A Prediction Model of Mortality in Patients Hospitalized with Diabetic Ketoacidosis in a Tertiary Referral Hospital in Surabaya, Indonesia

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Abstract

Background: The mortality rate of diabetic ketoacidosis (DKA) remains high in Indonesia. Different patterns were contributing to DKA mortality from previous studies. We aim to identify clinical and laboratory findings as mortality predictors of DKA.

Methods: This retrospective study was conducted in a tertiary referral hospital in Surabaya. Medical records of DKA patients from January 2016 to December 2018 were analyzed. Clinical and laboratory data were obtained from medical records for three years period. Clinical outcome was defined as either discharged home or death.

Results: Fifty-six among 116 DKA patients did not survive during hospitalized. Age of 60 or older, the depressed mental state with GCS below 13, potassium serum less than 3.5 mmol/L, and bicarbonate serum less than 15 mmol/L are found to be significant as independent factors of mortality in DKA patients.

Conclusion: The mortality rate of DKA patients in this study is still high. It independently associated with the age of 60 years or older, depressed mental state, hypokalemia, and low bicarbonate level. Early stratification of these predictors would help to treat patients accordingly.

Keywords: *prediction model, mortality, diabetic ketoacidosis*

Introduction

Diabetic ketoacidosis (DKA) is an acute complication of diabetes, still has a high mortality rate in Indonesia [1,2]. There is always a lack of annual incidence and mortality data in Indonesia, but two previous studies show that mortality was higher than another Asia and Africa countries [3–5]. The mortality rate of DKA in Cipto Mangunkusumo General Hospital compared to overall UK and US are 40% and <1% respectively [2,6]. This high mortality rate was associated with the characteristic of patient in tertiary hospital that tend to have low income, comorbidities, delayed in seeking medical treatment and severe infections [2].

DKA is characterized by a triad of hyperglycemia, ketonemia and metabolic acidosis [7]. It usually presents in short period of time associated to infections, drug or insulin noncompliance [8]. DKA could evolves rapidly and the diagnosis requires quick information obtained from Initial history taking, physical diagnosis and

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quick laboratory testing [6]. Treatment of DKA involves rehydration, correction of electrolyte derangements and metabolic acidosis, administration of insulin and treatment of precipitants [9]. Inadequate of either diagnosis or treatment of DKA could be a fatal prognosis [2,5,10]. Limited capacity of intensive care unit in Indonesia helps to stratify DKA patients to be treated at general or high-care wards.

The independent parameters associated to mortality of DKA were vary from each study [1–3,5,10,11]. Not only evaluated initial condition of DKA patients, some of these studies used patient's history or from evolving condition for following days [1,3,10]. Depressed mental state is most common variable that significantly independent to mortality of DKA [1–3,10]. Different study design, hospital regulation and demographic characteristic were taking account for different predictors of mortality. High mortality rate of DKA patients in Indonesia and in our hospital particularly, also limited availability of intensive- and high-care wards encouraged us to conducted a study using all available medical records.

The aim of this study is to analyze a prediction model for mortality of DKA using data obtained from initial patient's admission. It will help for better understandings in quick stratification and further management strategies despite a limited resources and facilities in our hospital.

Materials and Methods

This retrospective study was conducted in tertiary hospital of Dr. Soetomo General Hospital, Surabaya. All medical records under diagnosis of DKA from January 2016 to December 2018, aged ≥ 18 years were analyzed. All diagnosis of DKA in discharge resume were included, either in primary, diagnosis or complication diagnosis. Patients who discharged against medical advice were excluded.

Clinical outcome was defined as discharged home or death. Clinical and laboratory were obtained from emergency department at initial admission. All available data of demographic, clinical and laboratory were collected. Nine predictors were analyzed: age, Charlson's comorbidity index (CCI), depressed mental state, white blood cells (WBC), serum bicarbonate, osmolarity, albumin, potassium, and anion gap. The study was approved by the Local Ethics Committee.

