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ORIGINAL INVESTIGATION

# All-cause mortality prognostic factors in type 2 diabetes-associated ketosis and ketoacidosis

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**Abstract**

**Background:** Diabetic ketoacidosis (DKA) represents a life-threatening acute diabetic complication attributed to type 1 diabetes. In the past decades, the presence of DK or even DKA has been increasingly recognized among patients with type 2 diabetes mellitus (T2DM).

**Aim of the Study**: We aimed to analyze characteristics and mortality rate prognostic factors in patients with T2DM presenting with non-ketotic hyperglycemia (NKH), DK, and DKA.

**Methods:** Population-based retrospective study at the Emergency Department of Clinical Hospital Center Sestre Milosrdnice, Zagreb, Croatia, was conducted. DKA was defined as plasma glucose >13.9 mmol/L, ketonuria >2+, and capillary blood bicarbonate levels <18 mmol/L or capillary blood pH <7.30. 137 patients with T2DM presenting with DKA and 137 age- and gender-matched patients with NKH and DK were included in the study. We analyzed general anthropometric characteristics, precipitating factors, signs and symptoms, medications, alcohol, and cigarette consumption.

**Results:** Patients with DKA had significantly higher mortality rates when compared with DK (HR 2.55, 95% CI 1.65–3.92, P < 0.001) and NKH (HR 1.27, 95% CI 1.05–1.53, P = 0.01). Older age, higher blood urea nitrogen, and calcium channel antagonists use were adverse prognostic factors across all groups. Acetylsalicylic acid and insulin in DKA and furosemide use in DK group were associated with increased mortality. Conversely, alcohol and tobacco use was associated with lower mortality in DKA group. These variables predicted 1-year mortality with and accuracy of 81% in DK group and 88% in DKA group.

**Conclusion:** Prognostic factors and all-cause mortality differ between patients with NKH, DK, and DKA. Further, prospective trials should evaluate whether the addressing prognostic factors could improve patient outcomes.

**Key words:** Type 2 diabetes mellitus; hyperglycemia; diabetic ketosis; diabetic ketoacidosis; mortality; prognostic factor

## 1. Introduction

Diabetic ketoacidosis (DKA) represents a life-threatening acute diabetic complication with estimated mortality rate of up to 5% [1]. It is a condition characterized by ketonemia and ketonuria, acidemia and usually, but not always hyperglycemia [2]. The mechanism of hyperglycemia in DKA is due to increased glucose production from gluconeogenesis and glycogenolysis and simultaneously reduced uptake by peripheral muscles and fat tissue [2-4]. Insulin inhibits gluconeogenesis and glycogenolysis; however, in insulin-resistant states, it is unable to effectively control glucogenic enzymes and consequently increasing glucose output from the liver [5]. In insulin-resistant states, the antilipolytic effects of insulin remain because the amount of insulin required to prevent lipolysis is one-tenth of required for glucose utilization [6]. Type 2 diabetes mellitus (T2DM) is characterized by dysglycemia and dyslipidemia due to increased insulin resistance and relative or even absolute insulinopenia, especially in terms of long disease duration. In the past decades, the presence of DK or even DKA has been increasingly recognized among patients with T2DM [7-9]. Various precipitating factors including undercurrent infection/illness, omission of regular insulin, initial presentation of diabetes, and cardiovascular or cerebrovascular events have been acknowledged [10-12]. Aforementioned suggests that DKA to occur in patients with T2DM when the insulin production is insufficient (or absent) to prevent ketone production with or without precipitating factors. Patients, with T2DM and DKA also tend to be older, have a higher body mass index (BMI), prominent features of insulin resistance but shorter duration of diabetes with an older age of onset [11].

Most of the studies on this topic considered DK and DKA as a same clinical entity or on the same spectrum of hyperglycemic crisis while none of them examined these two conditions separately in patients with T2DM. Furthermore, there are no data on mortality rate prognostic factors following DKA in patients with T2DM. Therefore, the aim of this study was to identify possible mortality rate prognostic factors following DKA in patients with T2DM and compare it with T2DM patients presenting with non-ketotic hyperglycemia (NKH) and DK.

