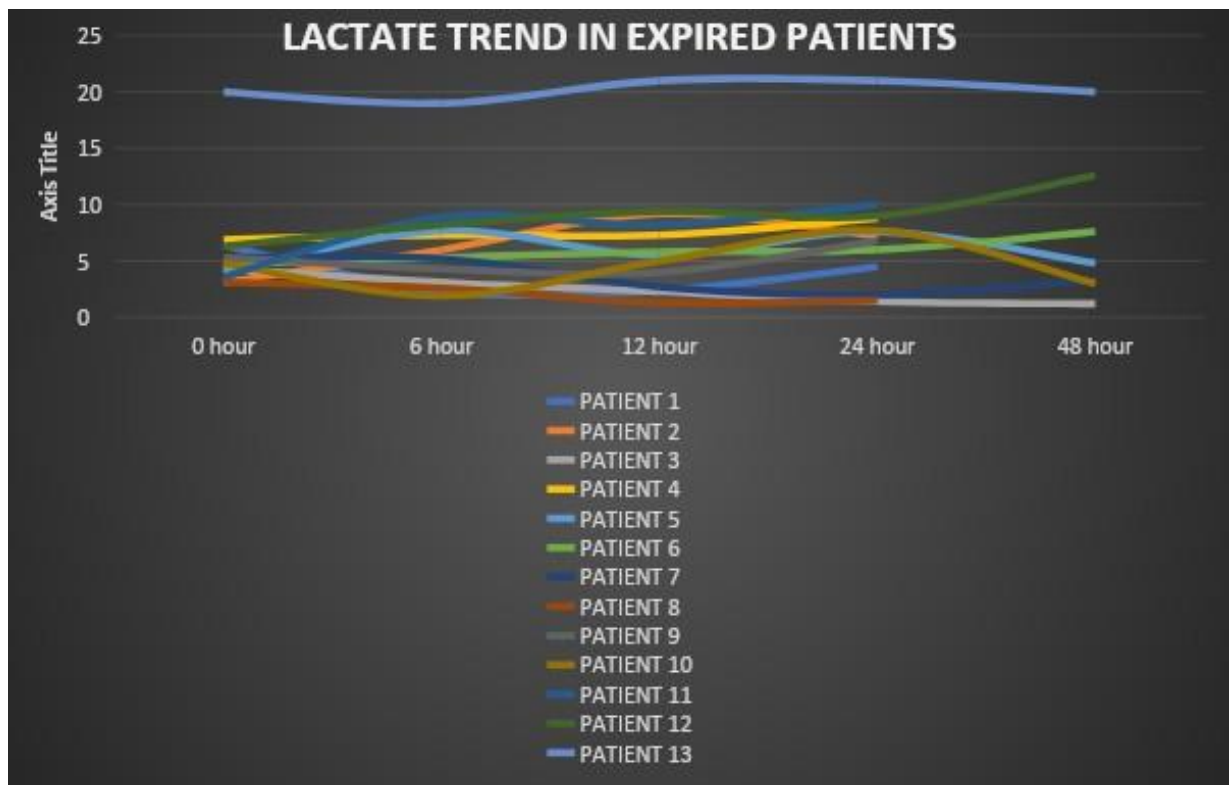


FIGURE 4: This graph shows serum lactate level at 0, 6, 12, 24, and 48 hours in expired patients. Lactate clearance was defined as decrease in repeat lactate by 10% or greater from the initial value and Lactate non clearance was defined as decrease in repeat lactate by less than 10% from initial value.

Serum lactate	Mortality (no of patients)	Survival (no of patients)
Non-Clearance	9	2
Clearance	4	35