All analyzed statistics were performed using Statistical Package for the Social Sciences. Subject's characteristics are presented as the mean with standard deviation or median with minimum and maximum range for continuous variables. The number of subjects for categorical data are presented as percentage. Chi-square test was used to analyze group differences for categorical variables. Multivariate analysis was done using all variable with p value < 0.25 from bivariate analysis. A p value < 0.05 from multivariate are considered as significant and formulated to be in prediction model.

Results

A hundred and twenty-three records were identified as DKA patients from discharged final diagnosis. Seven subjects were discharged against medical advice, left a hundred and sixteen subjects to be analyzed (**Table 1**). Deceased subjects had shorter length of stay (LOS) than discharged subjects (3 vs 8 days). Urinary tract infection (UTI) and pneumonia were most infections accompanied DKA subjects in this study. They took a proportion of 23.3% and 20.7% of infections respectively.

Table 1. Characteristics of subjects

Characteristics	Value (n=116)
Gender	
Male (n/%)	43/ 37.1
Female (n/%)	73/ 62.9
Outcome	
Discharged (n/%)	60/ 51.7
Deceased (n/%)	56/ 48.3

Cont... **Table 1. Characteristics of subjects**

Length of stay (days) Discharged (median/min-max) Deceased (median/min-max)	 8/ 3-19 3/ 1-11
Age (years) Discharged (median/min-max) Deceased (mean/SD)	 53/ 20-74 55.02/ 12.98
Referred from another hospital Referred (n/%) Non-referred (n/%)	 79/ 68.1 37/ 31.9
Ward Intensive/ high-care (n/%) Low care (n/%)	 45/ 38.8 71/ 61.2
Symptoms Depressed mental state (n/%) Dyspnea (n/%) Nausea (n/%) General weakness (n/%) Others (n/%)	 41/ 35.3 24/ 20.7 14/ 12.1 11/ 9.5 26/ 22.4
Glasgow Coma Scale Discharged (median/min-max) Deceased (median/min-max)	 15/ 3-15 12/ 3-15
Systolic blood pressure (mmHg) Discharged (median/min-max) Deceased (median/min-max)	 130/ 60-250 120/ 80-200
Diastolic blood pressure (mmHg) Discharged (median/min-max) Deceased (median/min-max)	 80/ 40-120 70/ 40-110
Infections Urinary tract infection (n/%) Pneumonia (n/%) Diabetic foot infection (n/%) Others (n/%)	85/ 73.3 27/ 23.3 24/ 20.7 11/ 9.5 23/ 19.8

Variables that had very high statistically significant were depressed mental status, potassium, and bicarbonate ($p < 0.001$). Osmolarity and WBC were found to be statistically very significant ($p < 0.01$). The rest of the variables in **Table 2** were not statistically significant as mortality predictors in DKA.

Table 2. Associations between categorical profiles and final outcome

Variables	Deceased		Discharged		p	OR	95% CI	
	n	%	n	%			Lower	Upper
Age*								
≥ 60 years	23	41.1	14	23.3	0.064	1.49	1.04	2.14
< 60 years	33	58.8	46	76.7				
Charlson's Comorbidity Index*								
≥ 3	12	21.4	13	21.7	1.000	0.99	0.63	1.57
< 3	44	78.6	47	78.3				
GCS*								
3-12	40	71.4	10	16.7	<0.001	2.53	1.76	3.65
13-15	16	28.6	50	83.3				
White blood cells**								
≥ 15000/mm3	15	26.8	2	3.3	0.002	1.89	1.30	2.74
< 15000/mm3	41	73.2	58	96.7				
Potassium**								
< 3.5 mmol/L	21	37.5	1	1.7	<0.001	2.56	1.94	3.38
≥ 3.5 mmol/L	35	62.5	59	98.3				
Albumin*								
< 3.5 g/dL	35	62.5	29	48.3	0.178	1.35	0.91	2.02
≥ 3.5 g/dL	21	37.5	31	51.7				
Bicarbonate*								
≤ 15 mmol/L	48	85.7	29	48.3	<0.001	3.04	1.60	5.78
> 15 mmol/L	8	14.3	31	51.7				
Osmolarity**								
≥ 320 mOsml/L	15	26.8	4	6.7	0.005	1.87	1.34	2.60
< 320 mOsml/L	41	73.2	56	93.3				
Anion gap**								
> 12 mmol/L	52	92.9	50	83.3	0.156	1.74	0.76	4.17
≤ 12 mmol/L	4	7.1	10	16.7				

*Chi Square test; **Fisher test

Eight out of nine variables that had $p < 0.25$ were analyzed in multivariate logistic regression. Statistically significant predictor from multivariate analysis were defined as $p < 0.05$. There were five variables in **Table 3** as

predictors of mortality in DKA patients. Depressed mental status had been highest statically significant predictors among others ($p < 0.001$).