## 2. Materials and Methods

This was a retrospective population-based, case–control study performed at the Emergency Department of Clinical Hospital Center Sestre Milosrdnice, Zagreb, Croatia. We performed a comprehensive medical electronic record review from all patients diagnosed with T2DM and hyperglycemia at the admission who had complete records on plasma glucose (PG), qualitative urine analysis for the presence of ketones (range 0–4+) and acid-base status (pH) at admission between January 1, 2010, and December 31, 2014. The patient was considered to have a diagnosis of T2DM listed on the admission history, problem list, or any emergency department documentation that gives clear evidence that the T2DM was diagnosed following the World Health Organization diagnostic criteria, the revised form from 2011 [12]. Patients, who did not have their C-peptide or autoantibody measured, were excluded from the study. Moreover, due to high prevalence of T1DM in patients younger than 40 years of age [13], we included only patients older than 40, regardless of their C-peptide concentration or autoantibody positivity. DK was defined as PG >13.9 mmol/L, presence of ketonuria >2+, and capillary blood bicarbonate levels >18 mmol/L or capillary blood pH >7.30, while DKA was defined as PG >13.9 mmol/L, ketonuria >+2, and capillary blood bicarbonate levels <18 mmol/L or capillary blood pH <7.30. Mild DKA was defined as capillary bicarbonate levels between 15 and 18 mmol/L, moderate DKA as 10–15 mmol/L, and severe DKA as capillary bicarbonate levels <10 mmol/L. Patients with PG >13.9 mmol/L and undetectable ketones in urine were classified as NKH [14].

Finally, 137 patients with T2DM presenting with DKA and 137 age- and gender-matched patients with NKH and DK were included in the study. The following parameters were analyzed: General anthropometric characteristics (age, gender, readmissions, hospitalization, and place of residency); precipitating factors (infection, therapy omission, or newly diagnosed diabetes without signs of infection); signs and symptoms (weight loss, polyuria and polydipsia, increased body temperature, vomiting, abdominal pain, dyspnea, mental status changes, systolic and diastolic blood pressure, heart rate, and electrocardiograms); medication (angiotensin-converting enzyme inhibitors, calcium channel antagonists, beta-

blockers, furosemide, thiazide diuretics, acetylsalicylic acid [ASA], statins, antipsychotics, benzodiazepines, sulfonylureas, metformin, insulin, alcohol, and cigarette consumption). The presence of infection was defined as C-reactive protein (CRP) >5 mg/L or increased body temperature (>38°C) or episodes of increased body temperature within 1 week before admission.

All-cause mortality data were obtained from the Croatian Department of Public Health.

The study protocol was approved by the Ethics Committee of the Sisters of Mercy University Hospital Center, Zagreb, Croatia, and the study was performed according to the Declaration of Helsinki and "good clinical practice" guidelines.

The normality of distribution was examined by Shapiro–Wilk test. If the distribution was not normal, the logarithmic transformation was performed, thus all the numerical variables are presented as mean ± SD, while nominal variables were given as number and percentage. Continuous variables were compared with one-way analysis of variance and Bonferroni method was used for *post hoc* analysis. Categorical variables were analyzed using the Chi-square test. Cox proportional hazard models were used to analyze the link between patient characteristics and mortality. Backward conditional stepwise approach was used to determine variables independently associated with survival. Stepwise conditional backward Cox regression was performed separately in each group of variables. Afterward, a nomogram was constructed in the form of a regression equation based on unstandardized correlation coefficients derived from the final step of stepwise conditional backward Cox regression. Receiver operating characteristic analysis was performed to determine the sensitivity, specificity, and positive likelihood ratio of the nomogram in predicting all-cause mortality. $P < 0.05$ was considered statistically significant. The statistical analysis was done using SPSS Version 20.0.

## 3. Results

There were no differences regarding age, gender, diabetes duration, BMI, place of residency, or readmission rates in between DKA, DK, and NKH group. However, the patients in the DK group had higher rate of newly diagnosed diabetes while patients in the DKA group had higher hospitalization rate [Table 1]. When compared with the NKH and DK group, patients in the DKA group had higher PG, leukocyte count, CRP, and base excess while lower serum sodium, capillary blood pH, and bicarbonate levels. Although DKA group had highest CRP levels, the prevalence of infection as a precipitating factor was similar in all three groups. The DK group had lower urea and creatinine levels while higher estimated glomerular filtration rate compared with both groups. The DK group had the highest prevalence of newly diagnosed diabetes without infection. The most common reason for admission in the DKA group was hyperglycemia, while patients with NKH had a higher rate of admission due to renal or heart failure.

In the DKA group, the use of insulin was higher while metformin and sulfonylurea use was lower. They also used more benzodiazepines and antipsychotics while less furosemide, ASA, beta-blockers, and calcium channel antagonists.

