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Lactate serial measurements and predictive validity of early mortality in trauma patients admitted to the intensive care unit[☆]



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ABSTRACT

Introduction: Patients who have experienced trauma usually develop hypovolemic shock, which determines different levels of tissue hypoperfusion. The determination of lactate levels has been used as a reliable biomarker in the assessment of the magnitude of hypoperfusion. Additionally, it has been established that lactic clearance in the first 6 h has value as a prognostic measurement for the mortality rate of these patients. However, beyond 6 h its utility is controversial.

Objective: To evaluate the predictive capacity of serial lactic acid as well as clearance (at the time admitted, 12 and 24 h) in mortality cases for trauma patients admitted to the ICU.

Materials and methods: During the period between 2010 and 2014, an observational longitudinal cohort study was conducted with trauma patients admitted to the Intensive Care Unit (ICU) at the Clínica Universidad de la Sabana. The clinical and demographic data was registered in a data base using Microsoft Excel and analyzed in STATA 12[®] statistical software.

In order to determine the association between each measurement with mortality after seven days, serial measurements of lactic acid were taken at admission time, 12–24 h as well as the clearance of lactic acid at 12 and 24 h.

Results: 233 patients participated during the time of the study. The average age was 38 years. 78% of the patients were male, with 21% of the mortality at seven days in the ICU. Among the severity indexes, an average of 14 in APACHE II, 9 in SOFA and 25 in ISS was found. The average of length of stay for survive patients was nine days in contrast to five days of mortality patients.

In brief, the lactic acid average was associated with mortality at seven days in the three time measurements.

On the other hand, the values of the receptor curve operating showed the best performance of the discrimination at 24 h with a 2.35 cut-off point and OR 1.65 (CI 95% 1.27–2.13).

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Conclusions: Our findings determined a similar performance of the lactic acid as compared to other studies, especially in the lactic acid level at 24 h with relevant discrimination over 2.35 mEq/L at 24. Nonetheless, reverse causality can eventually occur.

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Mediciones seriadas del lactato y su validez predictiva de la mortalidad temprana en los pacientes con politrauma que ingresan a la unidad de cuidado intensivo

R E S U M E N

Palabras clave:

Acidosis láctica
Mortalidad
Cuidados críticos
Heridas y lesiones
Choque hemorrágico

Introducción: Los pacientes con trauma habitualmente cursan con choque hipovolémico que determina diferentes grados de hipoperfusión tisular. La determinación de los niveles de lactato ha sido utilizada como un biomarcador fiable en la evaluación de la magnitud de la hipoperfusión. Adicionalmente se ha establecido que el aclaramiento del lactato en las primeras seis horas, constituye una medida pronóstica de mortalidad de estos pacientes, sin embargo más allá de estas seis horas su utilidad es controvertida.

Objetivo: evaluar la capacidad de predicción del lactato seriado y su aclaramiento (al ingreso, 12 y 24 horas) en la presentación de la mortalidad de los pacientes con trauma, que ingresaron a la unidad de cuidado intensivo.

Materiales y método: Se realizó un estudio observacional de cohorte longitudinal, en pacientes ingresados a la unidad de cuidados intensivos de la Clínica Universidad de la Sabana, con diagnóstico de trauma, durante el periodo comprendido entre 2010 y 2014, de manera concurrente fue registrada en una base de datos creada en Microsoft Excel y analizada en el paquete estadístico STATA 12 (Data analysis and statistical software).

Mediciones seriadas de ácido láctico fueron realizadas al ingreso, 12 y 24 horas. Con el fin de determinar la asociación de cada una de las mediciones, así como el aclaramiento del ácido láctico a las 12 y 24 horas con la mortalidad a los siete días.

Resultados: 233 pacientes fueron incluidos durante el periodo de estudio, la edad promedio fue de 38 años, 78% fueron hombres con una mortalidad del 21%. Dentro de los índices de severidad, se encontró promedio de APACHE II de 14, SOFA de 9 y ISS de 25. La estancia hospitalaria para los no sobrevivientes fue de 4,7 días mientras que para los sobrevivientes fue de 9 días. Los valores promedios de las tres mediciones de lactato se asociaron a la mortalidad a los 7 días, teniendo mayor capacidad de discriminación el valor de lactato a las 24 horas con un punto de corte de 2,35 y un OR de 1,65 (IC 95% 1,27 – 2,13).

