Predicting diabetic ketoacidosis severity score: proposal of a therapeutic strategy adapted to the emergency department

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Abstract

Background: We investigated independent severity predictors of diabetic ketoacidosis and developed a prediction rule for emergency physicians to classify patients into severity groups.

Methods: This study was performed in a university-affiliated medical center. Consecutive adult patients (>15 years old) visiting the emergency department (ED) between July 2016 and July 2018 were enrolled when they met the criteria of DKA. Hospitalization in an intensive care setting was the primary endpoint.

Results: We included 176 patients diagnosed with (Diabetic Ketoacidosis) DKA in the ED. We found 7 independent severity predictors: Altered mental status, venous pH, bicarbonate level, blood glucose, Serum creatinine, H4 serum chloremia, and effective serum osmolality at admission. After assigning weights to each predictor, we developed a predicting DKA severity score that stratifies patients into groups: low severity (score<3): treatment in a general ward or the ED; and high (score≥3): treatment in the ICU. The area under the curve for the rule was 0.863.

Conclusions: The score is a simple and rapid rule for predicting severity and classifying patients with DKA.

Keywords: Diabetic ketoacidosis; Severity score; Outcomes; Emergency department,

INTRODUCTION

Diabetes is a public health problem and pathology burdened with significant morbidity and mortality due to its acute and chronic complications (1).

Diabetic ketoacidosis (DKA) is a serious complication of diabetes. It may be the initial mode of presentation for patients with new-onset T1D. It results from an absolute or relative insulin deficit with the immediate consequence of hyperglycemia and ketosis, which is itself responsible for water depletion and electrolyte disorders (2). Regardless of the observed decrease in the death rate, DKA remains a serious health problem, especially in developing and undeveloped countries (1). A better understanding of the pathophysiology combined with more uniform diagnostic and therapeutic treatment has led to a marked decline in developed countries, where its mortality varies between 0% and 5% (3-5). This metabolic disorder constitutes one of the main reasons for admission to the emergency department (ED) [1]. Several series studied mortality predictors and classified them in scores (6-9).

In this present study, we aimed to identify the clinical and evolutionary profile of the population admitted to the ED with a diagnosis of DKA, through a multivariate logistic regression analysis investigating independent severity predictors. We also aimed to develop a prediction rule useful for ED physicians to make an appropriate management decision (treatment in the Intensive care unit (ICU), a general ward, or only in the ED).

METHODS

- **Study design, setting, population, and selection of participants:** This study was performed in a university-affiliated medical center in Tunisia with an ED staffed with board-certified emergency physicians. Consecutive adult patients (>15 years old) visiting the ED with a diagnosis of DKA, between July 2016 and July 2018 were enrolled (3). DKA was defined as plasma glucose >2.5g/L, a high anion gap metabolic acidosis (serum HCO3 <15 mmol/L, and pH >7.3), and positive urine ketones or serum ketones.

Any other mode of decompensation: simple hyperglycemia, simple ketosis, hyperosmolar, a combination of hyperglycemia-hyperosmolar state (osmolarity> 320 mOsm/L) or a mixed ketoacidosis syndrome and hyperosmolar was excluded. The effective serum osmolality was calculated with this formula: 2[measured Na+ (mEq/L)] + [glucose (mg/dL)]/18.

Data collection

Patients were prospectively selected in the ED. Insufficient information was retrospectively collected by checking medical records after the patients had been discharged from the hospital. The processing of the files was carried out based on a pre-established sheet. The data has been grouped into five themes: General data (age, sex, background, and the evolutionary profile of diabetes); clinical data; biological data at admission, at H4, at H8, and H12; and the analysis of triggering factors (therapeutic errors, infectious states, etc.). Therapeutic management and progressive characteristics (length of stay,

mortality, and complications) were noted. We collected the quantity of insulin administered during the first 24 hours, the methods of its administration, as well as the other adjuvant therapies: rehydration, and antibiotic treatment.

