Predictors of Five Days Mortality in Diabetic Ketoacidosis Patients: a Prospective Cohort Study

Suhendro Suwarto[1], Bambang Sutrisna[2], Sarwono Waspadji[1], Herdiman T. Pohan[1]

[1] Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[2] Department of Epidemiology, Faculty of Public Health Universitas Indonesia.

Correspondence to:
Division of Tropical and Infectious Disease, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital. Jl. Diponegoro no. 71, Jakarta 10430, Indonesia. email: suhendro@ui.ac.id.

ABSTRAK

Tujuan: *untuk menentukan peran laktat serum dan derajat beratnya ketoasidosis diabetikum (KAD) dalam memprediksi mortalitas lima hari pasien KAD.* ***Metode:*** *penelitian kohort prospektif dilakukan pada pasien KAD yang masuk perawatan di ruang gawat darurat RS Cipto Mangunkusumo, Jakarta, Indonesia pada periode tahun 2007-2008. Prediktor mortalitas 5 hari yang diteliti meliputi laktat serum dan derajat beratnya KAD (glukosa plasma, pH arteri, bikarbonat serum, osmolalitas, anion gap, dan perubahan kesadaran) pada awal perawatan. Cox's proportional hazard regression model digunakan untuk menentukan prediktor independen terhadap mortalitas 5 hari pada pasien KAD.* ***Hasil:*** *dari enam puluh pasien yang diikutkan dalam penelitian, 24 (40%) pasien di antaranya meninggal dalam waktu 5 hari perawatan. Pada analisis multivariat, konsentrasi laktat ≥4 mmol/L (HR, 3,09; 95% IK, 1.36-7.05), dan tingkat kesadaran stupor/koma (HR, 3,38; 95% IK, 1,45-7,87) diidentifikasi sebagai prediktor independen terhadap mortalitas 5-hari pasien KAD dewasa.* ***Kesimpulan:*** *konsentrasi laktat ≥4 mmol/L dan tingkat kesadaran stupor/koma dapat digunakan untuk memprediksi mortalitas 5-hari pada pasien KAD.*

Kata kunci: *ketoasidosis diabetik, sepsis, konsentrasi laktat, tingkat kesadaran, mortalitas.*

ABSTRACT

Aim: *to determine the role of serum lactate and diabetic ketoacidosis (DKA) severity as predictors for five-days mortality in DKA patients.* ***Methods:*** *a prospective cohort study was conducted in DKA patients admitted to emergency department (ED) at Cipto Mangunkusumo Hospital, Jakarta, Indonesia, during 2007-2008 periods. Predictors for 5 days mortality in DKA patients in this study including serum lactate and DKA severity (plasma glucose, arterial blood pH, serum bicarbonate, osmolality, anion gap, and alteration in sensorium) at admission. Cox's Proportional Hazard Regression Analysis was used to determine independent predictors for 5-days mortality among study population.* ***Results:*** *sixty patients with diabetic ketoacidosis were enrolled in the study; in which 24 (40%) patients were died within 5 days after admission. In the multivariate analysis, the lactate level ≥4 mmol/L (HR, 3.09; 95% CI, 1.36-7.05) and altered in sensorium stuporous/comatose (HR, 3.38; 95% CI, 1.45-7.87) were identified as independent predictors for 5-days mortality in DKA adult patients.* ***Conclusion:*** *lactate level ≥4 mmol/L and altered in sensorium stuporous/comatose can be used to predict 5-days mortality in adult patients with DKA.*

Key words: *diabetic ketoacidosis, sepsis, lactate level, alteration in sensorium mortality.*

INTRODUCTION

Diabetic ketoacidosis (DKA) is the most serious and life-threatening acute complication of diabetes and is characterized by hyperglycemia, ketosis, and acidosis.[1,2] The current diagnostic criteria and classifications of the severity of DKA are based on plasma glucose, arterial pH, serum bicarbonate, serum osmolarity, anion gap, and mental state alterations.[2,3] The majority of DKA cases are precipitated by infections,[2] which have a high incidence rate, especially in developing countries.[4] Despite significant improvements in monitoring and therapy, the mortality rate remains high, especially in DKA patients with sepsis.[5]