Table 4 Association between serum lactate clearance and mortality

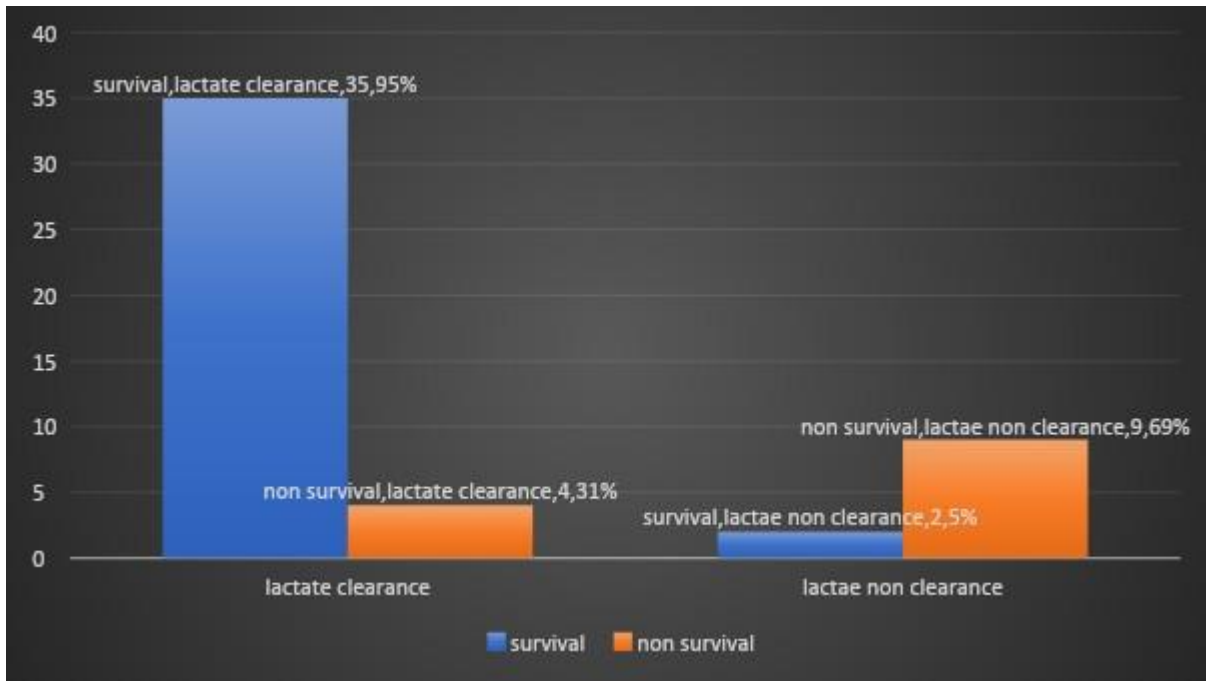


FIGURE 5: LACTATE CLEARANCE AND MORTALITY

	No. Of non-survival patients in lactate clearance group	No. Of survived patients in lactate clearance group
ACUTE PHYSIOLOGY AND CHRONIC HEALTH EVALUATION II score >20 (> 50 % mortality prediction)	2	5
ACUTE PHYSIOLOGY AND CHRONIC HEALTH EVALUATION II score <20 (<50% mortality prediction)	2	30

Table 5 Correlation between lactate clearance and ACUTE PHYSIOLOGY AND CHRONIC HEALTH EVALUATION II score to predict mortality in sepsis patients.

- Cohen's Kappa statistics = 0.82

	No. of expired patients in lactate non clearance group	No. of survival patients in lactate non clearance group
ACUTE PHYSIOLOGY AND CHRONIC HEALTH EVALUATION II score >20 (> 50 % mortality prediction)	7	0

ACUTE PHYSIOLOGY AND CHRONIC HEALTH EVALUATION II score <20 (<50% mortality prediction)	2	2
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Table 6. Correlation between lactate non clearance and ACUTE PHYSIOLOGY AND CHRONIC HEALTH EVALUATION II score to predict mortality in sepsis patients.

- Cohen's Kappa statistics = 0.81

THE KAPPA STATISTIC VARIES FROM 0 TO 1, WHERE.

- 0 = agreement equivalent to chance.
- 0.1 – 0.2 = slight agreement.
- 0.21 – 0.40 = fair agreement.
- 0.41 – 0.60 = moderate agreement.
- 0.61 – 0.80 = substantial agreement.
- 0.81 – 0.99 = near perfect agreement
- 1= perfect agreement.

3.2 DISCUSSION

In this multicenter model of patients with severe sepsis. We found that early lactate clearance was a strong independent analyst of in-hospital death. The cause of raised serum lactate in patients with sepsis can be multifactorial. Lactate elevation may result from acute tissue hypoperfusion and anaerobic metabolism other possible causes may contain (a) sepsis encouraged impairment of pyruvate-dehydrogenase enzyme activity, (b) increased lactate production through catechol amine-driven pathways, and (c) decreased lactate clearance due to hepatic dysfunction [2,3,4].

Regardless of etiology of an elevated serum lactate, lactate elevation in sepsis has been dependably linked to increased mortality. Initial reports of lactate clearance in sepsis were published more than 16 years ago, evaluating lactate trends in dangerous patients are not yet part of the current consensus recommendations for sepsis management and is not routinely performed in practice. Our data show that assessment of lactate clearance is significant as a predictor of mortality. These data suggest that serial lactate measurement may provide unique and important information. Total 50 patients were registered in our study. The age range was from 18 years to 82 years. The mean age of the study population was 48 years. The maximum numbers of patients were found in the age group of 18-35 years and they constitute about 34% of the study population [4,6].

In our study the numbers of males were 36 (72 %) and females were 14 (28%). 13 (26%) patients had ARDS and 12 (24%) patients had community acquired pneumonia. So, 25 (50%) of patients had respiratory system involvement. Septicemia of unknown etiology was second most common diagnosis which included 13 (26%) patients. Rest of the patients had pyelonephritis 4 (8%), inflammatory bowel disease 2 (4%), spontaneous bacterial peritonitis 4 (8%), and meningitis 2 (4%). We had compared our study with a reference study of Arnold et al. which is multicenter prospective

study of 166 patients which was published in SHOCK (Augusta Ga.) international journal in august 2009 [10]. In our study, 39 patients were in lactate clearance group out of which 35 (89%) survived and 4 (11%) expired. While Arnold et al. study had survival rate of 122(81%) in lactate clearance group of 151 patients. Both studies had p-value < 0.01, so there is significant correlation between serum lactate clearance and mortality. There were several shortcomings in this study including the small sample size, short follow up and single center study. All our patients were not culture proven sepsis. Larger multi-centric studies with longer duration of patients' follow up will be useful.