Data analysis

Descriptive statistics (mean and standard deviation [SD] for continuous variables and frequencies and proportions for categorical variables) were calculated. Comparisons between the two groups were made using either an independent-samples t-test (assuming normal distribution) for the continuous variables. Either a $\chi 2$ test was used for categorical variables. Odds ratios (ORs), along with the corresponding 95% confidence intervals (CIs), were also computed as appropriate. The area under the receiver operating characteristic (ROC) curves was used to compare a model's specifications along with its sensitivity and specificity.

The patients were prospectively assigned to 2 groups as follows: *1*) the first group consisted of the patients who were admitted to the intensive care unit; *2*) the second group consisted of the patients who were admitted to the General ward (endocrinology). They were compared to detect patients requiring intensive care upon admission to the emergency room. A multiple logistic regression analysis with stepwise variable selection using backward selection was performed and odds ratios with 95% confidence intervals were calculated for each predictor. The results were used to develop a clinical and biological severity score, to detect patients who need admission to ICU. A weight was assigned to each element of this score according to its predictive β value. Finally, it was calculated for each patient in our population.

The scores on each different weight were used to determine their respective cutoff points for risk stratification the by ROC curve with the highest sum of sensitivity and specificity. For all analyses, a result was considered statistically significant at the $P < .05$ level of significance.

RESULTS

A total of 176 cases of DKA were included. The mean age was 35.3 +/- 18.6 years, 32.4% were aged between 20 and 30 years, and 77 patients were male (M/F sex ratio = 0.77). Diabetes was known in 150 patients with past medical history (85.2%), of whom 60.8% were type 1 diabetics. 14.8%of patients were admitted for a primary diagnosis of DKA. The most common symptoms at presentation were abdominal pain (41.5%), and lethargy (13.1%). Other signs and symptoms at presentation were fever (9.1%), polyuria and polydipsia (8%), Kussmaul breathing (5.7%), and chest pain (1.7%). The most frequent decompensation factors were infection in 36.9% and discontinuation of treatment in 23.9%of cases.

The average blood glucose was 28 +/- 7.6 mmol/L, the mean venous pH was 7.14+/-0.12, and blood HCO3- was 7.9 +/- 3.98 mmol/L. The main hydration solution was a 0.9% saline solution. The mean serum amount infused was 3.90±2.02 L/24h. The mean dose of intravenous insulin infused in the first 24 hours was 43.94±12.74 IU / 24h. The mean time to switch to subcutaneous insulin therapy was 24.8±16.4

hours. Only five patients with hypoglycemia were noted during treatment (2.8%). The length of stay in the ED was 16.1±13.5 hours. 19.7% of patients were discharged from the ED, after clinical and biological recovery as well as the control of the cause of decompensation. In contrast, 121 patients (68.8%) were transferred to an endocrinology ward, and 13 (7.4%) were admitted to the intensive care unit. The average total hospital length of stay was 6.41±6 days. Five cases of death (2.8%) were described in our study. Four deaths in group 1 and one death in group 2. Table 1 details the comparison of these two groups.

Seven independent severity predictors were retained: Altered mental status, venous pH, bicarbonate level, blood glucose, Serum creatinine, H4 serum chloremia, and effective serum osmolality at admission. A weight was assigned to each element of this score according to its predictive β value (table 2).

The mean score was 5.5 ± 1.4 for those who were admitted to the intensive care unit, and 2.8 ± 1.9 for the rest of the patients (p = 0.0001). Our population can then be classified into two severity groups: low with a score of <3 and high with a score ≥3 [OR (95% CI), 10.7 (1.36-84.5)]. A Score greater than 3 is predictive of severity. It has high predictive power (The area under the ROC curve is 0.863, with 100% sensitivity and 71.2% specificity) (Figure 1).

