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Differences in Clinical Characteristics and Outcomes According to Subtypes of Hyperglycemic Crises

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ABSTRACT

Differences in Clinical Characteristics and Outcomes According to Subtypes of Hyperglycemic Crises

By Francisco Pasquel, M.D.

Background: Many patients with hyperglycemic crises present with combined features of diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS).

Methods: This study aimed to determine the proportional distribution of hyperglycemic crises (isolated HHS, isolated DKA and combined DKA-HHS) in adult patients admitted to two academic centers between 2005 and 2015.

Results: Among 1211 patients, 465 (38%) had DKA (ICD-code and bicarbonate ≤18 mEq/L on presentation), 421 (35%) patients had HHS (ICD-code, effective osmolality ≥300, and bicarbonate >18 mEq/L) and 325 (27%) had combined features of DKA-HHS (DKA + osmolality ≥ 300). HHS patients were older, more likely to be African American, and had higher BMI. Cerebral edema and rhabdomyolysis were uncommon. Age was independently associated with increased mortality [adjusted OR (aOR): 1.05, 95% confidence interval (CI): 1.03-1.07]. After adjusting for age, gender, BMI and race, subjects with combined DKA-HHS had higher mortality compared to subjects with isolated hyperglycemic crises (aOR: 2.5, CI: 1.4-4.6). Hypokalemia (≤3mEq/L) was common (N: 326, 27.37%) but did not differ among groups. Severe hypokalemia (potassium <2.5 mEq/L) occurred in 75 subjects (6.3%) and was associated with increase in mortality (OR 3.17, 95% CI: 1.49, 6.76). This association remained significant after adjusting for hyperglycemic crises categories, demographic variables and metabolic parameters on admission (aOR 4.49, 95% CI: 1.82, 11.0.9). A combination of age (>50 years) and effective osmolality (≥300 mOsm/kg) increases the sensitivity and specificity (c-statistic: 0.70) to discriminate case fatalities.

Conclusions: A combination of HHS and DKA increase the risk of mortality among patients presenting with hyperglycemic crises. Predictors of mortality included age, effective osmolality, and severe hypokalemia. Revision of current hyperglycemic crises subtypes classification and diagnostic criteria for hyperosmolality may be considered.

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INTRODUCTION

Hyperglycemic crises are severe complications of diabetes that include the hyperosmolar hyperglycemic state (HHS) and diabetic ketoacidosis (DKA). A large proportion of studies investigating these severe complications have largely focused on DKA, a much more common hyperglycemic emergency. HHS, a syndrome characterized by severe hyperglycemia, hyperosmolality and dehydration in the absence of ketoacidosis has a high mortality rate, estimated to be up to 10 times higher than the mortality observed in patients with DKA.[1] About 4 to 9% of admissions related to diabetes as a primary diagnosis are related to DKA, [2,3] accounting for more than 140,000 hospital admissions per year.[4,5] The proportion of patients presenting with HHS, however, is not well defined. Most cases of HHS are seen in elderly patients, but recent reports suggest an increase in incidence of HHS cases in children and young adults.[6] Infection and comorbidities such as stroke, myocardial infarction, and trauma are potential precipitating causes of HHS. Furthermore, features of HHS can be observed in cases of DKA, but limited data are available regarding the prognosis of patients with combined features of DKA and HHS. Some studies have reported that up to 20% of patients with DKA have combined characteristics of HHS and DKA.[7,8] The clinical characteristics and hospital outcomes of patients with combined DKA-HHS are not known.[1]

In general, the recommendations for the management of hyperglycemic crises are similar for DKA and HHS, but the mortality rate in patients with HHS appears to be much higher than in patients with DKA.[7,9] Thus, further research is needed to understand the clinical

characteristics of patients with different subtypes of hyperglycemic crises including combined DKA-HH, to assess the rate of complications associated with severity of disease, and to identify predictors associated with worse outcomes.

We analyzed individual level data of a large sample of patients admitted to Emory Hospitals over a 10-year period to: a) determine the frequency distributions of HHS, DKA and combined DKA-HHS among patients presenting with hyperglycemic crises; b) to identify associated comorbidities; and c) to examine the relationship and predictive value of markers of disease severity on admission with outcomes.