Conclusiones: El estudio permite determinar un comportamiento del lactato similar al encontrado en otras publicaciones, con evidencia de mayor capacidad de discriminación cuando este permanece elevado por encima de 2,35 a las 24 horas, pudiéndose explicar por la presencia de causalidad reversa.

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Introduction

Trauma is the third leading cause of death worldwide, notably affecting the population under 40 years of age. Of all causes, traffic accidents are responsible for the largest number of patients. Around the world every day, about 3000 people die from injuries resulting from traffic accidents. These especially affect the 15–29 year-old age group, according with WHO reports.^{1,2} In Colombia, trauma is a public health problem, where traumatic injuries due to violence and traffic accidents

are among the top causes of morbidity and mortality.^{3,4} Therefore, there is a need for a biomarker that allows us to quickly and reliably assess the diagnostic process of hypoperfusion during its early stage, in order to take the pertinent steps to reduce these mortality figures.^{5–7} This why lactate represents an important tool within this scenario, being a widely studied biomarker.^{8,9}

Several publications show the relationship between lactate intake, early clearance and mortality. However, beyond these 6 h, its usefulness is controversial.^{8,10–19} In the present

article, we tried to establish the predictive capacity of serial lactate and its clearance (at admission time, 12 and 24 h) when mortality occurred in patients with trauma who entered the intensive care unit.

Materials and methods

An observational longitudinal cohort study was conducted in patients admitted to the Intensive Care Unit (ICU) of the Universidad de la Sabana Clinic (located in Chía, Cundinamarca, Colombia) between January 1st, 2010 and January 1st, 2014. The clinic is located in a busy traffic area where a large number of patients suffer traffic accidents. After the approval by the institutional ethics committee, the information of all patients diagnosed with trauma who survived at least 24 h was recorded concurrently. Socio-demographic, clinical and paraclinical variables, as well as APACHE II, SOFA and ISS severity indexes were taken into account.²⁰⁻²⁴ Also, measurements of serum lactate upon admission to the ICU, at 12 and 24 h were considered. All patients with incomplete measurements or data and those referred from other institutions were excluded.

Statistical analysis

For the elaboration of the database we used Microsoft Excel 2011, version 14.0 and for the processing of data we used the statistical package STATA 12.0. Descriptive statistics were performed and the association between the averages for each of the three lactate measurements with early mortality at seven days was determined. The clearance of lactate levels was evaluated, considering the percentage of lactate cleared with respect to the previous measurement, with the following equation: $\% \text{ Clearance} = ((\text{basal lactate} - \text{lactate control}) / \text{basal lactate}) \times 100$.^{13,25}

In addition, discrimination capacity was determined by calculating the area under the ROC curve and the highest discrimination cut-off point by the Liu method, which maximizes the product of the sensitivity and specificity from which the lactate measurements were dichotomized. OR estimates were obtained in relation to mortality. All calculations were performed with a significance level of <0.05.

Results

A total of 309 polytraumatized patients were admitted to the ICU during the study period. 233 patients met the inclusion criteria for information recording as shown in flow chart 1 (Fig. 1).

Of the total number of patients with polytraumatism, 184 patients (78%) were male. Early mortality, described as less than 7 days, was 21%, being higher in the male group compared to the female group (58% vs 42%, respectively).

All measurements of lactate inflow to the unit were performed within the first 28 h SD (10) of admission to the hospital. The time of admission to the UCI was considered as hour "zero". The second measurement was performed at

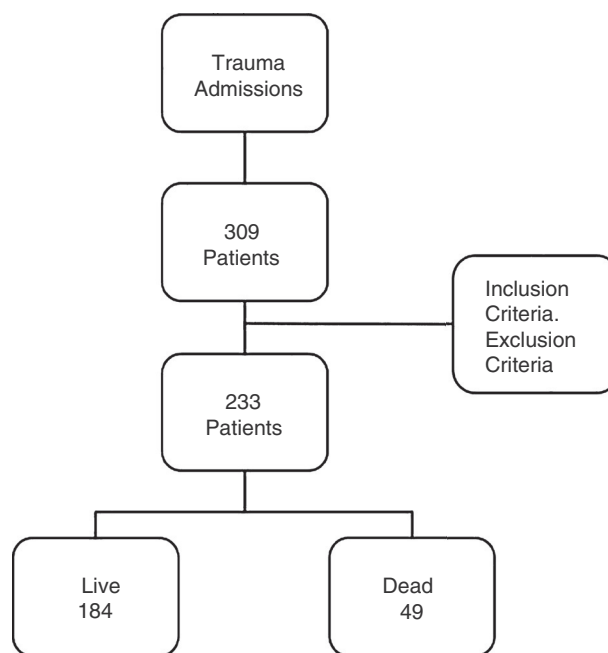


Fig. 1 – Flow chart No. 1. Patients of the study.
Source: Authors.

