Effectiveness of Lactate Clearance to Predict In-Hospital Mortality in Patients with Upper Gastrointestinal Bleeding

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ABSTRACT

Objective: To determine the performance of lactate clearance to predict prognosis in patients with upper gastrointestinal bleeding (UGIB).

Study Design: Observational study.

Place and Duration of the Study: Department of Emergency Medicine, Sisli Hamidiye Etfal Training and Research Hospital, Istanbul, Turkey, from January 2018 to 2022.

Methodology: This study was conducted with 141 patients with UGIB. Lactate clearance was calculated based on the lactate levels at the time of admission and 6^{th} hour. The primary outcome was survival. The secondary outcomes were the need for intensive care unit, endoscopic intervention, blood transfusion, and length of hospital stay.

Results: The median age of the patients was 71 years and 65.2% were males. In the non-survivor group; systolic blood pressure, diastolic blood pressure, base deficit, delta lactate, and lactate clearance were significantly lower; however, heart rate, baseline lactate and final lactate were significantly higher. The median lactate clearance of survivors and non-survivors were 23.61 and -0.51, respectively ($p = 0.002$). A unit decrease in lactate clearance increased mortality 1.011-fold. The performance of lactate clearance in predicting mortality was followed as; sensitivity 76.4, specificity 51.4 (AUC = 0.673, $p = 0.002$), and the cut-off value was 21.51. Lactate clearance was not statistically significant in determining the need for intensive care ($p = 0.110$), endoscopic intervention ($p = 0.152$) and blood transfusion ($p = 0.266$) in UGIB.

Conclusion: Lactate clearance was an independent predictor of in-hospital mortality in UGIB. It is thought that the study will guide clinicians in the differentiation of critically-ill patients and an effective treatment planning.

Key Words: *Upper gastrointestinal haemorrhage, Lactate, Lactate clearance, Mortality, endoscopy, Blood transfusion, Intensive care.*

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INTRODUCTION

Bleeding originating proximal to the ligament of Treitz in the gastrointestinal tract is defined as upper gastrointestinal bleeding (UGIB).[1] The patients with UIGB have high mortality and morbidity rates and require rapid intervention in the emergency department. Although the mortality rate varies between 3-15%, this rate may be even higher in haemodynamically unstable patients.[2] The incidence of UGIB is 103-172/100000.[3,4] In gastrointestinal bleeding, risk stratification is important in terms of patient prognosis, optimising patient care, efficient use of resources and reducing costs.

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Various scoring systems and biomarkers have been used to predict prognosis and develop optimal treatment strategies in patients with UGIB. However, the lack of an ideal biomarker and limited and difficult usability of scoring systems for an emergency department have guided to this study. This is the first study to investigate whether lactate clearance is a valuable biomarker in predicting prognosis in patients with UGIB.

Approximately 1500 mmol of lactate is produced per day from various organs including muscle, red blood cells, brain, skin, and intestines in physiological conditions, and 60% is metabolised by the liver and 30% by the kidneys.[5] Normal blood lactate concentration is about 1 mEq/L.[6] Lactate level is widely used as an indicator of altered tissue perfusion in critically-ill patients. A high lactate level indicates increased production or decreased elimination. Therefore, dynamic assessment of serial lactate concentrations may be more predictive than a single lactate value. Lactate clearance may be an ideal biomarker for monitoring patient prognosis and response to therapy in critically-ill patients such as gastrointestinal bleeding because it is cheap and fast.

Recently, lactate clearance has been shown to be an effective biomarker for predicting mortality in sepsis, trauma, respiratory failure, and cardiac arrest.[7-9] This study aimed to reveal the efficacy of lactate clearance to predict prognosis in patients presented to the emergency department with UGIB.

METHODOLOGY

This study was conducted between 2018 and 2022 at Istanbul Sisli Hamidiye Etfal Training and Research Hospital's Emergency Department. An ethical approval was obtained from the local Ethics Committee of the hospital. Patients admitted to the emergency department who were diagnosed with gastrointestinal bleeding based on examination and laboratory findings of the physicians of the emergency department and who were consulted to gastroenterology consequently were included in the study. Data were obtained from the hospital database system. Patients under the age of 18, pregnant women, patients whose mortality information is unknown, and patients whose first lactate or 6th hour lactate values could not be reached were excluded from the study.

Systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse, haemoglobin (Hb), platelet (PLT), pH, base excess (BE), initial lactate and final lactate values at the admission to the emergency department were recorded. Blood gas lactate was analysed with the "Siemens Rapidlab 1265" device in the emergency room and normal reference values were 0-2 mmol/L. Delta lactate value and lactate clearance were calculated with the first lactate (initial lactate) and last lactate (6th hour) values. Lactate clearance was calculated using the following formula suggested by Nguyen *et al*. Lactate clearance = (first lactate - final lactate) x 100 / initial lactate.[9] Delta lactate variable was constructed using the formula (initial lactate-6th hour lactate). In this way, a higher delta lactate value indicated a greater decrease in lactate values at 6th hour compared to the baseline. Patients were classified as; discharge, inpatient clinic admission and intensive care unit admission according to their outcome in the emergency department. Blood transfusion was considered in patients with shock findings, hypotension, clinical deterioration or haemoglobin below 7 g/dl. Blood transfusion requirement information during the hospitalisation was obtained from the hospital database. Band ligation, sclerotherapy, hemoclip and embolisation procedures performed in patients with active bleeding during endoscopy were defined as an endoscopic intervention. When performing correlation analysis between the hospitalisation day and lactate clearance, 34 patients with in-hospital mortality were excluded.

The primary outcome of the study was defined as the change in lactate clearance between surviving and non-surviving groups. The secondary outcomes were hospitalisation day, need for intensive care unit admission, endoscopic intervention, and blood transfusion.

Shapiro-Wilk test was used to test the normality of numerical variables. They were presented as mean ± standard deviation when normally distributed, otherwise, median (minimum-maximum) values were given. Independent samples t-test or Mann-Whitney U-test was performed for comparing two independent groups when the data were normally and non-normally distributed, respectively. The categorical variables were expressed by counts and percentages. Comparisons between the groups were performed with Pearson Chi-square test for categorical variables. Receiver operating characteristics (ROC) curve analysis was performed to evaluate the performances of delta lactate and lactate clearance in predicting in-hospital mortality, need for intensive care unit, endoscopic therapy, and blood transfusion. Youden J index was used to determine the optimal cut-off value in ROC curve analysis. The relationship between the duration of stay in hospital and lactate measurements were evaluated with the Spearman's correlation coefficient. Risk factors for in-hospital mortality were also evaluated with multivariate binary logistic regression analysis. A value of $p < 0.05$ was considered statistically significant. Two separate models were created, model-1 (for delta lactate) and model-2 (for lactate clearance).

Statistical analyses were performed with IBM SPSS Statistics version 22.0 (IBM Corp., USA) and MedCalc version 12.3.0.0.

RESULTS

A total of 141 patients were included in the study; 92 (65.25%) were males and 49 (34.75%) were females. The median age of 141 patients was 71 (minimum-maximum: 27-97) years. When the survived and mortality groups were compared, there was a significant difference between the two groups in terms of SBP, DBP, pulse, BE, first lactate, final lactate, delta lactate and lactate clearance values. In the mortality group, SBP, DBP, BE, delta lactate, and lactate clearance were significantly lower, but heart rate, initial lactate, and final lactate were significantly higher (Table I).

In model-1, logistic regression which included delta lactate, (Omnibus test: $p < 0.001$; Hosmer-Lemeshow test: $p = 0.584$), delta lactate, and heart rate was still significant in the presence of other variables. One unit increase in delta lactate level decreased the mortality risk 0.735 times (or 1 unit decrease increased the mortality risk 1/0.735 = 1.361 times) ($p = 0.017$). A 1-unit increase in heart rate increased the risk of mortality 1.037 times ($p = 0.015$).

In model-2, logistic regression model which included lactate clearance, lactate clearance, and heart rate were found to be statistically significant among the variables lactate clearance, heart rate, SBP, DBP, BE, age, and gender (Omnibus test for the model: $p = 0.001$; Hosmer-Lemeshow test: $p = 0.174$). A one-unit increase in lactate clearance reduced the mortality risk by 0.989 times (or a one-unit decrease increased the mortality risk by 1/0.989 = 1.011 times) ($p = 0.006$). A one-unit increase in heart rate increased mortality risk by 1.033 times ($p = 0.028$).

The initial and last lactate levels were considerably higher in the ICU group ($p = 0.001$ and $p < 0.001$, respectively) when the patients who required and did not require ICU admission were compared, the delta lactate and lactate clearance were not statistically different between the two groups. The only difference between the groups with and without blood transfusion was initial lactate levels ($p = 0.044$), and there was no difference between the groups with and without endoscopic intervention (Table II).

Table I: Comparison of the survived and mortality groups.