3.3 CONCLUSION

Our study confirms the prognostic value of serial serum lactate monitoring and its clearance for prediction of mortality. Lactate values probably need to be followed for longer periods of time in critical patients even when they have tided over the present crisis. This study indicates that it is better to monitor serial lactate levels rather than going for single lactate value. If lactate levels are static or increasing than prognosis is grave and if its clearing than prognosis is good. The serial serum lactate levels between 6 hours to 36 hours are best predictor of mortality. We conclude that early lactate clearance can be used as an independent predictor of survival in patients with presumed sepsis.

Ethical Approval And Consent

The study was directed with the approval of the Institutional Ethical Committee. Volunteers eligible for the study were well-versed of the potential risks and benefits of the medication. Before the start of the study, volunteers signed consent forms. They were recruited in Department of General Medicine at SMIMER, Surat, Gujarat, India.

Refernces

1. Stacpoole PW, Wright EC, Baumgartner TG, Bersin RM, Buchalter S, Curry SH, et al. A Controlled Clinical Trial of Dichloroacetate for Treatment of Lactic Acidosis in Adults. *N Engl J Med* [Internet]. 1992 Nov 26 [cited 2019 Aug 8];327(22):1564–9. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/1435883>
2. Berg KM, Gautam S, Saliccioli JD, Giberson T, Saindon B, Donnino MW. Intravenous Thiamine Is Associated with Increased Oxygen Consumption in Critically Ill Patients with Preserved Cardiac Index. *Ann Am Thorac Soc* [Internet]. 2014 Dec [cited 2019 Aug 8];11(10):1597–601. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25390455>
3. Casserly B, Phillips GS, Schorr C, Dellinger RP, Townsend SR, Osborn TM, et al. Lactate Measurements in Sepsis-Induced Tissue Hypoperfusion. *Crit Care Med* [Internet]. 2015 Mar [cited 2019 Aug 8];43(3):567–73. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25479113>
4. De Corte W, Vuylsteke S, De Waele JJ, Dhondt AW, Decruyenaere J, Vanholder R, et al. Severe lactic acidosis in critically ill patients with acute kidney injury treated with renal replacement therapy. *J Crit Care* [Internet]. 2014 Aug [cited 2019 Aug 8];29(4):650–5.

Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24636927>

5. Russell JA, Walley KR, Singer J, Gordon AC, Hébert PC, Cooper DJ, et al. Vasopressin versus Norepinephrine Infusion in Patients with Septic Shock. *N Engl J Med* [Internet]. 2008 Feb 28

[cited 2019 Aug 8];358(9):877–87. Available from:
<http://www.ncbi.nlm.nih.gov/pubmed/18305265>

6. Haas SA, Lange T, Saugel B, Petzoldt M, Fuhrmann V, Metschke M, et al. Severe hyperlactatemia, lactate clearance and mortality in unselected critically ill patients. *Intensive Care Med* [Internet]. 2016 Feb 10 [cited 2019 Aug 8];42(2):202–10. Available from:
<http://www.ncbi.nlm.nih.gov/pubmed/26556617>
7. Puskarich MA, Trzeciak S, Shapiro NI, Albers AB, Heffner AC, Kline JA, et al. Whole Blood Lactate Kinetics in Patients Undergoing Quantitative Resuscitation for Severe Sepsis and Septic Shock. *Chest* [Internet]. 2013 Jun [cited 2019 Aug 8];143(6):1548–53. Available from:
<http://www.ncbi.nlm.nih.gov/pubmed/23740148>
8. Lokhandwala S, Andersen LW, Nair S, Patel P, Cocchi MN, Donnino MW. Absolute lactate value vs relative reduction as a predictor of mortality in severe sepsis and septic shock. *J Crit Care* [Internet]. 2017 Feb [cited 2019 Aug 8];37:179–84. Available from:
<http://www.ncbi.nlm.nih.gov/pubmed/27771598>
9. Dettmer M, Holthaus C V., Fuller BM. The Impact of Serial Lactate Monitoring on Emergency Department Resuscitation Interventions and Clinical Outcomes in Severe Sepsis and Septic Shock. *Shock* [Internet]. 2015 Jan [cited 2019 Aug 8];43(1):55–61. Available from:

<http://www.ncbi.nlm.nih.gov/pubmed/25186838>

10. Ryan Arnold;Nathan Shapiro;Alan Jones;Christa Schorr;Jennifer Pope;Elisabeth Casner;Joseph Parrillo;R. Phillip Dellinger;Stephen Trzeciak; multicenter study of early lactate clearance as a determinant of survival in patients with presumed sepsis. *shock*. 32(1):35-39, july 2009: DOI: 10.1097/SHK.0b013e3181971d47,PMID: [19533847](https://pubmed.ncbi.nlm.nih.gov/19533847/) Issn Print: 1073-2322 Publication Date: July 2009: Available from:
<https://www.ncbi.nlm.nih.gov/pubmed/19533847>