During a median follow-up of 35 months, 55 (39.9%) patients in the NKH group, 32 (23.2%) patients in the DK group, and 61 (44.2%) patients in the DKA group died. Mortality was the highest within the first 3 months following DKA: 23.4% at 1$^{st}$ month, 31.4% at 3$^{rd}$ month, and 40.1% at 12$^{th}$ month [Figure 1]. Mortality rates in patients with NKH were 4.3% at 1$^{st}$ month, 5.8% at 3$^{rd}$ month, and 15.2% at 12$^{th}$ month. Patients in the DK group had the lowest mortality rates: 5.1% at 1$^{st}$ month, 8.0% at 3$^{rd}$ month, and 13.8% at 12$^{th}$ month. Patients with DKA had significantly higher mortality rates when compared with both DK group (HR 2.55, 95% CI 1.65–3.92, $P < 0.001$) and NKH group (HR 1.27, 95% CI 1.05–1.53, $P = 0.01$).

Age was independently associated with mortality across all groups. Among the general anthropometric characteristics, rural residency and hospitalization were adverse prognostic factors in the NKH group while readmissions were adverse prognostic factors in DK group. Among physical examination parameters and symptoms, the presence of dyspnea, arrhythmia, and mental status was adverse prognostic factors in NKH group while weight loss before admission was

**Table 1: Characteristics of the studied population divided based on the presence of NKH, DK, and DKA**

| Variable | NKH (A) | DK (B) | DKA (C) |
|---|---|---|---|
| Age (years) | 63.7±13.2 | 63.7±12.4 | 64.8±14.4 |
| Male gender % (n) | 60.6 (83) | 56.2 (77) | 56.2 (77) |
| Duration of diabetes (years)† | 11.4±9.4 | 8.2±8.4 | 8.2±9.8 |
| BMI (kg/m$^2$)† | 29.2±5.6 | 30.2±6.3 | 27.2±5.7 |
| Rural residency % (n) | 39.4 (54) | 52.6 (72) | 45.3 (62) |
| Readmissions % (n) | 22.6 (31) | 28.5 (39) | 21.2 (29) |
| Newly diagnosed DM % (n) | 16.8 (23) | 24.1 (33)$^C$ | 13.9 (19) |
| Hospitalized % (n) | 32.1 (44) | 42.3 (58) | 72.3 (99)$^{AB}$ |
| Laboratory findings | | | |
| PG (mmol/L) | 20.3±6.3 | 20.7±5.1 | 28.7±13.3$^{AB}$ |
| Leukocytes (109/L) | 10.9±5.2 | 11.1±4.0 | 14.3±6.7$^{AB}$ |
| Hemoglobin (g/L) | 135.6±21.8 | 142.7±17.4$^A$ | 140.7±20.8 |
| Urea (mmol/L) | 9.4±7.3 | 7.1±3.7A$^C$ | 10.7±6.6B |
| Creatinine (µmol/L) | 124.4±57.7 | 96.2±27.5$^{AC}$ | 135.8±86.3 |
| Sodium (mmol/L) | 134.6±4.8 | 134.6±4.1 | 132.4±7.4$^{AB}$ |
| Potassium (mmol/L) | 4.3±0.5 | 4.2±0.5 | 4.5±0.8B |
| CRP (mg/L) | 50.5±83.6 | 60.1±98.1 | 88.1±122.4$^{AB}$ |
| eGFR (ml/min) † | 74.2±36.0 | 96.0±41.7 | 66.9±28.9$^B$ |
| HbA1c (%) † | 9.2±2.1 | 9.0±2.5 | 7.8±2.4 |
| HbA1c (mmol/mol) | 77±1 | 75±4 | 62±3 |
| pH | 7.42±0.06 | 7.43±0.04 | 7.30±0.15$^{AB}$ |
| Base excess (mmol/L) | −0.7±3.8 | −0.9±2.6 | −11.6±6.6$^{AB}$ |
| Bicarbonates (mmol/L) | 22.6±5.0 | 22.8±2.6 | 13.0±4.7$^{AB}$ |
| Cause of hyperglycemia | | | |
| Infection % (n) | 38.0 (52) | 38.0 (52) | 38.0 (52) |
| Therapy omission % (n) | 9.5 (13) | 8.8 (12) | 8.0 (11) |
| Newly diagnosed without infection | 10.2 (14) | 20.4 (28)$^{AB}$ | 11.7 (16) |
| Unknown % (n) | 42.3 (58) | 32.8 (45)$^{AB}$ | 42.3 (58) |
| Symptoms % (n) | | | |
| Polyuria and polydipsia | 19.0 (26) | 25.5 (35) | 25.6 (35) |
| Weight loss | 11.7 (16) | 13.1 (18) | 15.3 (21) |