Variables	Survive (n=107)	Mortality (n=34)	All patients (n=141)	p-value
Age (year)[a]	70.00(27.00/97.00)	76.00(27.00/95.00)	71.00(27.00/97.00)	0.086
Sex[b]				
Male	68 (63.55)	24 (70.59)	92 (65.25)	0.453
Female	39 (36.45)	10 (29.41)	49 (34.75)	
Symptom[b]				0.812
Haematemesi	38 (35.51)	14 (41.18)	52 (36.88)	
Melena	57 (53.27)	17 (50)	74 (52.48)	
Haematochezia	12 (11.21)	3 (8.82)	15 (10.64)	
Endoscopic[b] intervention	23 (21.50)	6 (17.65)	29 (20.57)	0.629
Blood transfusion[b]	71 (66.36)	27 (79.41)	98 (69.50)	0.150
SBP (mm Hg)[a]	117.00(74.00/207.00)	100.00(70.00/150.00)	110.00(70.00/207.00)	0.002
DBP (mm Hg)[a]	70.00(30.00/95.00)	60.00(40.00/99.00)	68.00(30.00/99.00)	0.015
Heart rate (bpm)[c]	90.46±16.01	104.74±19.38	93.90±17.89	<0.001
Hb (g/dL)[a]	8.60(3.50/14.40)	7.90(3.40/13.80)	8.20(3.40/14.40)	0.769
PLT (10^9/L)[a]	238.00(64.00/621.00)	202.00(16.00/554.00)	231.00(16.00/621.00)	0.067
pH[a]	7.38(7.08/7.55)	7.39(6.90/7.55)	7.38(6.90/7.55)	0.763
BE (base excess)[a]	-0.70(-15.00/8.20)	-3.95(-24.10/4.70)	-1.10(-24.10/8.20)	0.006
Initial lactate[a] (mmol/L)	2.01(0.78-7.91)	3.07(0.70-18.35)	2.10(0.70-18.35)	0.002
Last lactate[a] (mmol/L)	1.47(0.50-5.20)	3.28(0.70-24.45)	1.58(0.50-24.45)	<0.001
Delta lactate[a] (mmol/L)	0.40(-3.00/5.28)	0.05(-10.00/6.83)	0.34(-10.00/6.83)	0.010
Lactate clearance[a] (%)	23.61(-187.50/80.00)	-0.51(-500.00/82.79)	18.52(-500.00/82.79)	0.002

[a]Mann-Whitney U-test was used for comparison and data were presented with median (minimum/maximum). [b]Pearson Chi-square test was used for comparison and data presented with n (%). [c]Independent samples t-test was used for comparison and data presented with mean±standard deviation.

Table II: Lactate levels in relation to ICU admission, endoscopic intervention, and blood transfusion.

		No	Yes	All patients	p-value
ICU admission	Initial lactate (mmol/L)	1.94 (0.78/7.91)	2.70 (0.70/18.35)	2.10 (0.70/18.35)	0.001
	Last lactate (mmol/L)	1.49 (0.50/5.20)	2.37 (0.70/24.45)	1.58 (0.50/24.45)	<0.001
	Delta lactate (mmol/L)	0.35 (-3.00/5.28)	0.30 (-10.00/6.83)	0.34 (-10.00/6.83)	0.204
	Lactate clearance (%)	21.46 (-187.50/79.03)	9.62 (-500.00/82.79)	18.52 (-500.00/82.79)	0.110
Endoscopic intervention	Initial lactate (mmol/L)	2.00 (0.70/18.35)	2.51 (1.04/6.80)	2.10 (0.70/18.35)	0.084
	Last lactate (mmol/L)	1.57 (0.50/24.45)	1.70 (0.70/6.60)	1.58 (0.50/24.45)	0.957
	Delta lactate (mmol/L)	0.30 (-10.00/6.83)	0.60 (-2.27/2.80)	0.34 (-10.00/6.83)	0.181
	Lactate clearance (%)	17.22 (-500.00/82.79)	27.27 (-168.15/80.00)	18.52 (-500.00/82.79)	0.152
Blood transfusion	Initial lactate (mmol/L)	1.90 (0.80/7.29)	2.33 (0.70/18.35)	2.10 (0.70/18.35)	0.044
	Last lactate (mmol/L)	1.53 (0.80/12.00)	1.61 (0.50/24.45)	1.58 (0.50/24.45)	0.516
	Delta lactate (mmol/L)	0.30 (-10.00/4.22)	0.50 (-9.69/6.83)	0.34 (-10.00/6.83)	0.198
	Lactate clearance (%)	17.65 (-500.00/79.03)	19.97 (-318.57/82.79)	18.52 (-500.00/82.79)	0.266

Mann-Whitney U test was used for all comparisons and data were presented with median (minimum/maximum).