METHODS

Data source

We conducted an observational study analyzing individual-level admission and hospitalization data of patients admitted with hyperglycemic crises at Emory Hospitals (Emory University Hospital and Emory University Hospital Midtown) between 06/01/2005 to 06/30/2015. Data was obtained through the Clinical Data Warehouse (CDW) infrastructure program. Patients were identified with the utilization of ICD-9 codes for DKA and HHS. Cases were confirmed according to standard definitions [10]. Data was extracted for each patient during the index hospitalization; including demographics and anthropometrics (age, BMI, gender, race); admission and inpatient laboratory values [hemoglobin A1C, plasma glucose, arterial/venous pH, ketones, total serum osmolality (2(Na) +18/glucose + BUN/2), effective serum osmolality

(2(Na) +18/glucose), anion gap, total and corrected serum sodium, serum creatinine, estimated glomerular filtration rate (eGFR), lactic acid, CPK]; and hospital complications using ICD-9 codes, to include data on comorbidities and complications including: hypokalemia, acute kidney injury, cardiac complications, deep vein thrombosis / venous thromboembolism, cerebral edema, rhabdomyolysis, length of hospital stay, and mortality within 30 days of hospitalization. Case definition of hyperglycemic crises was as follows: **1) HHS:** plasma glucose level greater than 600 mg/dL + plasma effective osmolality ≥ 300 mOsm/L and bicarbonate >18 mEq/L, or ICD-code + effective osmolality ≥300 mOsm/kg, and bicarbonate >18 mEq/L; **2) DKA:** ICD-code for DKA and bicarbonate ≤18 mEq/L on presentation; **3) Combined DKA-HHS:** DKA criteria plus effective osmolality ≥300 mOsm/kg.

Data Analysis

The primary aim of the study was to compare the relative proportion of hyperglycemic crises (DKA, HHS, and combined DKA-HHS) and comorbidities in hospitalized adult patients with diabetes. Demographics and clinical outcome measures were compared between subtypes of hyperglycemic crises. Analysis of variance was used to compare differences among continuous variables. Chi-squared analysis was used to compare differences among categorical variables. Multiple logistic regression models with adjusted odds ratios controlling for covariates were used to determine the influence of demographic and clinical characteristics on complications, mortality rates and length of stay according to DKA, HHS, and DKA-HHS categories. Metabolic parameters (blood glucose, anion gap, bicarbonate, effective osmolality) were evaluated as

Continuous variables and according to categories (quartiles). Models evaluating the role of metabolic parameters on outcome were adjusted for demographic variables. Metabolic parameters that are correlated or determined by each other (e.g. anion gap and bicarbonate, or effective osmolality and glucose) were not included in the adjusted models evaluating the role of each parameter on outcomes. Receiver operating characteristic (ROC) curves were used to relate admission effective osmolality cut points and age on the rate of hospital outcome. The area under the curve (AUC), or c-statistic, was utilized as measure of the predictive accuracy. A p-value of <0.05 was considered significant. All analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC). The study protocol was approved by the Emory University Institutional Review Board.

RESULTS

A total of 1907 patients with 2950 episodes of hyperglycemic crises were identified. After confirmation criteria for DKA and HHS, a total of 1211 subjects on a first admission were included. Among 1211 patients, 465 (38%) had isolated DKA, 421 (35%) patients had isolated HHS and 325 (27%) had combined features of DKA-HHS (DKA + osmolality ≥ 300 mOsm/kg). HHS patients were older, more likely to be African American (83%), and had higher BMI (28.9 kg/m^2), Table 1. Age was independently associated with hospital mortality (aOR: 1.05, CI: 1.03, 1.07). Patients with combined DKA-HHS were more likely to have a prolonged length of stay (>3.7 days, median) compared to patients with isolated hyperglycemic crises (aOR: 1.33, CI: 1.01, 1.76).

Hyperglycemic crises categories and mortality

Hyperglycemic crises categories: After adjusting for age, sex, BMI and race, subjects with combined DKA-HHS had higher mortality compared to subjects with isolated hyperglycemic crises [aOR, CI:1.4-4.6], Table 2.