Table 3. Multivariate analysis of variables independent to DKA mortality

Variables	p	b	OR	95% CI	
				Lower	Upper
Age ≥ 60 years	0.013	1.593	4.92	1.41	17.18
GCS < 13	0.001	2.144	8.54	2.47	29.49
Potassium < 3.5 mmol/L	0.001	4.844	126.9	7.82	2058
Bicarbonate ≤ 15 mmol/L	0.001	2.569	13.05	3.06	55.71
Constant (a)	<0.001	-4.320	0.013		

The prediction model of mortality was formulated from dividing the coefficient b by the standard error (SE) of all four were statistically significant variables ($p < 0.05$) in multivariate analysis. The prediction models were presented in **Table 4**. A Hosmer-Lemeshow test was shown good calibration in this prediction model ($p>0.05$). A good discrimination was shown from receiving operator curve (ROC) curve at **Figure 1** and presented area under the curve (AUC) value of 86.1% (95% CI 79.4–92.8).

Table 4. Formulated predictor scoring from significant variables

Variables	β	SE	β/SE	(β/SE)/2.114	Rounded value
Age ≥ 60 years	1.593	0.638	2.497	1	1
GCS < 13	2.144	0.633	3.387	1.35	1
Potassium < 3.5 mmol/L	4.844	1.422	3.406	1.36	1
Bicarbonate ≤ 15 mmol/L	2.569	0.74	3.472	1.39	1
Total score					4

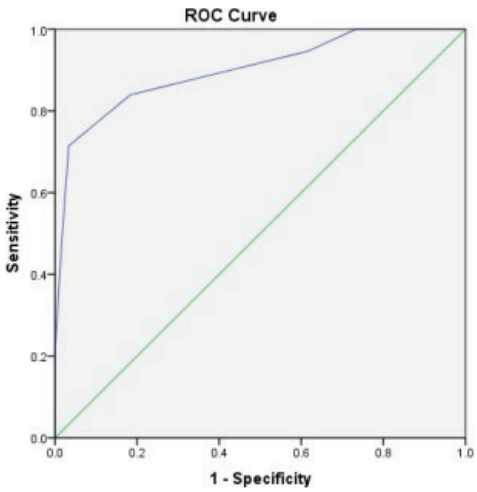

Figure 1. Area Under Curve (AUC) of prediction model after ROC

The probability of death for DKA patients based on 0–4 points for the total score in the prediction model as shown at **Table 5**. **Table 6** shows a prediction model of mortality in DKA patients. Sensitivity and specificity of this prediction model were 76.79% and 85% respectively.

Table 5. Mortality prediction based on patient score

Total score	y*	Probability (p)**
0	-3.175	4.01%
1	-1.047	25.98%
2	1.081	74.67%
3	3.209	96.12%
4	5.337	99.52%

$*y = -3.175 + 2.128(total\ score) y = -3.175 + 2.128(total\ score)$

$**p = 1/(1 + e^{-y}) p = 1/(1 + e^{-y})$

Table 6. Prediction model of mortality in DKA patients

No	Variables	Yes	No	Score
1.	Age ≥ 60 years	1	0	
2.	GCS ≤ 13	1	0	
3.	potassium < 3.5 mmol/L	1	0	
4.	Bicarbonate ≤ 15 mmol/L	1	0	
Total score:				

