ORIGINAL ARTICLE http://dx.doi.org/10.3126/njms.v5i1.36709

Lactate Clearance as a Predictive Marker of Mortality in Adult Intensive Care Unit

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Received: October 1, 2020 **Accepted:** December 5, 2020 **Published:** December 30, 2020

Cite this paper:
Joshi SR, Gurung R, Acharya SP, Parajuli B, Bista NR. Lactate Clearance as a Predictive Marker of Mortality in Adult Intensive Care Unit. *Nepal Journal of Medical Sciences*. 2020;5(2):32-38.**http://dx.doi.org/10.3126/njms.v5i1.36709**

ABSTRACT

Introduction: Lactate clearance has been widely investigated. Serial lactate concentrations can be used to examine disease severity and predict mortality in the intensive care unit. We investigated the diagnostic accuracy of lactate concentration and lactate clearance in predicting mortality in critically ill patients during the first 24 hours in Intensive Care Unit (ICU).

Methods: It was a Prospective, observational study conducted in ICU. Sixty eight consecutive patients having blood lactate level >2 mmol/L were included irrespective of disease and postoperative status. We measured blood lactate concentration at ICU admission(H0), at six hours(H6), 12 hours(H12), and 24 hours(H24). Lactate clearance was measured for H0-H6, H0-H12 and H0-H24 time period.

Results: ICU mortality was 33.8%. Lactate clearance was 15.80 ± 17.21% in survivors and 1.73±11% in non survivors for the H0-H6 ($p = 0.001$) and remained higher in survivors than in non survivors over the study period of 24 hours; 17.97±15 vs. -2.04±19.84% for H0-H12 and 27.40 ± 11.41% vs. -14.83 ± 26.84% for the H0-H24 period ($p < 0.001$ for each studied period). There was significant difference in lactate concentration (static) between survivors and non survivors during the course of initial 24 hours. The best predictor of ICU mortality was lactate clearance for the H0-H24 period (AUC =0.89; 95% CI 0.78-1.01). Logistic regression found that H0-H24 lactate clearance was independently correlated to a survival status ($p = 0.005$, OR = 0.922 and 95% CI 0.871-0.976).

Conclusion: Blood lactate concentration and lactate clearance are both predictive for mortality during initial 24 hours of ICU admission.

Keywords: *Critically Ill Patients; Diagnostic Accuracy; Lactate Clearance; Mortality; Predictive*

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INTRODUCTION

First investigation of increase in blood lactate level of critical illness was in 1800s. In 1950s, Huckabee examined the relationship of blood lactate and pyruvate levels to different oxygen-deficient states. Dynamic assessments of metabolic values are more efficient than static values for death prediction. Therefore, measurement of lactate clearance can be a surrogate marker in critically ill patients to guide therapy.

Studies in severe sepsis and septic patients exhibit the prediction of day-28 survival from the significance of blood lactate clearance in the initial six hours of resuscitation. Monitoring of lactate clearance for longer duration may produce better outcome, but there is a short of statistics following the initial six hours of treatment. Our hypothesis was that lactate clearance could remain predictive for outcomes during initial 24 hours of ICU admission. Thus, we evaluated lactate concentration and clearance for the initial 24 hours period in ICU for the prognostic value of death.

METHODS

Ethical approval obtained from the Institution Review Board. It was a prospective and observational study carried in 68 patients at 11 bed multidisciplinary ICU for a period of six months. All consecutive cases admitted to ICU with high initial lactate level (>2mol /L) were included. Patients with total ICU stay duration <24 hrs, leave against medical advice to home or other hospitals, discharged on request, withdrawal of Active Life supportive treatment, and death within 24 hours were excluded from the study. The time of ICU admission is a zero hour (H0). Provisional diagnosis at admission, chronic health variables required to calculate APACHE II score, mechanical ventilator support required or not, vasopressors and ionotropes used or not and pre ICU hospital stay in emergency department or any other ward were recorded. Physical examination done regularly and all base line investigations sent at H0 as per ICU protocol. Initial lactate level measured at H0. Lactometer with the lactate stripe measured blood lactate level. Patients having high blood lactate level (> 2 mmol/L) at H0 were included. Serial lactate levels measurement done at six hours (H6), 12 hours (H12) and 24 hours (H24). The lactate clearance = {(lactate initial – lactate delayed)/ lactate initial} ×100%. Lactate level at H0 is lactate initial. Blood lactate level at H6, H12 or H24 is lactate delayed. A positive lactate clearance value show a fall in lactate level over time. A negative lactate clearance value indicates increase in lactate level over time. Calculation of APACHE II score at admission done based on physiological values at admission, age and chronic health status of the patient using online calculator. Patients were followed until; death/ discharge from ICU/ left against Medical Advice/ withdrawal of Active Life Support/ transfer to other hospital. Total duration of ICU stay was recorded. Statistics: Data collected and analyzed using SPSS 17.0 version. We recorded quantitative variables as mean with standard deviation and qualitative data as number and percentage. Kolmogorov-Smirnov test assessed normal distributions of data. Independent T test compared survivors and non-survivors for continuous variables with normal distribution, by Mann-Whitney U test for continuous variables without normal distribution, by Chi- square test for categorical variables and discrimination test with the help of area under Receiver Operating Characteristic (ROC) Curve for lactate clearance at different time intervals were plotted and compared among them-selves. Multiple logistic regression analysis tested whether lactate clearance was independently associated with mortality.