Table 1: Comparison between the ICU group and the Endocrinology Ward Group

	Group 1 (n=13)	Group 2 (n=121)	P
Age (years); mean±SD	37.2±19.2	35.1±18.6	0.694
DM duration	7.5±5.8	7±6.8	0.773
Males; n(%)	7 (53.8)	75(61.9)	0.106
Pulse rate (bpm); mean±SD	107.5±20.5	109.2±21.1	0.784
Systolic Blood Pressure (mmHg); mean±SD	12.7±1.7	12.1±2.3	0.395
Diastolic Blood Pressure (mmHg); mean±SD	6.8±1.4	4±1.4	0.693
Respiratory Rate (CPM); mean±SD	27.8±3.8	25.9±6.8	0.297
GCS;mean±SD	14.2±2	14.8±0.7	0.002
Blood analyses on admission			
Blood glucose (mmol/l); mean±SD	34.3 ± 8.5	27.6 ±7.4	0.002
Urea (mmol/l); mean±SD	11.7 ± 11	7.2± 4.8	0.02
Serum creatinine (µmol/l); mean±SD	166±196	94.7±89.4	0.025
Serum sodium (mmol/l); mean±SD	132.3±6.4	131.6±4.8	0.62
Serum potassium (mmol/l); mean±SD	4.7±0.9	4.5±0.9	0.3
pH H; mean±SD	7±0.10	7.20±0.10	p<0.001
HCO3- (mmol/l); mean±SD	4.5±3.4	8.2± 3.9	0.001
Osmolarity(mosmol/l); mean±SD	298.9±14.4	290.7±10.7	0.01
Blood analyses at H4			
pH; mean±SD	7.20 ± 0.10	7.30 ± 0.10	0.001
HCO3-(mmol/l); mean±SD	8.1 ± 3.5	12.6± 4.7	0.001
Serum sodium (mmol/l); mean±SD	134.1 ± 6.4	134±4.6	0.95
Serum potassium (mmol/l); mean±SD	4 ± 0.8	3.7± 0.8	0.218
Serum chloride (mmol/l); mean±SD	110.1 ± 6.4	103.7± 3.7	0.005
Blood analyses at H8			
pH; mean±SD	7.20± 0.10	7.30 ±0.10	<0.001
HCO3-(mmol/l); mean±SD	10.3 ±4.3	14.5 ±4.3	0.002
Blood analyses at H12			
pH; mean±SD	7.20 ± 0.10	7.30 ± 0.10	0.003
HCO3-(mmol/l); mean±SD	11.2 ± 5.1	15.2 ± 4.2	0.007
Serum sodium (mmol/l); mean±SD	133.8 ± 6.4	135± 4.2	0.396
Serum potassium (mmol/l); mean±SD	3.8± 0.9	3.7 ±0.7	0.466
Serum chloride (mmol/l); mean±SD	111 ± 5.4	105 ± 6.4	0.007
Mortality rate	4	1	<0.001

DM= diabetes mellitus; ICU= intensive care unit; PR=pulse rate; RR= respiratory rate; SBP= systolic blood pressure; DBP=diastolic blood pressure;

Table 2: Predicting DKA Severity Score

Variable	Weights
Glasgow Coma Scale (GCS)< 15	1
Venous pH < 7.14	2
Serum HCO3-< 7.7m moles/l	1
Blood glucose> 28,1 m moles/l	1
Serum creatinine> 100	1
chloremiaat H4 > 104	1
Serum Osmolarity> 291m osm/l	1

Low severity: score<3; High severity: score≥3

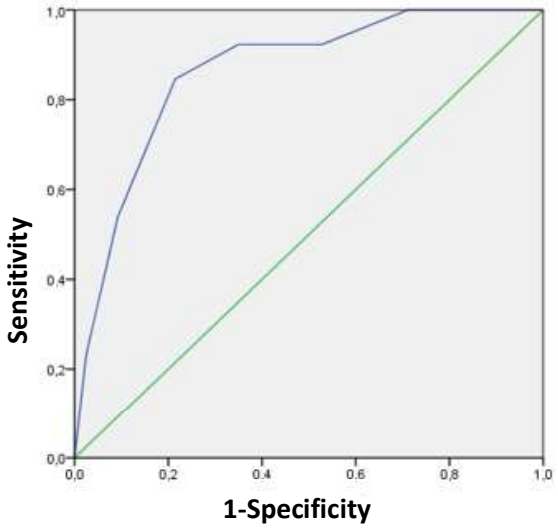

Figure 1: ROC Curve showing the correlation of the score with the patients' severity score