*(Contd...)*

**Table 1:** ***(Continued)***

| Variable | NKH (A) | DK (B) | DKA (C) |
|---|---|---|---|
| Vomiting | 12.4 (17) | 24.8 (34)[A] | 30.7 (42)[A] |
| Abdominal pain | 23.3 (32) | 33.0 (45) | 33.0 (45) |
| Physical examination | | | |
| Dyspnea % (n) | 11.0 (15) | 3.6 (5) | 22.6 (31)[AB] |
| Mental status | | | |
| Somnolence % (n) | 0.0 (0) | 2.9 (4) | 10.2 (14)[AB] |
| Sopor % (n) | 0.7 (1) | 0.0 (0) | 5.1 (7)[AB] |
| Coma % (n) | 0.7 (1) | 0.0 (0) | 0.7 (1) |
| Systolic blood pressure (mmHg) | 143.3±26.1 | 140.6±22.2 | 136.4±28.2 |
| Diastolic blood pressure (mmHg) | 83.3±13.2 | 84.1±12.9 | 80.2±14.3 |
| Heart rate (beats/min) | 89.9±22.0 | 92.2±18.2 | 101.3±21.0[AB] |
| Arrhythmia % (n) | 20.4 (28) | 5.8 (8)[AB] | 14.6 (20) |
| Reason for admission % (n) | | | |
| Hyperglycemia | 41.6 (57) | 44.5 (61) | 56.9 (78)[AB] |
| Myocardial infarction | 2.9 (4) | 7.3 (10) | 8.0 (11) |
| Heart failure | 5.1 (7)[BC] | 0.7 (1) | 0.0 (0) |
| GI bleeding | 1.4 (2) | 3.6 (5) | 2.2 (3) |
| Pancreatitis | 2.9 (4) | 2.9 (4) | 4.4 (6) |
| Liver cirrhosis | 5.1 (7) | 2.2 (3) | 1.4 (2) |
| Renal failure | 8.0 (11)[BC] | 1.4 (2) | 2.2 (3) |
| Habits, treatment, and concomitant medication % (n) | | | |
| Alcohol | 9.5 (13) | 17.5 (24) | 19.0 (26)[A] |
| Smoking | 12.4 (17) | 19.0 (26) | 19.7 (27) |
| Sulfonylureas | 33.6 (46) | 40.9 (56)[C] | 27.0 (37) |
| Metformin | 25.5 (35) | 38.0 (52)[AC] | 22.6 (31) |
| Insulin | 22.6 (31) | 21.2 (29) | 33.6 (46)[AB] |
| Statins | 21.2 (29) | 17.5 (24) | 17.5 (24) |
| Benzodiazepines | 6.6 (9) | 5.1 (7) | 13.1 (18)[B] |
| Antipsychotics | 3.6 (5)[BC] | 13.1 (18) | 17.5 (24) |
| Glucocorticoids | 2.2 (3) | 1.4 (2) | 2.9 (4) |
| Proton-pump inhibitors | 4.7 (6) | 5.1 (7) | 6.6 (9) |
| ASA | 18.3 (25)[C] | 13.1 (18) | 9.5 (13) |

*(Contd...)*

**Table 1:** ***(Continued)***

| Variable | NKH (A) | DK (B) | DKA (C) |
|---|---|---|---|
| Furosemide | 19.7 (27)[BC] | 8.0 (11) | 2.9 (4) |
| Thiazide diuretics | 23.4 (32) | 20.4 (28) | 21.2 (29) |
| ACE inhibitors | 40.9 (56) | 37.9 (52) | 34.3 (47) |
| Beta-blockers | 30.6 (42)[BC] | 13.9 (19) | 18.3 (25) |
| Calcium channel antagonists | 32.8 (45)[BC] | 16.8 (23) | 15.3 (21) |

CRP: C-reactive protein, BMI: Body mass index, DM: Diabetes mellitus, eGFR: Estimated glomerular filtration rate, HbA1c: Hemoglobin A1c, GI: Gastrointestinal, ACE: Angiotensin-converting enzyme, ASA: Acetylsalicylic acid, †Data available for 72 patients in NKH group, 68 patients in DK group, and 50 patients in the DKA group. NKH: Non-ketotic hyperglycemia, DK: Diabetic ketosis, DKA: Diabetic ketoacidosis, A: $P < 0.05$ when compared with NKH, B: $P < 0.05$ when compared with DK, C: $P < 0.05$ when compared with DKA