RESULTS

We enrolled total 68 cases [male 36(52.9 %) and female 32(47.1%)]. Mean age of the patients was 46.01 ± 19.53 years. Length of ICU stay was between one to ten days with mean duration of 2.85±2.03 days. Out of 68 patients, 23(33.8%) patients had surgery. Forty (58.8%) required mechanical ventilation while 49 (72.1%) patients needed ionotropic support. Regarding outcome of ICU stay, 45(66.2%) patients survived and transferred

out of the ICU, remaining 23(33.8%) patients expired in ICU. APACHE II score of the patients ranged from five to thirty-one, while mean score being 13.8±6.3. Mean Lactate level (static in mmol/L) at H0 was 4.02±1.46, at H6 was 3.62±1.57, at H12 was 3.6±1.6, and at H12 was 3.56±2.01. Mean Lactate clearance at H0-H6 (11.05± 16.74%), H0-H12 (11.20± 19.18%), and H0-H24 (13.12±26.97%).

All non-survivors required mechanical ventilation, while 28 (62.2%) of the survivors required mechanical ventilation (p<0.001). (Table2) Among the patients who received ionotropic support, 26 (53.1%) patients survived and 23 (46.9%) patients died. All the patients who did not require ionotropic support survived (p < 0.001). (Table 2)

There was no significant difference between survivors and non-survivors regarding age and length of stay (LOS). Survivors had lower mean APACHE II score as compared to non-survivors (p < 0.001). (Table 1)

Table 1: Comparison of age, duration of stay and APACHE II score

Variables	Survivors		Non survivors		p- value
	Mean	SD	Mean	SD	
Age (in years)	43.8	19.02	50.26	20.24	0.214
ICU LOS (in days)	2.97	2.14	2.61	1.82	0.496
APACHE II score	11.67	3.24	17.61	5.31	<0.001

Table 2: Mechanical Ventilation and Ionotropic/vasopressors supports in survivors and non-survivors

Mechanical ventilation	Survivors	Non survivors	p-value
Yes	28(62.2%)	23(100%)	<0.001
No	17(37.8%)	0(0%)	
Ionotropic/vasopressor support	Survivors	Non survivors	
Yes	26(53.1%)	23(46.9%)	0.001
No	19(100%)	0(0%)	

In survivor mean blood lactate concentrations at H0 was lesser than in non-survivor but no statistical difference. In later period, survivors had lower blood lactate concentrations than in non-survivors (p<0.001 for each studied period). (Table 3) Lactate clearance was 15.80 ± 17.21% in survivors and 1.73 ± 11% in non-survivors for the H0-H6 period (p = 0.001) and remained higher in survivors than in non-survivors throughout studied duration. (P < 0.001 for each studied duration).