12 h with an average of 10.2 h and a SD of 11.8 h. The third measurement was performed at 24 h with an average of 24.4 h and a SD of 13 h. The analysis of variance for the three measurements showed differences between the three groups of measurements with a *p*-value < 0.001.

The variables that were associated with early mortality were APACHE II, SOFA and ISS, as well as the lactate levels in each of the measurements. See Table 1.

The average stay for living patients was 9 days whereas for those who did not survive it was 4.7 days.

Trend of lactate levels

As shown in Table 1, the value of lactate levels decreased as time progressed from admission to 12 h and 24 h, with averages and standard deviations of: 3.28 (2.46) (CI 95% (2.92–3.64)); 2.73 (2.24) (CI 95% (2.39–3.67)); 2.21(1.68) (CI 95% (1.93–2.49)), respectively. When the lactate averages between live and dead patients are compared, statistically significant differences in the mean values at admission, 12 and 24 h of –2.11–1.79 and –1.77 were found.

Regarding the lactate clearance, an association in the differences between the admission time and the 24 h and between 12 and 24 h was found, but not between admission and the first 12 h.

Discrimination capacity of lactate for early mortality in each of the three time periods

In Table 2, the values of the area under the ROC curve of the three moments of lactate measurement are recorded. A trend

Table 1 – General characteristics and biomarkers in trauma patients.

	Live N = 184	Dead N = 49	p-value
Male gender n (%)	155 (84)	28 (57)	0.001
Age, mean (SD)	35.61 (13.36)	44 (19.40)	0.001
IQR	24–44	30–52	
APACHE II, mean (SD)	13.20	21.40	0.001
IQR	8–17	16.5–27	
Lactate at admission, mean (SD)	2.81 (1.55)	4.92 (3.97)	0.001
IQR	1.85–3.45	2.4–5.8	
Lactate at 12 h, mean (SD)	2.35 (1.58)	4.14 (3.51)	0.001
IQR	1.2–3	1.4–5.7	
Lactate at 24 h, mean (SD)	1.9 (1.14)	3.67 (2.79)	0.001
IQR	1.3–2.2	1.6–5	
Stay in UCI, mean (SD)	9.33 (8.22)	5.05 (7.39)	0.001
IQR	3.66–13	1–5	
SOFA, mean (SD)	8.73 (3.04)	10.5 (2.41)	0.001
IQR	7–11	9.5–12	
ISS, mean (SD)	21.07 (14.87)	39.2 (25.95)	0.001
IQR	12–24	18–75	
% Lactate-clearance admission – 12 h			
Mean (SD)	5.64 (62.7)	–2.68 (61.9)	0.48
% Lactate-clearance admission – 24 h			
Mean (SD)	20.7 (51.9)	–3.23 (65.8)	0.04
% Clearance – 12 h–24 h			
Mean (SD)	9.5 (39.7)	–44.5 (138)	0.001

Mortality measured at 7 days.

SD: standard deviation, IQR: interquartile range; SOFA: Sequential Organ Failure Assessment; ISS: Injury Severity Score; APACHE II: Acute Physiology and Chronic Health Evaluation.

Source: Authors.

Table 2 – Discrimination capacity of lactate during the first 48 h for the prediction of mortality at seven days in trauma patients.

Measurement	ROC curve area (CI 95%)	Cut-off point (mEq/L)	Sensitivity	Specificity
Lactate admission	0.61 (0.48–0.73)	3.05	0.66	0.67
Lactate 12 h	0.55 (0.40–0.70)	3.65	0.46	0.84
Lactate 24 h	0.70 (0.58–0.83)	2.35	0.56	0.79

Source: Authors.

of greater discrimination was observed as time progresses. Additionally, cut-off point, sensitivity and specificity values were recorded for each of the moments in relation to early mortality (seven days).

Table 3 – Bivariate analysis of logistic regression: mortality at 7 days and lactate at three different moments.