Diagnostic criteria parameters on admission and hospital mortality

Mortality was not associated with admission plasma glucose (β: -0.00026, p-value: 0.63) or anion gap (β: -0.00350, p-value: 0.87) as continuous variables or categorized by quartiles in both adjusted and unadjusted analyses (data not shown).

Bicarbonate: Lower bicarbonate levels were associated with increased mortality after adjusting for covariates and hyperglycemic crises categories **(**β -0.0654, p-value: 0.0069), Table 2.

Effective osmolality: Effective osmolality was associated with age (Figure 2). Effective osmolality levels ≥ 300 mOsm/kg were associated with a 2.4 fold increase in mortality compared to lower levels (unadjusted OR: 2.43, 95% CI: 1.34, 4.4). This association remained significant after adjusting for age, BMI, gender, race, anion gap, and HCO3 on admission (OR: 3.41, 95% CI: 1.71, 6.81). Levels of osmolality >320 had good specificity (82%), but poor sensitivity (31%) to discriminate fatalities (c-statistic 0.57). A cut off of 300 mOsm/kg increased the sensitivity to 75% at an expense of lower specificity (44%). A combination of age (>50 years) and effective osmolality (≥ 300 mOsm/kg), increased the sensitivity to 82% and specificity to 52% (c-statistic: 0.70) (Figure 3) to discriminate case fatalities.

Acute complications

Hypokalemia: Hypokalemia (≤3mEq/L) was common (N: 326, 27.37%) but did not differ among groups (Table 1). Severe hypokalemia (potassium <2.5 mEq/L) occurred in 75 subjects (6.3%) and was associated with increase in mortality (OR 3.17, 95% CI: 1.49, 6.76). This association remained significant after adjusting for hyperglycemic crises categories, demographic variables and metabolic parameters on admission (OR 4.49, 95% CI: 1.82, 11.0.9). A higher drop in potassium levels from baseline was observed among non-survivors, p=0.02, Figure 1.

Rhabdomyolysis and cerebral edema: were uncommon. Rhabdomyolysis presented more commonly in subjects with isolated HHS (Table 1), however, there was no association with osmolality levels.

Cardiovascular Outcomes: cardiac complications where not different among patients with combined DKA-HHS compared to patients with isolated hyperglycemic crises (aOR: 1.01, CI: 0.71, 1.70), Figure 4.

Acute kidney injury: AKI defined as an increase in creatinine levels above 0.5 md/dL from baseline, was associated with increased mortality in adjusted and unadjusted analysis, Table 3, however it was not different according to hyperglycemic crises subtypes (aOR 0.79, CI: 0.44, 1.40).

Deep venous thrombosis and venous thromboembolism (DVT/VTE): Osmolality was independently associated with DVT/VTE (osmolality > 320 mOsm/kg, aOR: 2.71, CI: 1.09, 6.72).

This association was not significant at lower osmolality thresholds. Subjects with combined DKA-HHS had higher odds of DVT/VTE compared to subjects with isolated crises, however, the association was not significant (aOR: 2.22, CI: 0.91, 5.43), Figure 4.

DISCUSSION

Hyperglycemic crises are acute and severe complications of diabetes. This study showed that a significant proportion of subjects present with combined features of DKA and HHS, and that combined features of both abnormalities are associated with poor outcome. The prevalence and difference in clinical outcomes in patients with different subtypes of hyperglycemic crises in adult patients has not been well documented. According to smaller series, patients with HHS appear to have worse outcomes compared to patients with DKA, but data adjusting for covariates, and severity of disease, or evaluating the overlap of both conditions has not been reported previously. In this large group of subjects presenting with hyperglycemic crises, a combination of DKA and HHS was associated with a significantly higher mortality (8%) compared to isolated crises (5% for isolated HHS and 3% for isolated DKA).