Table 3: lactate level and Lactate Clearance at different time interval between survivors and non-survivors

Time	Lactate level (mmol/L)				p-value
	Survivors		Non survivors		
	Mean	SD	Mean	SD	
H0	3.70	1.27	4.65	1.62	0.010
H6	3.13	1.29	4.57	1.65	<0.001
H12	3.02	1.15	4.74	1.75	<0.001
H24	2.62	0.88	5.39	2.33	<0.001
H0-H6	15.80%	17.21%	1.73%	11.14%	0.001
H0-H12	17.97%	15.00%	-2.04%	19.84%	<0.001
H0-H24	27.40%	11.41%	-14.83%	26.84%	<0.001

Using the area under a receiver-operating characteristic (ROC) curve, we performed discrimination test for static lactate level, lactate clearance (Figure 1) and APACHE II score (Figure 2). It showed a good area under ROC curve for all variables with best area under a ROC curve was obtained for H0-H24 lactate clearance (0.89; 95% CI 0.78-1.01) followed by static lactate level at H24 and APACHE II score. (Table 4)

Discrimination Test:

Table 4: ROC curve analysis

Test Result Variable(s)	Area under curve	SE	p-value	95% Confidence Interval	
				Lower Bound	Upper Bound
Lactate Clearance H0-H6	0.76	0.06	0.001	0.64	0.87
Lactate Clearance H0-H12	0.80	0.06	<0.001	0.68	0.91
Lactate Clearance H0-H24	0.89	0.06	<0.001	0.78	1.01
Lactate Level H0	0.70	0.07	0.009	0.57	0.82
Lactate Level H6	0.79	0.06	<0.001	0.68	0.89
Lactate Level H12	0.80	0.06	<0.001	0.69	0.91
Lactate Level H24	0.87	0.06	<0.001	0.80	0.99
APACHE II	0.84	0.06	<0.001	0.73	0.95

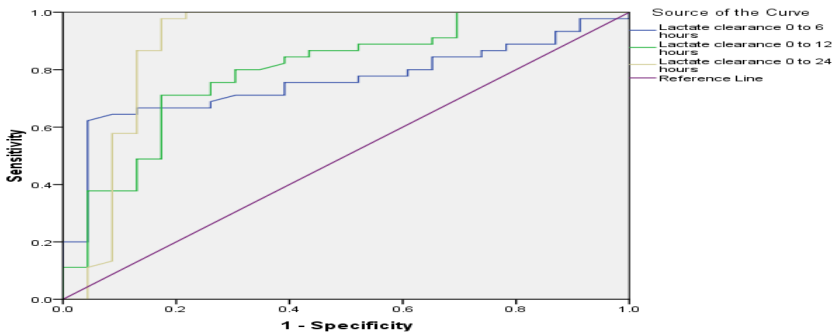

Figure 1: *ROC curve for lactate clearance at a different time interval (Predicting survival)*

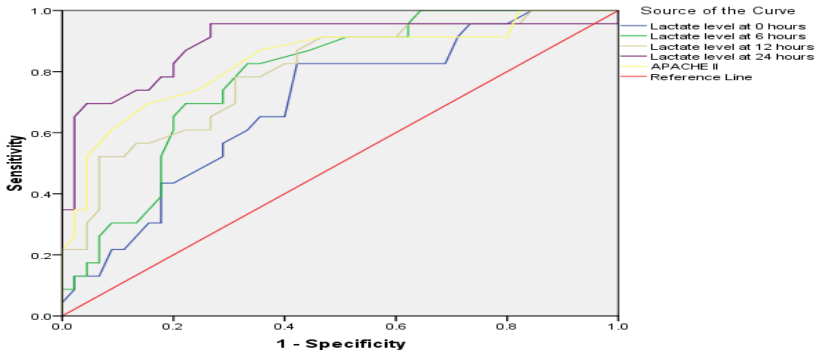

Figure 2: *ROC curve for lactate level at different point of time and APACHE II score predicting death)*

After adjusting for all the variables that were significant on univariate analysis, multiple logistic regression analysis found that only the lactate clearance over H0-H24 and APACHE II score were independently correlated to a survival status. (Table 5)

Table 5: Multiple logistic regression analysis

Variables	p-value	OR	95% C.I. for OR	
			Lower	Upper
Lactate Clearance H0-H6	0.81	0.993	0.94	1.049
Lactate Clearance H0-H12	0.784	1.009	0.947	1.075
Lactate Clearance H0-H24	0.005	0.922	0.871	0.976
APACHE II	0.015	1.352	1.061	1.724