Measurement	OR	Confidence interval 95%
Lactate admission	1.40	1.17–1.68
Lactate 12 h	1.35	1.14–1.60
Lactate 24 h	1.65	1.27–2.13

Source: Authors.

As can be seen in Table 3, the ORs for early mortality for each one of the moments were calculated from the values of the cut-off points. We found an OR of 1.4 (CI 95% (1.17–1.68)) for the lactate at admission when a lactate level is greater than 3.04 mEq/L; at 12 h, an OR of 1.35 (CI 95% (1.14–1.60)) with a lactate greater than 3.65 mEq/L; and at 24 h, an OR of 1.65 with (95% CI (1.27–2.13)) with a cut-off point of 2.35 mEq/L.

Fig. 2 shows the largest area under the curve for lactate levels at 24 h after admission (0.70) denoting a greater discriminatory power for early mortality, whereas the values of the area under the curve at admission time and 12 h are lower, 0.60 and 0.54 respectively.

Discussion

Lactate levels in the blood reflect the balance between lactate production and lactate uptake in tissues, which is usually

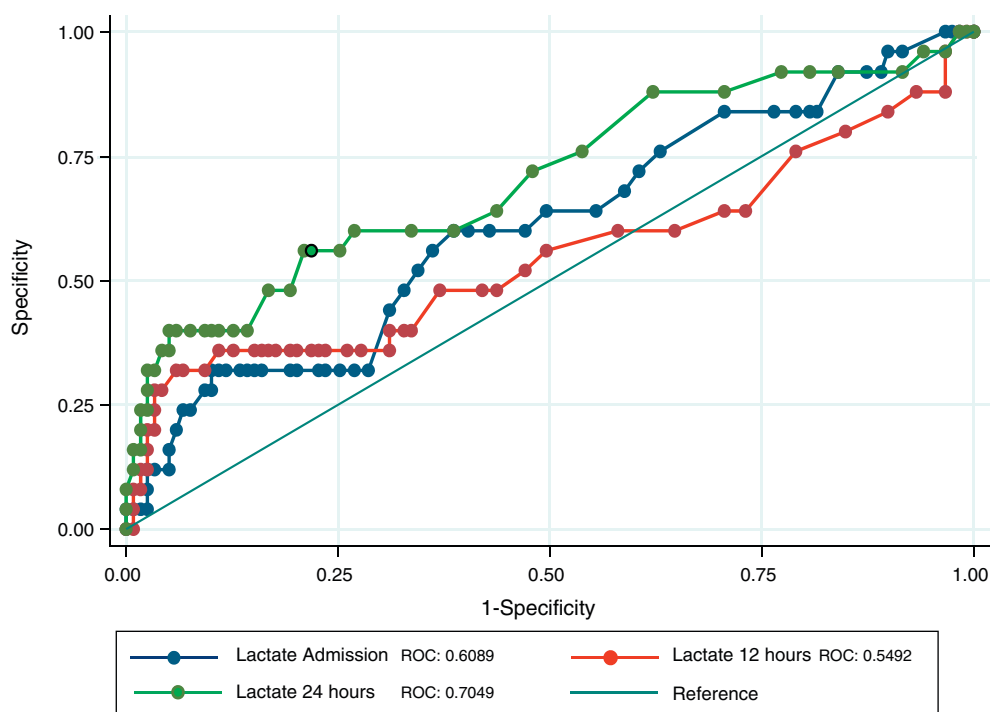


Fig. 2 – ROC curve for the different serum lactate measurements: admission, 12 h and 24 h.

Source: Authors.

in the range of 0.5–1.8 mM/L.²⁶ Numerous studies have established the use of lactate as a diagnostic, therapeutic and prognostic marker for tissue hypoxia. The vast majority of these studies have used 2.0 mM/L as a cut-off. This cut-off point has been established in different scenarios and different types of patients. That is how Kliegel et al. examine patients who were resuscitated from cardiac arrest and survived at least 48 h,²⁷ concluding that sustained hyperlactatemia (>2.0 mM/L after 48 h) is a predictor of mortality as well as of a poor neurological prognosis. Kruse et al. carried out a systematic review establishing that the cut-off point of >2 mM/L is most frequently associated with mortality in critical patients with some type of trauma. More recently, cut-off points have been classified according to their severity, into the levels low (<2.5 mg/dL), moderately elevated (2.5–3.9 mg/dL) and severely elevated (>4 mg/dL).^{26,28–30} One of the first studies that determined the association between lactate levels and mortality in trauma patients was performed by Abramson. He found that the delay in the normalization of lactate levels after 24 and 48 h was associated with increased mortality, whereas patients who normalized lactate values before 24 h had a 100% survival rate. In our study, this finding was not confirmed. Even patients with normal lactate during the first 12 h died, this probably due to the greater severity of our patients with a mean ISS of 30 whereas the one reported in Abrasom study was 22.¹⁰