In our tertiary hospitals, the mortality associated with DKA is likely to be high because, characteristically, these patients often have low incomes, comorbidities, delays in seeking medical care, and a high rate of infections. The initial fluid therapy protocol for treating DKA, which is based on evidence-based management, recommends that resuscitation should consist of isotonic saline (0.9% NaCl) infused at a rate of 15-20 mL/kg/h during the first hour.[3,6] In sepsis, where patients have hypoperfusion or septic shock, fluid resuscitation should follow the early goal-directed therapy (EGDT) protocol.[7] This approach seeks to achieve the following targets as a resuscitation end point: central venous pressure (CVP) of 8 to 12 mmHg, mean arterial pressure (MAP) ≥65 mmHg, and superior vena cava oxygenation (Scvo2) saturation ≥70%; these tests should be completed within the first 6 hours.[8] Early recognition and management of sepsis is key to improving patient outcomes.[8,9] The Surviving Sepsis Campaign (SSC) recommends that in septic patients, lactate measurement within 3 hours should be used as a marker of tissue hypoperfusion to help identify patients at high risk for death and those who will benefit from the EGDT approach. Hypoperfusion and perfusion abnormalities may include an acute alteration in mental status.[8]

Until now, there is no prospective study describing the prognostic value of serum lactate and DKA severity on emergency department (ED) admission as predictors of mortality in DKA patients, shortly after admission to the emergency department. Therefore, we conducted this study to determine the roles of mortality predictors in adult DKA patients using serum lactate and severity of DKA on ED admission.

METHODS

This was a prospective cohort study conducted at the Emergency Department of Cipto Mangunkusumo Hospital, a tertiary hospital in Jakarta, Indonesia. Diabetic ketoacidosis (DKA) patients, aged 16 years and older, who admitted from January 2007 through December 2008 and agreed to participate were included in the study, with exclusion criteria was pregnant women. Diabetic ketoacidosis was diagnosed when the blood glucose at admission was >250 mg/dL with ketonaemia and blood acidemia (pH <7.3 or a serum bicarbonate concentration of <15 mEq/L).[2] The University Ethics Committee approved the study, and informed consent was obtained from all patients or their representatives.

Identification of Predictors and Outcome

The classification severity of DKA was based on the following: plasma glucose, arterial blood pH, serum bicarbonate, osmolality, anion gap and alterations in sensorium.[2] Alterations in sensorium were stratified into 2 groups: alert/drowsy, and stupor/coma. Serum osmolality was derived from the following formula: 2x [measured Na+ (mEq/L)] + glucose (mg/dL) / 18. The anion gap was calculated using the following formula: [(Na+)–(Cl- + HCO3- (mEq/L)].[2]

Arterial lactate samples were collected with heparinized syringes, and the subsequent measurements were performed using a Hitachi 917 automated analyzer (Roche Diagnostics, Mannheim, Germany). The lactate results were stratified into 2 groups based on the cutoff values previously utilized by other authors[10]; these groups were as follows: <4.0 mmol/L and ≥4.0 mmol/L.[8,10]

The patient characteristics, comorbidities, triggers of DKA, vital signs, clinical findings, blood collection results, and lactate measurements were recorded for each individual upon arrival at the emergency department for enrollment. The criteria for sepsis was defined according to the 2001 SCCM/ESICM/ACCP/ATS/SIS

International Sepsis Definitions Conference.[11]

We defined the mortality outcome as any death occurring ≤5 days from the initial lactate measurement.[10,12,13] All patients were treated according to a DKA standardized Cipto Mangunkusumo hospital protocol.