Patients with combined characteristics higher odds of adverse hospital outcomes. Total and effective osmolality cut offs are derived from cases series of HHS described in the 1970's when increased interest grew on the role of hyperosmolality on the acute mental changes associated with severe hyperglycemia.[11-14] Furthermore, the cutoff of blood glucose > 600 mg/dL for the diagnosis of HHS was based on the observation that this levels were usually accompanied by total serum osmolality > 350 mOsm/kg (effective osmolality ~ 312 mOsm/kg in this database)

according to the experience of the investigators describing the initial case series.[11] In this study, higher osmolality (≥300 mOsm/kg) and age were associated with higher odds for mortality. A combination of age above 50 years along with osmolality ≥ 300 mOsm/kg appears to confer good prediction to discriminate hospital fatalities among patients presenting with severe hyperglycemic crises. The sensitivity of the effective osmolality cut-off of 320 mOsm/kg was very low. Our findings suggest that: **a)** an osmolality cut-off associated with significant mental status changes might not capture all patients at high risk for hospital complications; and **b)** the sensitivity of the current ADA recommended effective osmolality cut-off is too low to appropriately identify patients with high mortality risk.

Current diagnostic criteria of hyperglycemic crises recommended by the American Diabetes Association (ADA) and international guidelines include: **a) HHS:** plasma glucose level greater than 600 mg/dL, plasma effective osmolarity greater than 320 mOsm/L, and an absence of significant ketoacidosis, and **b) DKA:** plasma glucose above 250 mg/dL, arterial pH < 7.3, serum bicarbonate <18 mEq/L, positive urine or serum ketones, anion gap > 10 with or without altered mental status. [5,15,16] Our results highlight the implications of identifying patients with combined DKA-HHS, a distinctive high risk category that should be identified on hospital admission.

A common complication of intravenous insulin treatment is hypokalemia. In this study, patients who died had a more significant drop in potassium levels. Severe hypokalemia (≤ 2.5 mEq/L) was independently associated with a four-fold higher odds for mortality. Current

guidelines recommend the concomitant administration of potassium with intravenous insulin in patients with hyperglycemic crises and potassium levels <5.3 mEq/L and recommend holding insulin infusion for potassium levels <3.3 mEq/L.[5] Our results highlight the strong association between hypokalemia and mortality, and raise awareness for the need to implement effective protocols to closely monitor potassium levels during therapy with insulin. The role of lower doses of insulin in clinical trials enrolling patients with DKA should also be considered to evaluate the risk and benefits of rapid correction of acidosis compared to the risk of increased mortality with severe hypokalemia.

As previously suggested, our results confirmed an association of hyperosmolality with DVT and thromboembolism in patients with hyperglycemic crises.[1] This complication was more likely at higher osmolality levels.

Low-dose insulin infusion protocols designed for treating DKA appear to be effective; however, no prospective randomized studies have determined best treatment strategies for the management of patients with HHS or combined DKA-HHS and associated complications including thromboembolic events and rhabdomyolysis.[1] These complications were uncommon in this dataset, however information bias is plausible. Assessing clinical risk in patients that are along the continuum of DKA-HHS is complex and there is a need for clinical prediction tools for hospital morbidity and mortality.[17] Our results highlight the predictive role of age, osmolality, and hypokalemia on hospital mortality.

Since pH and beta-hydroxybutyrate levels are not consistently measured in clinical practice there is a potential for misclassification of hyperglycemic crises in this dataset. Cases with other

metabolic derangements (e.g. lactic acidosis) could have been included. Selection bias is possible, as patients with DKA diagnosis but bicarbonate levels >18 mEq/L were excluded. Therefore our findings might not be applicable to patients with very mild derangements in metabolic parameters. Also subjects with mixed metabolic disorders could also have been excluded. Despite this limitations, a large number of patients with hyperglycemic crises were included in this analyses.

CONCLUSIONS

In this large cohort including over 1,200 patients presenting with hyperglycemic crises, the following conclusions and recommendations can be drawn: **1)** a combination of HHS with DKA is not uncommon and is associated with increased mortality; **2)** hypokalemia is a common complication in patients presenting with hyperglycemic crises and is associated with increased mortality; and **3)** a threshold of hyperosmolality of 320 mOsm/kg has a low sensitivity to identify patients with increased mortality. Current guidelines should consider lowering the threshold of effective osmolality from 320 mOsm/kg to 300 mOsm/kg.