When it was explored which of the measures in the time (admission, 12 and 24 h) would have the greater discrimination capacity for survival, it was observed that those patients with

lactate above 2.35 mEq/L at 24 h presented the highest mortality rate. However, in 2012, Dr. Marie-Alix Régnier¹² found that measurements of clearance within the first four h based on lactate levels at admission, had an adequate ability to discriminate between the patients who died or survived, with an area under the ROC curve (0.78, 95% CI: 0.73–0.83). We only found that lower and later clearance was associated with mortality at 24 h, with an area under the ROC curve of 0.70 (0.58–0.83).

In 2013, Stephen R. Odom¹³ included 4742 trauma patients in his study, finding that initial lactate was the strongest predictor of mortality in the trauma patient when the first lactate was greater than 4 mEq/L. They also performed the calculation of lactate clearance in this group of patients, with a time interval of 6 h, finding that with lower clearance came higher mortality. Our study evaluated the clearance between admission, 12 and 24 h, only finding an association with the decrease of clearance at 24 h.

In 2015, Dr Dezman Zachary's work¹⁴ with 18,304 patients with trauma is published. Lactate clearance was evaluated at 24 h in 3887 patients and only 7.8% of the population achieved a lactate clearance of below 2 mEq/L. However, an adequate discriminatory capacity of lactate levels at 24 h with an area under the curve of 0.8 was found. The severity of the population of this study was lower than ours with an average of 25 in the ISS.

Our study has the limitation of not having evaluated lactate clearance within the first 6 h based on lactate levels at admission. Nevertheless, it does monitor lactate in the

first 24 h, showing a broader picture and demonstrating how the later worsening of lactate levels determines increased mortality.

Conclusions

Our study showed that lactate levels greater than 2.35 mEq/L at 24 h were associated with an increased risk of mortality. On the other hand, lower lactate clearance or even negative clearance led to increased mortality, especially at 24 h. It could not be established that early clearance would improve prognosis. The findings of the present study could be influenced by reverse causality in that those patients with the worse prognosis would be precisely those in which the goals of resuscitation would not be achieved.

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Conflict of interest

The authors declare that they have no conflicts of interest.