Statistical Analysis

The sample size of the study was estimated based on an assumption 81.25% incidence of mortality for high lactate concentrations.[14] Assuming the relative risk is 1.75, with $\alpha = 0.05$ and $\beta = 0.20$, minimal subjects required in the study was 58 patients. Univariate analysis comparing serum lactate levels and the classification of DKA severity on five-days mortality was performed to identify variables that potentially had a significant association with mortality. All variables with p-value <0.25 in univariate analysis were entered into a Cox's Proportional Hazard Regression Model using a backward selection algorithm to calculate the adjusted hazard ratios of mortality. Kaplan-Meier Curve for each significant predictors were presented. All statistical analyses were performed using the STATA statistical software version 9 (Stata Corp., College Station, TX, USA).

RESULTS

Patient Characteristics

A total of 60 patients with DKA were enrolled in the study with mean age of 50.97 (SD 2.05) years 36 (60%) of them were women and 35 (58%) patients were diagnosed DKA with sepsis. The main sites of infection in the septic group were the respiratory tract (51%), followed by soft tissue (34%), gastrointestinal tract (6%), abdomen (3%), and others (6%). The precipitating factors of DKA in the non-septic patients were insulin omission (32%), stroke (20%), new-onset diabetes (8%), trauma (8%), tumor (8%), and gastrointestinal bleeding (4%). Precipitating factors could not be identified in 20% of patients.

Out of the 60 patients, 24 (40%) died within 5 days. Mortality in the septic patients (57%) was significantly higher than in the non-septic patients (16%). Serum lactate in the septic patients (median: 2.89 mmol/L, range: 0.85 to 13.49 mmol/L) was significantly higher than in the non-septic patients (median: 1.67 mmol/L, range: 0.68 to 8.26 mmol/L). The patients' characteristics are presented in **Table 1**.

Table 1. Diabetic ketoacidosis patients: comparison of survivors and non-survivors

Variables	Survivors (n=36)	Non-survivors (n=24)
Sex (n, male/female)	17/19	7/17
Mean age (year)[a]	48.11 (SD 16.24)	54.92 (SD 15.97)
Blood pressure (SBP/DBP)[a]	118 (SD 19.93) / 67.22 (SD 23.37)	112.17 (SD29.30) / 63.75 (SD 28.41)
Temperature (°C)[a]	37.38 (SD 1.00)	37.04 (SD 1.79)
Heart rate (bpm)[a]	111.4 (SD 16.97)	111.4 (SD 14.35)
Respiration rate (bpm)[a]	29.00 (SD 8.36)	31.18 (SD 5.51)
Leukocyte count (/mm3)[a]	17,600 (SD 7715)	21,000 (SD 7500)
Serum lactate (mmol/L)[b]	1.70 (0.68-8.26)	4.2 (0.85-13.49)*
Glucose (mg/dL)[a]	442.33 (SD 140.47)	498.88 (SD 158.67)
Arterial pH[a]	7.31 (SD 0.13)	7.24 (SD 0.17)
Serum bicarbonate (mEq/L)[a]	12.11 (SD 5.12)	10.85 (SD 4.79)
Osmolality (mOsm/kg)[a]	295.07 (SD 23.04)	297.42 (SD 19.45)
Anion gap[a]	21.57 (SD 7.76)	24.03 (SD 5.53)
Sepsis (n,%)	15 (43%)	20 (57%)**

a data presented as the mean ± standard deviation
b data presented as median, range
* p<0.05 by Mann-Whitney U test, **p<0.05 by Chi-Square Tests

Twelve of the 17 patients (71%) with high lactate levels (≥4 mmol/L) had normal blood pressure. The neurological symptoms alertness/drowsiness and stupor/coma occurred in 40 (67%) and 20 (33%) patients, respectively. Eight drowsy patients (62%) and 13 out of 20 (65%) stupor/coma patients had accompanying sepsis. The univariate analysis to predict mortality using serum lactate and the classification of DKA severity are presented in **Table 2**. The variables that had a significant effect based on univariate analysis were submitted to Cox's Proportional Hazard Regression Model. The following variables were found to be independent predictors of mortality: serum lactate ≥4 mmol/L and alterations in sensorium stuporous/comatose.