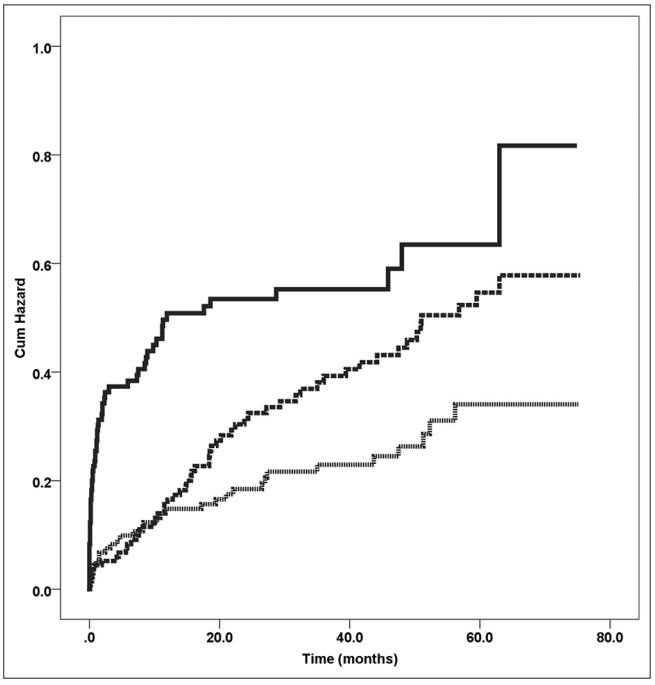


**Figure 1.** Kaplan-Meier curves showing cumulative hazard between patients with non-ketotic hyperglycemia (dotted line), diabetic ketosis (interrupted line), and diabetic ketoacidosis (full line)

favorable prognostic factor in DKA group. Increased body temperature was adverse prognostic factor in patients with DK, but favorable factor in DKA group. When assessing concomitant medication at admission, the use of calcium channel antagonists was associated with increased mortality both in DK and DKA group. Moreover, the use of ASA in DKA group and furosemide in DK group was associated with increased mortality. The association between antidiabetic medication and mortality was found in the DKA group, where the use of insulin was associated with 2-fold higher mortality risk; while in the NKH group, the use of sulfonylurea was adverse prognostic factor. Alcohol consumption and cigarette smoking were associated with decreased mortality only in DKA group. PG, total leukocyte count, sodium, and amylase were positively associated with mortality rate across NKH and DK group, while blood urea nitrogen and sodium were associated with mortality rate in DKA group [Table 2].

Therefore, we constructed three different nomograms in the form of regression equation for each group:

- NKH group: Age ×0.086 + rural residency ×0.656 + sulfonylureas ×0.817 + arrhythmia ×0.765 + dyspnea ×0.805 + mental status (0 - normal, 1 - somnolence, 2 - stupor, 3 - coma) ×1.566 + PG ×0.05 + amylase ×0.003 - hemoglobin ×0.022 + leukocytes ×0.070 + sodium ×0.081;
- DK group: Age ×0.094 + increased body temperature ×1.233 + blood urea nitrogen ×0.317 + calcium channel antagonists ×0.869 + furosemide ×1.212 + PG ×0.081 - hemoglobin ×0.025 - creatinine ×0.023;
- DKA group: Age ×0.06 - weight loss ×1.748 - increased body temperature ×1.554 + Ca channel antagonists ×1.051 + ASA ×1.842 + insulin ×1.405 - alcohol ×1.726 - smoking ×1.95 + blood urea nitrogen ×0.035 + sodium ×0.04.

Nomograms predicted 1-year mortality with very good accuracy in the NKH group (AUC 0.833, 95% CI 0.722–0.943, $P < 0.001$), DK group (AUC 0.809, 95% CI 0.695–0.922, $P < 0.001$), and DKA group (AUC 0.880, 95% CI 0.805–0.956) [Figure 2a-c]. Sensitivity, specificity, and positive likelihood ratios for each cutoff are presented in Table 3.

**Table 2: Results of stepwise conditional backward Cox regression in patients with DKA, showing independent predictors of all-cause mortality**