Table III: ROC curve analysis for delta lactate and lactate clearance in predicting in-hospital mortality, need for intensive care unit, endoscopic interventions, and blood transfusion.

	Delta lactate	Lactate clearance
Mortality		
AUC	0.647	0.673
p-value	0.016	0.002
Cut-off value	≤-1.2	≤21.51
Sensitivity	35.29 (19.7 - 53.5)	76.47(58.8 - 89.3)
Specificity	97.2 (92.0 - 99.4)	51.4(41.5 - 61.2)
ICU admission		
AUC	0.566	0.583
p-value	0.241	0.120
Cut-off value	≤-1.01	≤-35.05
Sensitivity	27.66 (15.6 - 42.6)	21.28 (10.7 – 35.7)
Specificity	95.74 (89.5 - 98.8)	93.62(86.6 – 97.6)
Endoscopic intervention		
AUC	0.581	0.587
p-value	0.189	0.155
Cut-off value	>1.09	>49.07
Sensitivity	41.38 (23.5 - 61.1)	37.93 (20.7 - 57.7)
Specificity	81.25 (72.8 - 88.0)	83.93 (75.8 - 90.2)
Blood transfusion		
AUC	0.568	0.559
p-value	0.159	0.221
Cut-off value	>0.6	>36.35
Sensitivity	45.92 (35.8 - 56.3)	39.80 (30.0 - 50.2)
Specificity	79.07 (64.0 - 90.0)	86.05 (72.1 - 94.7)

Correlation analysis was performed between the duration of stay in hospital and initial lactate, last lactate, delta lactate, and lactate clearance of 107 patients who were alive; only positive correlation was found between the initial lactate levels and the hospital duration (r = 0.211, p = 0.029). There was no relationship between the stay-in-hospital duration and the last lactate (r = 0.094, p = 0.335), delta lactate (r = 0.048, p = 0.622) and lactate clearance (r = 0.083, p = 0.398).

The efficacy of delta lactate and lactate clearance in predicting mortality, ICU need, endoscopic intervention, and blood transfusion requirement were evaluated by ROC analysis. AUC values for delta lactate and lactate clearance were 0.647 (p = 0.016) and 0.673 (p = 0.002), respectively. However, AUC values were moderate and sensitivity values were not satisfactory. There was no statistically significant difference between delta lactate and lactate clearance in terms of these AUC values (p = 0.254). According to Youden J index, the cut-off value for lactate clearance was 21.51 and -1.2 for delta lactate. Other findings of ROC curve analysis were not statistically significant (Table III, Figure 1).

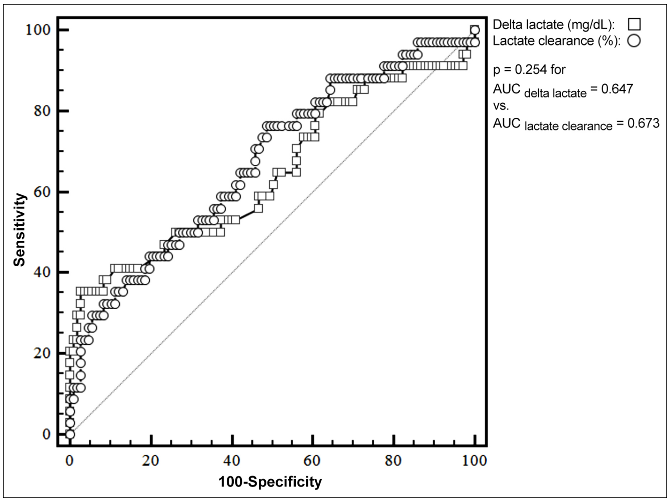

Figure 1: Receiver operating characteristic curve for delta lactate and lactate clearance in predicting in-hospital mortality.

DISCUSSION

The effectiveness of lactate level and lactate clearance, which had been used as prognostic markers in a variety of critical diseases, was investigated in UGIB patients in this study. Delta lactate value and lactate clearance were found to be good predictors for in-hospital mortality in UGIB, as assumed in the hypothesis. Therefore, it can be used as a valuable parameter in the differentiation of critically-ill patients. However, in UGBI patients, lactate clearance was not found to be a useful biomarker for identifying those who needed blood transfusions, endoscopic intervention, or intensive care unit admission. In this study, although there was no statistical difference between the survived and mortality groups in terms of endoscopic intervention, the number of endoscopic interventions was found to be less in the mortality group. This may be due to the clinical situation of the patients with high mortality who were not stable enough for endoscopy. In addition, SBP, DBP, heart rate, BE, and initial lactate levels were found to be valuable parameters in estimating mortality in gastrointestinal bleeding.