DISCUSSION

In Tunisia, the prevalence of diabetics was passed from 9% in 2007 to 15% in 2017. The age of onset is getting younger and younger, which exposes people to more acute and chronic complications (10-12). Acute complications of diabetes are a reason for frequent consultation and hospitalization in emergency departments (12,13). Among these complications, is ketoacidosis (DKA), which is an acute and severe complication, given the importance of its morbidity and mortality (3,14). Its annual incidence in the USA has been estimated between 4.6 and 8 episodes/1000 diabetics with a constant increase (10,12,15,16). This incidence is even greater in other countries, notably in England, Sweden, and developing countries (15). In a large study published in December 2015, admissions for DKA represented 1.1% of all ICU admissions in Australia and New Ireland between 2000 and 2013 (17).

In prior studies predictors of DKA mortality were studied and scored: A study carried out in Parakou hospital ICU in Benin over a period of 10 months, showed that the occurrence of complications was associated with advanced age, low socioeconomic level, high serum osmolarity, and long consultation time. It objectified a mortality rate of 14%, having as predictive factors the advanced age and long period before consultation (6). Another study done in Taiwan developed a mortality predictor score (Ph.D.) founding 6 independent mortality predictors: Absent tachycardia, Hypotension, Anemia, Severe coma, Cancer history, and Infection (7). The study by Stéphanie T. Chung (Jamaica 2006) concluded that mortality increased significantly with age and that the main mortality predictors were altered mental status on admission, co-morbidity, age, diabetes duration, and association of DKA with the hyperosmolar syndrome (8). For Stamatis P. et al, mortality predictors were co-morbidity, pH <7.0, the total dose of IV insulin injected in the first 12 hours> 50 IU, blood glucose> 16.7 mmol/L after 12 hours of treatment, altered mental status, and persistent fever after 24 hours (18). Several series studied mortality predictors and ranked them as scores, but there were enough series that studied severity predictors and admission risk ICU.

We developed a novel decision rule to predict the severity and manage ED patients with DKA. ED and ICU physicians can usefully evaluate 7 variables. Patients with a high score should be deemed critically ill and sent to the ICU for advanced treatment such as aggressive fluid resuscitation, strict intravenous insulin control, detailed investigation and management of the precipitating factors, and careful prevention of possible treatment complications. For patients with a low score, a general ward admission or ED treatment may be sufficient, which would help preserve medical resources for patients in greater need.

Blood PH at admission, with a high β-value, was the strongest severity predictor. Altered mental status has been proposed as the only independent severity predictor, which is easier to quantify in clinical practice. Blood PH and effective serum osmolality are important for evaluating DKA; these two factors appear to be significant severity predictors in our study. Blood creatinine, which reflects the importance of water deficit, can be at the origin of functional renal failure (19). It can also be falsely high due to the presence of ketone bodies. Chloremia at H4 is a variable that was kept in our score as a severity factor. Indeed, rehydration with isotonic saline serum promotes the appearance of hyperchloremic acidosis which should be avoided (3).

Limitations

This study has several limitations. First, some clinical presentations or records may not have been completely documented. Second, this was a single-center study. Third, the sample size might not be large enough to make conclusions with good statistical power. Additional studies with larger sample sizes are necessary. Fourth, although we have validated the prediction rule in a prospective cohort, external validation in other populations is necessary.

CONCLUSION

Diabetic ketoacidosis occurs in young people treated with insulin therapy. Infection appears to be the most implicated factor in decompensation. A Score greater than 3 is predictive of severity, requiring care in an ICU with a mortality rate remaining low thanks to this score.

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