Table 2. Univariate analysis of the risk factors for mortality

Variables	Hazard ratio	95% confidence interval
Serum lactate ≥4 mmol/L	3.76	(1.69-8.38)
Glucose (mg/dL)	1.00	0.99-1.00
Arterial pH	0.21	0.02-2.23
Serum bicarbonate (mEq/L)	0.97	0.90-1.06
Osmolality (mOsm/kg)	1.00	0.98-1.02
Anion gap	1.03	0.97-1.08
Alterations in sensorium Stuporous/Comatose	4.24	(1.86-9.64)

Table 3. Final Cox's proportional hazard regression model to predict mortality

Variables	Hazard ratio	95% confidence interval
Serum lactate ≥4 mmol/L	3.09	1.36-7.05
Alterations in sensorium Stuporous/Comatose	3.38	1.45-7.87

DISCUSSION

As reported by others, sepsis is one of the most common precipitating factors of DKA.[3,5] Mortality in sepsis may occur in the early phase (in the first 5 days) or the late phase (after 5 days).[10,12,13] The mechanisms of mortality in the early phase are generally due to cardiovascular collapse, metabolic derangements, and multiple

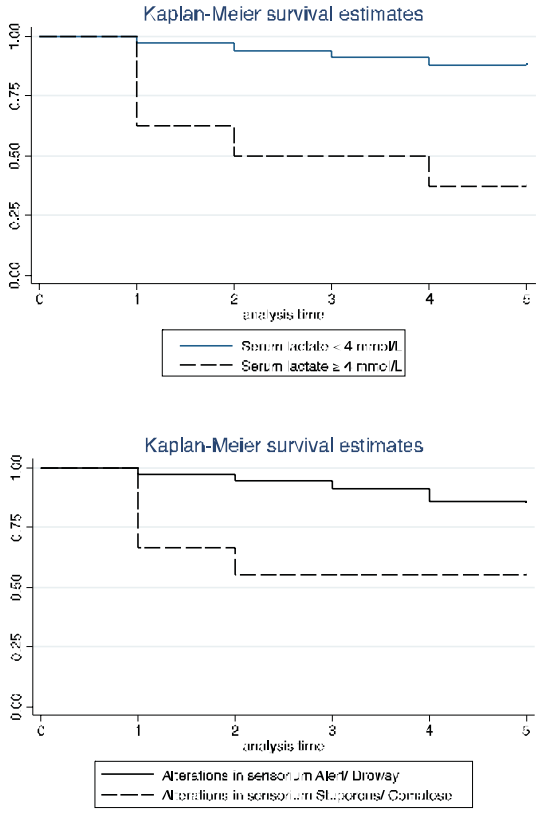

FIgure 1. Kaplan-Meier survival estimates

organ dysfunctions.[15] Tissue hypoperfusion is an important factor in the development of multiple organ failure. Therefore, the early recognition of sepsis-induced tissue hypoperfusion is crucial in implementing aggressive resuscitation to prevent organ damage.[16] Markers of tissue hypoperfusion include lactate levels.[8]

Our prospective study identified prognostic factors to predict 5-day mortality. Two variables were independently associated with mortality, specifically, serum lactate and alterations in sensorium. As reported by others, lactate levels were significantly higher in septic patients. Azoulay et al.[17] studied a retrospective analysis of 113 DKA patients treated in a medical ICU. They found that the lactate levels ranged from 1.9 to 3.3 mmol/L (median: 2.7) in patients with infection and from 1.3 to 1.8 mmol/L (median: 1.4) in patients without infection. Other authors have reported that the lactate levels were 2.61 SD 0.56 mmol/L in DKA septic patients and 1.32 SD 0.24 mmol/L in non-septic patients.[5] In the present study, we observed that DKA

patients with high lactate levels (≥4.0 mmol/L) had significantly higher mortality than patients with low lactate levels (<2.0 mmol/L). To our knowledge, no other prospective studies have reported high lactate levels in DKA and its association with high mortality. A potential reason that may explain our result was the patients' delays in seeking medical care, which resulted in more severe disease and, therefore, higher mortality rates. Rivers et al.[9] demonstrated a significant mortality benefit for patients with severe sepsis and septic shock when early diagnosis and rapid intervention was provided within the first 6 hours. Furthermore, our data demonstrated that blood pressure levels were not different between survivors and non-survivors. In addition, we found patients who had a lactate level ≥4.0 mmol/L in the presence of normal blood pressure. These results confirm that normotensive patients with high lactate levels or cryptic shock have a higher risk of death than patients with normal serum lactate.[18] Puskarich et al.[19] reported that the risk of death in patients with high lactate levels was similar between those with cryptic and overt shock. These results are consistent with other studies that have reported that a lactate level ≥4.0 mmol/L increases the probability of acute mortality.[10,12]