REFERENCES

- Murray CJ, Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease Study. *Lancet*. 1997;349:1269-76.
- DiMaggio C, Ayoung-Chee P, Shinseki M, Wilson C, Marshall G, Lee DC, et al. Traumatic injury in the United States: in-patient epidemiology 2000-2011. *Injury*. 2016;47:1393-403.
- Sauaia A, Moore FA, Moore EE, Moser KS, Brennan R, Read R, et al. Epidemiology of trauma deaths: a reassessment. *J Trauma*. 1995;38:185-93.
- Ordóñez CA, Pino LF, Tejada JW, Badiel M, Loiza JH, Mata LV, et al. Experience of two first level hospitals in the southwest region of Colombia on the implementation of the Panamerican Trauma Society International Trauma Registry. *Rev Col Bras Cir*. 2012;39:255-62.
- Riou B, Landais P, Vivien B, Stell P, Labbene I, Carli P. Distribution of the probability of survival is a strategic issue for randomized trials in critically ill patients. *Anesthesiology*. 2001;95:56-63.
- Suarez-de-la-Rica A, Maseda E, Anillo V, Tamayo E, García-Bernedo CA, Ramasco F, et al. Biomarkers (Procalcitonin, C reactive protein, and lactate) as predictors of mortality in surgical patients with complicated intra-abdominal infection. *Surg Infect*. 2015;16:346-51.
- Blow O, Magliore L, Claridge JA, Butler K, Young JS. The golden hour and the silver day: detection and correction of occult hypoperfusion within 24 hours improves outcome from major trauma. *J Trauma*. 1999;47:964-9.
- Zhang Z, Xu X, Chen K. Lactate clearance as a useful biomarker for the prediction of all-cause mortality in critically ill patients: a systematic review study protocol. *BMJ Open*. 2014;4:e004752.
- Watson NC, Heard SO. The use of lactate as a biomarker. *J Intensive Care Med*. 2010;25:301-2.
- Abramson D, Scalea TM, Hitchcock R, Trooskin SZ, Henry SM, Greenspan J. Lactate clearance and survival following injury. *J Trauma*. 1993;35:584-8, discussion 8-9.
- Husain FA, Martin MJ, Mullenix PS, Steele SR, Elliott DC. Serum lactate and base deficit as predictors of mortality and morbidity. *Am J Surg*. 2003;185:485-91.
- Régner MA, Raux M, Le Manach Y, Asencio Y, Gaillard J, Devilliers C, et al. Prognostic significance of blood lactate and lactate clearance in trauma patients. *Anesthesiology*. 2012;117:1276-88.
- Odum SR, Howell M, Silva GS, Nielsen V, Gupta A, Shapiro N, et al. Lactate clearance as a predictor of mortality in trauma patients. *J Trauma Acute Care Surg*. 2013;74:999-1004.
- Dezman ZD, Comer AC, Smith GS, Narayan M, Scalea TM, Hirshon JM. Failure to clear elevated lactate predicts 24-hour mortality in trauma patients. *J Trauma Acute Care Surg*. 2015;79:580-5.
- Freitas AD, Franzon O. Lactate as predictor of mortality in polytrauma. *Arq Bras Cir Dig*. 2015;28:163-6.
- de Vries HM, Dekker SE, Boer C. Lactate clearance as a predictor of mortality. *J Trauma Acute Care Surg*. 2014;77:183.
- Nichol A, Bailey M, Egi M, Pettila V, French C, Stachowski E, et al. Dynamic lactate indices as predictors of outcome in critically ill patients. *Critical Care (London, England)*. 2011;15:R242.
- Pal JD, Victorino GP, Twomey P, Liu TH, Bullard MK, Harken AH. Admission serum lactate levels do not predict mortality in the acutely injured patient. *J Trauma*. 2006;60:583-7, discussion 7-9.
- McNelis J, Marini CP, Jurkiewicz A, Szomstein S, Simms HH, Ritter G, et al. Prolonged lactate clearance is associated with increased mortality in the surgical intensive care unit. *Am J Surg*. 2001;182:481-5.
- Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med*. 1985;13:818-29.
- Ferreira FL, Bota DP, Bross A, Melot C, Vincent JL. Serial evaluation of the SOFA score to predict outcome in critically ill patients. *JAMA*. 2001;286:1754-8.
- Baker SP, O'Neill B. The injury severity score: an update. *J Trauma*. 1976;16:882-5.
- Antonelli M, Moreno R, Vincent JL, Sprung CL, Mendonça A, Passariello M, et al. Application of SOFA score to trauma patients. Sequential Organ Failure Assessment. *Intensive Care Med*. 1999;25:389-94.
- Cerovic O, Golubovic V, Spec-Marn A, Kremzar B, Vidmar G. Relationship between injury severity and lactate levels in severely injured patients. *Intensive Care Med*. 2003;29:1300-5.
- Nguyen HB, Loomba M, Yang JJ, Jacobsen G, Shah K, Otero RM, et al. Early lactate clearance is associated with biomarkers of inflammation, coagulation, apoptosis, organ dysfunction and mortality in severe sepsis and septic shock. *J Inflamm*. 2010;7:6.
- Kruse O, Grunnet N, Barfod C. Blood lactate as a predictor for in-hospital mortality in patients admitted acutely to hospital: a systematic review. *Scand J Trauma Resusc Emerg Med*. 2011;19:74.
- Kliegel A, Losert H, Sterz F, Holzer M, Zeiner A, Havel C, et al. Serial lactate determinations for prediction of outcome after cardiac arrest. *Medicine*. 2004;83:274-9.
- Callaway DW, Shapiro NI, Donnino MW, Baker C, Rosen CL. Serum lactate and base deficit as predictors of mortality in normotensive elderly blunt trauma patients. *J Trauma*. 2009;66:1040-4.

29. Shapiro NI, Howell MD, Talmor D, Nathanson LA, Lisbon A, Wolfe RE, et al. Serum lactate as a predictor of mortality in emergency department patients with infection. *Ann Emerg Med.* 2005;45:524-8.
30. Howell MD, Donnino M, Clardy P, Talmor D, Shapiro NI. Occult hypoperfusion and mortality in patients with suspected infection. *Intensive Care Med.* 2007;33:1892-9.