| Non-ketotic hyperglycemia | B | SE | HR | 95% confidence interval | | *P* |
|---|---|---|---|---|---|---|
| General anthropometric characteristics | | | | | | |
| Age | 0.086 | 0.014 | 1.090 | 1.060 | 1.120 | 0.000 |
| Rural residency | 0.656 | 0.312 | 1.926 | 1.044 | 3.553 | 0.036 |
| Hospitalization | 1.102 | 0.274 | 3.010 | 1.761 | 5.147 | 0.000 |
| Physical examination and symptoms | | | | | | |
| Abnormal mental status | 1.566 | 0.357 | 4.787 | 2.376 | 9.645 | 0.000 |
| Arrhythmia on ECG | 0.765 | 0.318 | 2.149 | 1.152 | 4.007 | 0.016 |
| Dyspnea | 0.805 | 0.325 | 2.237 | 1.183 | 4.233 | 0.013 |
| Medication | | | | | | |
| Sulfonylureas | 0.817 | 0.345 | 2.264 | 1.150 | 4.455 | 0.018 |
| Laboratory parameters | | | | | | |
| PG | 0.050 | 0.023 | 1.051 | 1.006 | 1.099 | 0.026 |
| Leukocyte count | 0.070 | 0.023 | 1.072 | 1.026 | 1.121 | 0.002 |
| Hemoglobin | −0.022 | 0.006 | 0.978 | 0.966 | 0.990 | 0.000 |
| Sodium | 0.081 | 0.029 | 1.085 | 1.024 | 1.149 | 0.006 |
| Amylase | 0.003 | 0.001 | 1.003 | 1.001 | 1.004 | 0.000 |
| Diabetic ketosis | | | | | | |
| General anthropometric characteristics | | | | | | |
| Age | 0.094 | 0.017 | 1.099 | 1.062 | 1.137 | 0.000 |
| Readmissions | 1.395 | 0.474 | 4.036 | 1.593 | 10.223 | 0.003 |
| Physical examination and symptoms | | | | | | |
| Increased body temperature | 1.233 | 0.380 | 3.432 | 1.630 | 7.227 | 0.001 |
| Medication | | | | | | |
| Calcium channel antagonists | 0.869 | 0.418 | 2.385 | 1.052 | 5.406 | 0.037 |
| Furosemide | 1.212 | 0.460 | 3.361 | 1.363 | 8.288 | 0.008 |
| Laboratory parameters | | | | | | |
| PG | 0.081 | 0.040 | 1.085 | 1.003 | 1.174 | 0.043 |
| Hemoglobin | −0.025 | 0.009 | 0.975 | 0.958 | 0.993 | 0.005 |
| Blood urea nitrogen | 0.317 | 0.081 | 1.373 | 1.173 | 1.608 | 0.000 |
| Creatinine | −0.023 | 0.009 | 0.977 | 0.959 | 0.995 | 0.011 |

*(Contd...)*

**Table 2:** ***(Continued)***

| Non-ketotic hyperglycemia | B | SE | HR | 95% confidence interval | | *P* |
|---|---|---|---|---|---|---|
| Diabetic ketoacidosis | | | | | | |
| General anthropometric characteristics | | | | | | |
| Age | 0.060 | 0.010 | 1.061 | 1.041 | 1.083 | 0.000 |
| Physical examination and symptoms | | | | | | |
| Weight loss | −1.748 | 0.729 | 0.174 | 0.042 | 0.727 | 0.020 |
| Increased body temperature | −1.554 | 0.767 | 0.211 | 0.047 | 0.951 | 0.040 |
| Medication and habits | | | | | | |
| Calcium channel antagonists | 1.051 | 0.413 | 2.860 | 1.272 | 6.432 | 0.010 |
| ASA | 1.842 | 0.459 | 6.310 | 2.565 | 15.527 | 0.000 |
| Insulin therapy | 1.405 | 0.414 | 4.078 | 1.813 | 9.173 | 0.001 |
| Alcohol | −1.726 | 0.849 | 0.178 | 0.034 | 0.939 | 0.040 |
| Smoking | −1.950 | 0.597 | 0.142 | 0.044 | 0.459 | 0.001 |
| Laboratory parameters | | | | | | |
| Blood urea nitrogen | 0.035 | 0.017 | 1.035 | 1.002 | 1.070 | 0.040 |
| Sodium | 0.040 | 0.017 | 1.041 | 1.007 | 1.076 | 0.020 |

B: Unstandardized correlation coefficient, SE: Standard error, HR: Hazard ratio

## 4. Discussion

To the best of our knowledge, this is the first study analyzing mortality rate prognostic factors following DKA in patients with T2DM. We demonstrated substantial differences in mortality rate following an episode of NKH, DK, and DKA in patients with T2DM which was lowest in patients with DK, followed by NKH and DKA, with the majority of deaths occurring within the first 3 months after the DKA episode. In comparison, a retrospective cohort study of DKA admissions in patients with T1DM demonstrated significantly lower mortality rates during a follow-up of 4.9 years [15]. Multivariate analysis identified a greater number of DKA admissions, longer diabetes duration, previous psychiatric admissions, and older age at diagnosis as independent mortality rate predictors.