Discussion

The number of female subjects in this study were larger than male, that were consistent with other two previous study in Indonesia [1,2]. Out of 116 subjects, 56 subjects died (48.3%). This was higher mortality rate compared to other studies and was contrast compared to overall UK and US mortality rate that less than 1% [1–6,10,12,13]. This high mortality rate was associated with the characteristic of patient in tertiary hospital that tend to have low income, comorbidities, delayed in seeking medical treatment and severe infections [2]. three days (1-11 days) LOS of deceased subjects were similar with study from Efstathiou et al [10]. Most of DKA patients in this study were treated in low-care wards due to the limited intensive and high-care units. Most of DKA patients accompanied by comorbid conditions such myocardial infarction, congestive heart failure, acute renal failure, acute respiratory failure, altered mental status, coma, shock, hypothermia, sepsis, pancreatitis, gastrointestinal bleeding, uncontrolled hypertension end stage renal disease and hyperkalemia [14].

Depressed mental state was most clinical symptom found in the subjects (35.3%). Lower median of GCS in deceased subject compared to survivors that were related to the severity of acidosis and hyperosmolarity [15]. Other symptoms such dyspnea, nausea vomiting, and general weakness were consistent to be related to acidosis, electrolyte disturbance and dehydration [15]. Lower systolic and diastolic blood pressure in deceased group were consistent with study from Agarwal et al [5]. Lower blood pressure was related to severity of acidosis and dehydration [4].

Infection is most common precipitating factor of DKA in Indonesia [1]. In this study, infections were accompanied for 73.3% subjects. UTI and pneumonia had the largest proportion of infections that accounted for 23.3% and 20.7% respectively and consistent to other study [5]. The cause of death was mostly septic shock that could be associated to infections. Similar cause of death

was shown at study from Efstathiou et al. that systemic inflammatory response syndrome (SIRS) as cause of death [10].

Four variables that had highest statistically significant were known as predictor mortality in others study [1–3,11]. These were depressed mental state, leukocytosis, hypokalemia and low bicarbonate. Depressed mental state as predictor mortality in DKA and as most of clinical founding in the subjects, is related to severity of acidosis, hyperosmolarity and subject's comorbidity [4,16]. Leukocytosis in DKA may designate infection and need to be evaluated for source of infection [17,18]. Hypokalemia in DKA patient mainly caused by osmotic diuresis and may lead to decreased myocardial contractility and respiratory muscles [19,20]. Hypokalemia as one of significant predictor of DKA mortality in this study could be result as limited of intensive- and high-care wards that lead to suboptimal for evaluating electro-cardiac changes and potassium levels. Bicarbonate serum depletes during DKA, is a parameter of acidosis severity and could disrupt myocardial contractility [21]. Just like potassium, acid base correction with bicarbonate infusion requires close monitoring that were limited in our study center. Hyperosmolarity is related to osmotic diuresis and lead to hypovolemia and depletes electrolytes [6]. In this study, hyperosmolarity has statistically significant as predictor mortality of DKA subjects but not found to be significant in multivariate analysis.

Along with depressed mental state, hypokalemia and bicarbonate; Elderly was found to be significant as predictor mortality in multivariate analysis. This result was consistent with study from Mahesh et al [3]. Elderly as locally defined as age $\geq$ 60 years, tend to has severe comorbidity and lower insulin sensitivity were contributed to worse outcome and longer hospital stays [22–24]. The mortality prediction model was derived from these four parameters statistically significant from regression logistic. It is used as simple mortality prediction in term of risk at first admission. Each of four parameters is weighted as 1 in this scoring system as seen in table 6. Calibration and discrimination tests of this prediction model were found to be good with AUC is 86.1%. Sensitivity and specificity of this prediction model are 76.79% and 85%.

Our study provided simple risk prediction model that could help early assessment in admission. it consists of several clinical and laboratory parameter that can immediately obtained. Our study limitation that accessible medical records were only available in last three years' periods. Retrospective study design was failed to obtain some important data such history of previous ketoacidosis, type of diabetes, previous medical treatment and/or treatment compliance and complete history of subject's comorbidity.

Conclusion

The mortality rate of DKA patients in this study is 48.3%. High mortality rate in developed country still required specific attentions and further studies. Sixty years or older, depressed mental state, hypokalemia, and low bicarbonate level were associated with higher mortality rate.

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