Altered mental status was another predictor of mortality in our study. The cause of altered sensorium in DKA remains unclear; it may be due to various possibilities, including reduced cerebral blood flow, reduced glucose utilization, hyperosmolality and high blood glucose concentrations, acidosis, or a direct effect of ketone bodies or other factors.[20] According to the recent International Sepsis Definitions Conference, the diagnostic criteria for sepsis now includes altered mental status as a marker of global hypoperfusion.[8] Tissue hypoperfusion is an important factor in the development of multiple organ failure, which is a major cause of death in septic patients.[15,16] In our study, 65% of the stupor/coma patients at admission also had an accompanying diagnosis of sepsis, and these characteristics were significantly related to mortality. These results are consistent with other studies that have reported that DKA patients who present with disorientation, confusion, or stupor at admission are more likely to also have infections.[17] In septic patients, encephalopathy was associated with mortality when graded by the Glasgow Coma Score. A score of 15 had a 16% mortality rate, 13 to 14 had a 20% mortality rate, 9 to 12 had a 50% mortality rate, and 3 to 8 had a 63% mortality rate ($p < 0.05$) (21). Chung et al.[22] conducted a retrospective study of 164 patients with hyperglycemic crises to determine the clinical characteristics and predictors of mortality. They found that infection (74%) was the most common trigger of hyperglycemic crises. In a multivariate analysis, altered mental status on admission and age were associated with mortality.[22]

In the population that we studied, there were 35 patients (58%) with sepsis. Mortality was significantly higher in these patients than in the non-septic patients. This indicates that a patient with serum lactate ≥4 mmol/L and alteration in sensorium stuporous/comatose is likely due to sepsis-induced tissue hypoperfusion, and in such cases, patients should be immediately resuscitated.

This mortality prediction may help clinicians to identify the possibility of sepsis as a trigger of DKA patients. Based on DKA guidelines, the initial fluid therapy in DKA should consist of isotonic saline (0.9% NaCl) at a rate of 15-20 mL/kg/h or 1-1.5 L within one hour. Therefore, rehydration should be guided by the hemodynamic status, state of hydration, serum electrolyte levels, and urinary output.[3,6] However, according to the Surviving Sepsis Campaign, the goals of initial resuscitation of sepsis-induced hypoperfusion should include CVP 8 to 12 mmHg, MAP ≥65 mmHg, and Scvo2 ≥70% (EGDT), and these goals must be achieved within the first 6 hours.[8] This strategy has demonstrated a significant reduction of in-hospital mortality compared with the standard therapy (30.5% vs. 46.5%).[7] Recent studies have shown that the outcome of sepsis may be improved with early recognition of hypoperfusion and optimal resuscitation.[23] By using this mortality prediction may provide an initial risk-stratification tool to identify patients at high risk of death, and may help clinicians can consider to determine the appropriate resuscitation protocol to be

used for a particular patient. This study has several limitations that need to be considered. First, we did not consider the effects of patient comorbidities, which may have influenced the outcomes. Second, definite causes of the patients' altered mental status were not identified. Third, because our study was conducted at a single institution, a tertiary referral hospital in Jakarta, Indonesia, the results may not be representative of all DKA patients.

CONCLUSION

Lactate level and altered in sensorium (stuporous/comatose) on admission to the emergency department can be used to predict acute mortality in DKA adult patients.