In addition, we showed some unusual findings: The use of ASA, beta-blockers, and calcium channel antagonists was independently associated with all-cause mortality in patients with DKA. Since we cannot speculate on the causal relationship, the most likely explanation of this association is that those patients had higher cardiovascular risk. Alcohol and cigarette consumption were independently associated with decreased mortality. This association is well known for moderate alcohol use, but the association with smoking is unclear. We can speculate that because addiction is fairly common in the general population, cigarette smoking might be less harmful than overeating in this subgroup of patients with DKA. Increased body temperature was a positive prognostic factor in patients with DKA which suggests that patients who developed DKA due to infection had more favorable outcomes. Although patients with DKA had increased CRP levels, there was no difference in the presence of infection between the three groups. Therefore, increased CRP may be due to another condition leading to inflammation and future studies should address the relationship between CRP and DKA.

Weight loss before the DKA episode was a favorable prognostic factor. Weight loss in patients with T2DM implies insulinopenia and lower degree of insulin resistance, which is associated with favorable outcomes due to decreased cardiovascular risk. In addition, patients

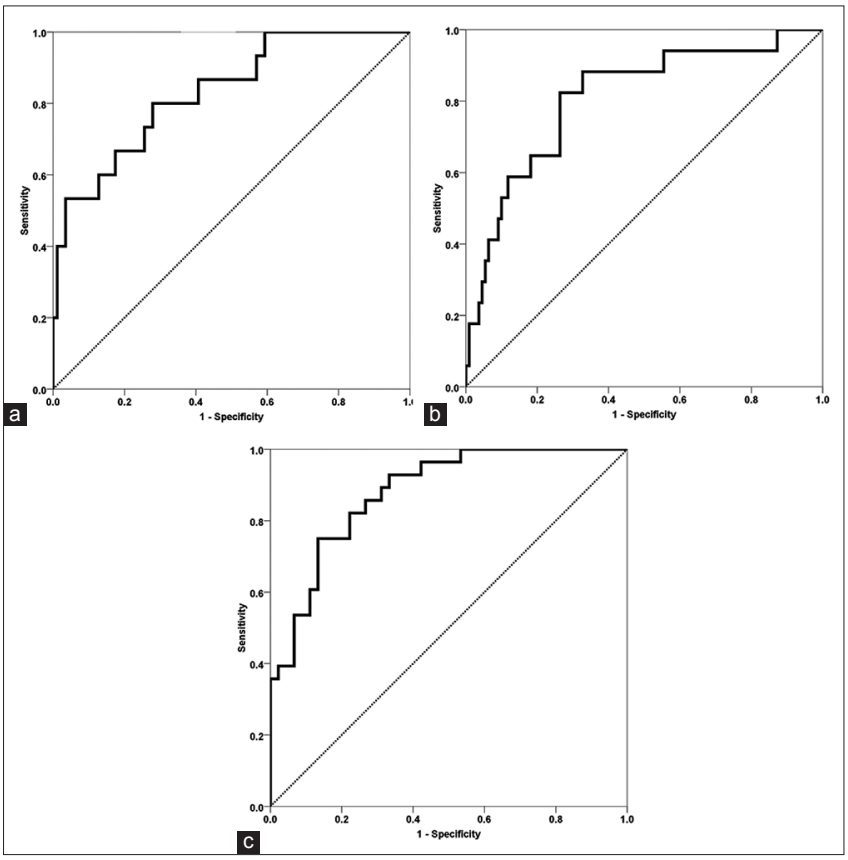


**Figure 2.** Receiver operating characteristic curve showing the diagnostic performance of nomograms in predicting all-cause mortality in patients with non-ketotic hyperglycemia (a), diabetic ketosis (b), and diabetic ketoacidosis (c)

**Table 3: Sensitivity, specificity, and positive likelihood ratio for different cutoffs of prognostic nomogram in predicting 1-year all-cause mortality after each type of hyperglycemic crisis**

| Nomogram cutoff | Sensitivity (%) | 95% CI | Specificity (%) | 95% CI | PLR | 95% CI |
|---|---|---|---|---|---|---|
| NKH | | | | | | |
| >15.14 | 100.0 | 78.2–100.0 | 40.7 | 30.2–51.8 | 1.69 | 1.4–2.0 |
| >17.26 | 80.0 | 51.9–95.7 | 72.1 | 61.4–81.2 | 2.87 | 1.9–4.4 |
| >19.88 | 53.3 | 26.6–78.7 | 96.5 | 90.1–99.3 | 15.29 | 4.6–51.2 |
| DK | | | | | | |
| >2.07 | 100.0 | 80.5–100.0 | 12.7 | 7.1–20.4 | 1.15 | 1.1–1.2 |
| >5.60 | 82.4 | 56.6–96.2 | 73.6 | 64.4–81.6 | 3.12 | 2.1–4.6 |
| >8.51 | 23.5 | 6.8–49.9 | 96.4 | 91.0–99.0 | 6.47 | 1.8–23.5 |
| DKA | | | | | | |
| >8.10 | 96.4 | 81.7–99.9 | 57.8 | 42.2–72.3 | 2.28 | 1.6–3.2 |
| >10.18 | 75.0 | 55.1–89.3 | 86.7 | 73.2–94.9 | 5.63 | 2.6–12.2 |
| >12.01 | 39.3 | 21.5–59.4 | 97.8 | 88.2–99.9 | 17.68 | 2.4–129.6 |