DISCUSSION

In our study, both static lactate levels and lactate clearance over the 24 hours of ICU admission were predictive of mortality with good diagnostic accuracy. Mean blood lactate concentrations were lesser in survivors than in non-survivors at H0 (3.70 ± 1.27 mmol/L vs. 4.65 ± 1.62 mmol/L; p = 0.01) and remained significantly lower in survivors at each studied point of time. Thus, our study found that initial blood lactate level has a significant association with outcome and lactate level (static) remains predictive of outcome during the initial 24 hours of ICU admission. In a general ICU population, baseline lactate concentration, predict the risk of mortality with superior precision.[6] Study done in 2005 by Varpula et al. in septic shock patients found high initial lactate concentration in non-survivors (3.4 vs 2.1 mmol/l, p < 0.005).[7] In another study by Jansen TC et al. conducted in heterogeneous intensive care unit patient and found a strong relationship between blood lactate levels and SOFA scores. This relationship was stronger during the early phase of ICU stay.[8]

In an observational study, Nichol DA et al.[9] showed that high initial lactate level even within the normal range (<2mmol/L) was significantly associated with mortality in ICU patients.

This significant correlation was evident at lactate concentrations >0.75 mmol/L.[9] In a study, Cochran A et al. examined the association of serum lactate level and mortality in cohort burn patients. In non-survivors, serum lactate levels were significantly high than in survivors at admission and at 12, 18, and 24 hours after admission.[10] Lactate clearance was 15.80 ± 17.21% in survivors and 1.73 ± 11% in non-survivors for the H0-H6 period (p = 0. 001) and stayed elevated in survivors than in non-survivors for each studied period (17.97 ± 15% vs. -2.04 ± 19.84% for H0-H12 period and 27.40 ± 11.41% vs. -14.83 ± 26.84% for the H0-H24 period; P <0.001 for each studied period). For the death prediction, dynamic assessment of metabolic values may be more beneficial than static values. Studies have shown the importance of measurement of blood lactate clearance in severe septic patients in the initial six hours of resuscitation for the prediction of day-28 survival. For septic patients, a lactate clearance aimed treatment in the initial six hours look as effective as ScvO2.[11] In patients with hyperlactatemia, in general ICU, application of an 8-hour therapy to lactate clearance lowered the mortality rate compared with standard therapy.

In this study, a resuscitation customized with the goal of a 20% reduction in lactate level every two hours for eight hours reduced the mortality rate.[12] In one more research, supplementation of lactate clearance to the SSC resuscitation bundle is related to a superior result. According to this research, mortality in septic ICU patients is associated with a lack of lactate clearance in the initial 24 hours. Even though patients achieve to set the hemodynamic goal, we need to direct to aggressive implementation of therapy.[13] In a meta-analysis Zhang Z et al. demonstrated good sensitivity and specificity for lactate clearance to forecast mortality; 0.75 (95% CI, 0.58–0.87) and 0.72 (95% CI, 0.61-0.80), respectively.[14] The diagnostic implementation enhanced when the meta-analysis was limited to ICU patients, with sensitivity and specificity

of 0.83 (95% CI, 0.67–0.92) and 0.67 (95% CI, 0.59–0.75), respectively.[15] In a study, Wang H et al. found that 12 hour and 24-hour lactic acid clearance between survivor and the non-survivor group showed a statistically significant difference in critically ill patients, ($p<0.05$ and $p<0.01$ respectively). Discrimination for lactate level at different point of time (Static), lactate clearance at a different time interval and was tested using the area under a ROC curve. It showed a good area under the ROC curve for all tested variables with best ROC curves AUC was achieved for H0 -H24 lactate clearance (0.89; 95% CI 0.78-1.01) followed by static lactate level at H24 (0.87; 95% CI 0. 80 -0. 99) and APACHE II score (0.84; 95% CI 0. 73 -0.95). In a study conducted in critically ill children, Koliski A et al found that lactate level at 24 hours is a very good predictor of death with the area under a ROC curve of 0.809 (CI = 0. 664 to 0.910).[16] Multiple logistic regression analysis achieved that only the lactate clearance H0-H24 and APACHE II score were independently correlated to outcome, $p = 0.005$ {odds ratio = 0.922 (95% CI 0. 871 -0. 976)} and $p = 0.015$ {odds ratio = 1.532 (95% CI 1. 061-1.724)} respectively.

Our study has few limitations. We conducted in a single centre with a limited number of the study population; therefore, we cannot generalize the result to other centres. We could not assess long-term outcome after discharge from ICU as we followed the patient only until ICU discharge.

CONCLUSION

Blood lactate concentration and lactate clearance are both predictive for mortality during the initial 24 hours of ICU admission.

CONFLICT OF INTEREST

None

SOURCES OF FUNDING

None

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