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REFERENCES

1. Jervis A, Champion S, Figg G, Langley J, Adams GG. Prevalence of diabetes ketoacidosis rises and still no strict treatment adherence. Curr Diab Rev. 2013;9(1):54-61.
2. Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. Diab Care. 2009;32(7):1335-43.
3. Nyenwe EA, Kitabchi AE. Evidence-based management of hyperglycemic emergencies in diabetes mellitus. Diab Res Clin Pract. 2011;94(3):340-51.
4. Jayashree M, Singhi S. Diabetic ketoacidosis: predictors of outcome in a pediatric intensive care unit of a developing country. Pediatr Crit Care Med. 2004;5(5):427-33.
5. Gogos CA, Giali S, Paliogianni F, et al. Interleukin-6 and C-reactive protein as early markers of sepsis in patients with diabetic ketoacidosis or hyperosmosis. Diabetol. 2001;44(8):1011-4.
6. Westerberg DP. Diabetic ketoacidosis: evaluation and treatment. Am Fam Physician. 2013;87(5):337-46.
7. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001;345(19):1368-77.
8. Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med. 2013;41(2):580-637.
9. Rivers EP, McIntyre L, Morro DC, Rivers KK. Early and innovative interventions for severe sepsis and septic shock: taking advantage of a window of opportunity. CMAJ. 2005;173(9):1054-65.
10. Trzeciak S, Dellinger RP, Chansky ME, et al. Serum lactate as a predictor of mortality in patients with infection. Int Care Med. 2007;33(6):970-7.
11. Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med. 2003;31(4):1250-6.
12. Shapiro NI, Howell MD, Talmor D, et al. Serum lactate as a predictor of mortality in emergency department patients with infection. Ann Emerg Med. 2005;45(5):524-8.
13. Otto GP, Sossdorf M, Claus RA, et al. The late phase of sepsis is characterized by an increased microbiological burden and death rate. Crit Care.15(4):R183.
14. Singhal R, Coghill JE, Guy A, Bradbury AW, Adam DJ, Scriven JM. Serum lactate and base deficit as predictors of mortality after ruptured abdominal aortic aneurysm repair. Eur J Vasc Endovasc Surg. 2005;30(3):263-6.
15. Hotchkiss RS, Monneret G, Payen D. Immuno-suppression in sepsis: a novel understanding of the disorder and a new therapeutic approach. Lancet Infect Dis. 2013;13(3):260-8.
16. Casserly B, Read R, Levy MM. Hemodynamic monitoring in sepsis. Crit Care Clin. 2009;25(4):803-23.
17. Azoulay E, Chevret S, Didier J, Barboteu M, Bornstain C, Darmon M, et al. Infection as a trigger of diabetic ketoacidosis in intensive care-unit patients. Clin Infect Dis. 2001;32(1):30-5.
18. Howell MD, Donnino M, Clardy P, Talmor D, Shapiro NI. Occult hypoperfusion and mortality in patients with suspected infection. Int Care Med. 2007;33(11):1892-9.
19. Puskarich MA, Trzeciak S, Shapiro NI, Heffner AC, Kline JA, Jones AE. Outcomes of patients undergoing early sepsis resuscitation for cryptic shock compared with overt shock. Resuscitation. 2011;82(10):1289-93.
20. Nyenwe EA, Razavi LN, Kitabchi AE, Khan AN, Wan JY. Acidosis: the prime determinant of depressed sensorium in diabetic ketoacidosis. Diab Care. 2011;33(8):1837-9.
21. Eidelman LA, Putterman D, Putterman C, Sprung CL. The spectrum of septic encephalopathy. Definitions, etiologies, and mortalities. JAMA. 1996;275(6):470-3.
22. Chung ST, Perue GG, Johnson A, Younger N, Hoo CS, Pascoe RW, et al. Predictors of hyperglycaemic crises and their associated mortality in Jamaica. Diab Res Clin Pract. 2006;73(2):184-90.
23. Walker CA, Griffith DM, Gray AJ, Datta D, Hay AW. Early lactate clearance in septic patients with elevated lactate levels admitted from the emergency department to intensive care: time to aim higher? J Crit Care. 2013;28(5):832-7.