CI: Confidence interval, PLR: Positive likelihood ratio, NKH: Non-ketotic hyperglycemia, DK: Diabetic ketosis, Diabetic ketoacidosis

with insulinopenia have enhanced ketogenesis, which may be a positive prognostic factor in patients with cardiomyopathies, as hypertrophied and failing hearts shift to ketone body utilization for oxidative ATP production [16]. On the other hand, insulin therapy was independently associated with increased mortality. This observation was reported in large retrospective studies, which demonstrated that insulin treatment in patients with T2DM may even increase mortality [17,18]. The higher use of sulfonylurea in patients with DK and its association with mortality rate is in accordance with previous studies suggesting these groups of medications might have a protective effect on the DKA development in patients with T2DM and prevents recurrence of hyperglycemia in obese African-American patients with a history of hyperglycemic crises [19].

Patients in the NKH group had a higher prevalence of arterial hypertension, kidney disease, and heart failure, which are all associated with increased mortality. We already demonstrated that patients with DK had decreased all-cause mortality [20]. It remains unclear why patients with DKA have such high mortality rates. In patients with T1DM, mortality in hyperglycemic crises is primarily due to the underlying precipitating illness and rarely due to the metabolic complications of hyperglycemia or ketosis [21-23].

The metabolic disturbances that lead to transient beta cell dysfunction in T2DM patients remain unclear. Studies have demonstrated that short-term lipotoxicity (following infusion of fatty acids) does not alter beta-cell function or promote ketosis, highlighting that ketosis in these patients is not due to excessive fatty acid flux to the liver [24]. Furthermore, glucotoxicity may [25] or may not [26] affect beta-cell function, although this may depend on the duration and severity of hyperglycemia [26]. Ketosis in these patients occurred due to decreased fatty acid and ketone consumption rather than increased lipolysis and ketone production. This is a novel finding that demonstrates marked differences in the pathogenesis of ketosis and ketoacidosis in patients with T1DM and T2DM.

DK and DKA in patients with T2DM may not represent the same spectrum of hyperglycemic crises, but patients with DK may represent a unique subgroup of individuals with enhanced ketone utilization, despite similar rates of ketone production. We reported that patients with DK had a lower incidence of symptomatic heart failure and improved renal function compared to patients with NKH, with an overall reduction of all-cause mortality, suggesting that DK may be a compensatory mechanism rather than a complication of acute hyperglycemic crises [19]. Similarly, this study also demonstrated that patients with DK have decreased overall mortality in comparison to patients with NKH and DKA. Therefore, ketone production seems to be beneficial for survival. Both groups were able to synthesize ketone bodies, but patients with DKA may have had deficient ketone utilization, leading to increased serum ketone accumulation and subsequent oxidative stress. Therefore, the almost two-fold increase in mortality in patients with DKA may be due to differences in ketone metabolism.

This study has several limitations which should be pointed out: Retrospective design which limits the possibility of causal relationship determination, small number of patients, and a lack of quantitative urine ketone analysis.

Despite, we can conclude that parameters that define the severity of hyperglycemic crisis and those associated with renal and heart failure were associated with all-cause mortality in patients with NKH and DK. However, this was not the case in patients with DKA, who have distinct and rather unclear prognostic factors. Thus, our study suggests that DK and DKA represent two distinct subgroups of patients with T2DM, which should be analyzed separately in future clinical trials. Although we constructed three different nomograms for each group of patients, which have a diagnostic accuracy between 81% and 88%, further studies to validate these nomograms before their routine use in clinical practice are needed.

## Author contributions

IK gave the idea for the study, performed statistical analysis, participated in manuscript drafting and gave his final approval. MĆ and PĆ performed the data acquisition, critically reviewed the manuscript and gave the final approval. LSK and KB wrote the manuscript and gave the final approval. VO and MŠ designed electronic databases, participated in manuscript drafting and gave their final approval. MV gave advice regarding statistical analyses and data acquisition, critically reviewed the manuscript and gave his final approval.

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