The physiological basis of lactate clearance assumes that shock causes inadequate oxygen delivery, resulting in mitochondrial hypoxia. Under hypoxic conditions, mitochondrial oxidative phosphorylation fails, and energy metabolism becomes dependent on anaerobic glycolysis.[10,11] Volume reduction due to severe blood loss causes hypotension in patients with UGIB. The amount of oxygen delivered to the tissues decreases as a result of hypotension. An increase in blood lactate levels occurs after anaerobic respiration in tissues. The dynamic lactate level of the patient varies depending on the amount of blood loss, blood pressure, adequate volume therapy, and resuscitative treatment procedures.

Serial lactate measurements, according to the literature, are an important marker in the evaluation of treatment response and the monitoring of critical patients. The recent studies have shown that dynamic lactate measurements are better predictors than a single lactate value. In conditions like sepsis, trauma, cardiogenic shock, and acute respiratory failure, where tissue oxygenation is compromised, it has been demonstrated to be an important biomarker for the prediction of mortality.[12-15] Marbach *et al*. conducted a systematic review and meta-analysis of 12 studies on patients with cardiogenic shock, and it was discovered that survivors had better lactate clearance than non-survivors and 6-8-hour lactate clearance was 21.9% in survivors and 0.6% in non-survivors.[16] The median lactate clearance values of surviving and non-surviving patients in the study were 23.6% and -0.5%, respectively, which was consistent with the literature. In a meta-analysis of 1301 cases and 7 randomised controlled trials by Pan *et al*., lactate clearance and central venous oxygen saturation (ScvO2) were compared in treatment planning in sepsis patients. Early lactate clearance guided therapy was found to be more effective than ScvO2 focused therapy in terms of reducing mortality, ICU length of stay, mechanical ventilation, and APACHE-II scores. It was emphasised that measuring lactate every 2 hours until a lactate clearance of 10% or greater is achieved in patients may be useful in guiding treatment resuscitation.[17] Vincent *et al*. evaluated 96 studies involving critically-ill groups. According to the findings of this study, it is difficult to define an ideal time interval for lactate measurement, but lactate measurements at every 1-2 hours may be appropriate in critical situations. It was mentioned that decreased lactate concentration is an indicator of better prognosis, and it was emphasised to be a valuable marker not only in septic patients but also in all critical patient groups.[18]

In this study, lactate clearance in UGIB was found to be an effective biomarker in predicting in-hospital mortality. The median lactate clearance of survivors and non-survivors were 23.61 and -0.51, respectively (p = 0.002). A 1-unit decrease in lactate clearance increased mortality 1.011-fold. The effectiveness of lactate clearance in predicting mortality was significant in the ROC analysis (AUC = 0.673, p = 0.002). The sensitivity of lactate clearance was 76.4% and the specificity was 51.4%, while the cut-off value for mortality was 21.51. However, it was revealed in this study that lactate clearance was inefficient in determining the need for blood transfusion, intensive care, and endoscopic intervention in UGIB.

This study had several limitations. First and foremost, the study is retrospective, and hence data sample is limited. Because it is a single-centre study, it included patients who received similar treatment methods, so the population selection may show a bias. Moreover, it should be considered that there are many different factors other than hypoperfusion, which increases lactate values (liver diseases, malignancy, drug or toxins, hypoxia, etc.). One of the most important reasons for increasing lactate is hypoxia, but the blood gas samples are venous and the lack of information about the oxygenation status of the patients is another limitation of this study. Patients whose 6th hour lactate data and survival data could not be reached were excluded from the study. Although lactate clearance is calculated, serial measurements rather than just two values may give a more accurate and effective result. Considering these factors, additional researches with multicentres, and large population patient groups should be carried out to support the outcomes.

CONCLUSION

In this study, 6-hour lactate clearance was found to be an independent predictor of in-hospital mortality in UGIB. Although it is good for predicting mortality, this is insufficient in the decision of blood transfusion need, endoscopy decision, and critical patient management. Hence, larger, prospective randomised studies including serial lactate measurements are needed to confirm this hypothesis.

ETHICAL APPROVAL:
An approval was obtained from the Ethics Committee of Istanbul Sisli Hamidiye Etfal Research and Training Hospital, Istanbul, Turkey.

PATIENTS' CONSENT:
Since the study included a retrospective archive search, patients' consents were not required.

COMPETING INTEREST:
The authors declared no competing interest.

AUTHORS' CONTRIBUTION:
YEA: Statistic analysis, data collection, discussion, compilation of the results, and proofreading.
SK: Conceived and designed the study, paper write-up, and the compilation of the results.

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