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Table 1. Clinical Characteristics According to Subtypes of Hyperglycemic Crises

	DKA (n: 465)	HHS (n: 421)	Combined DKA / HHS (n: 325)	p-value
Age, years	43±17	57±4	49±18	<.0001
Gender female, n (%)	245 (52)	211 (50)	169 (52)	0.73
BMI, kg/m^2	27.3±3.2	28.9±8.3	26.5±6.7	<.0001
Race AA, n (%)	312 (67)	349 (83)	256 (79)	<.0001
Admit BG, mg/dL	490±197	797±287	828±296	<.0001
HbA1c (%)	11.7±2.9	12.1±2.8	11.6±2.7	0.12
HCO3, mEq/L	12.2±3.7	23.7±3.9	11.8±4.5	<.0001
Anion GAP	20.1±5.4	14.3±4.8	25.4±6.9	<.0001
Effective Osmolality, mOsm/kg	288± 8	316±18.9	316±15	<.0001
Sodium, mg/dL	130±6	136±10	134±7	<.0001
Beta-hydroxybutyrate, mmol/L	5.8±2.6	2.2±2.2	6.0±2.9	<.0001
Heart Failure, n (%)	37(8)	46 (11)	25 (8)	0.20
Stroke, n (%)	1 (0.2)	5 (1.2)	0 (0)	0.01
AMI, n (%)	10 (2)	15 (4)	10 (3)	0.08
DVT, n (%)	9 (2)	4 (1)	10 (3)	0.004
Hypokalemia, n (%)	95 (20)	71 (17)	72 (22)	0.17
Cerebral edema, n (%)	4 (0.9)	1 (0.2)	2 (0.6)	0.06
AKI, n (%)	34 (7)	32 (8)	18 (6)	0.50
Vasopressor use, n (%)	42 (9.0)	29 (6.9)	43 (13.2)	0.01
Rhabdomyolysis, n (%)	4 (0.9)	14 (3.3)	4 (1.2)	0.02
LOS, median (IQR)	3.3 (2.1-6.2)	3.8 (2.4-7.5)	3.8±(2.4-6.2)	0.02
Death (within 1 month)	14 (3.01)	20 (4.8)	27 (8.3)	0.004

Data is presented as mean ± SD or median and interquartile range (IQR). AKI: 0.5 mg/dL increase in creatinine level among subjects admitted with creatinine <5mg/dL; AA: African American; LOS: length of stay

Table 2. Association of Metabolic Abnormalities on Admission and Inpatient Mortality

	OR	Model 1[a]
Admission Glucose		
Q4	1.00 (Reference)	1.00 (Reference)
Q3	0.478 (0.21, 1.08)	0.73 (0.33, 1.66)
Q2	1.06 (0.55, 2.07)	1.14 (0.55, 2.39)
Q1	0.48 (0.21, 1.08	0.64 (0.26, 1.56)
Anion GAP		
Q4	1.0 (Reference)	1.0 (Reference)
Q3	1.92 (0.80, 4.59)	1.89 (0.72, 4.92)
Q2	2.29 (0.99, 5.32)	2.35 (0.93, 5.94)
Q1	2.14 (0.92, 4.98)	1.26 (0.47, 3.37)
HCO3		
Q4	1.0 (Reference)	1.0 (Reference)
Q3	2.60 (1.15, 5.90)	3.15 (1.23, 8.03)
Q2	2.04 (0.92, 4.51)	3.81 (1.52, 9.60)
Q1	1.31 (0.55, 3.10)	2.95 (1.05, 8.26)

[a]Model 1: adjusted for age, gender, BMI, race

Table 3. Predictors of Mortality According to Hyperglycemic Crises Categories and Acute Hospital Complications

	OR	Model 1[a]	Model 2[b]
DKA	1.00	1.00	
HHS	1.61 (0.80, 3.22)	0.65 (0.30, 1.43)	
DKA + HHS	2.92 (1.51, 5.66)	2.02 (0.99, 4.12)	
DKA	1.00	1.00	
DKA + HHS	2.95 (1.52, 5.66)	2.20 (1.07, 4.52)	
Hypokalemia	3.17 (1.49, 6.76)	4.23 (1.78, 10.10)	4.54 (1.84, 11.22)
Acute Kidney Injury	5.12 (2.72, 9.61)	5.44 (2.67, 11.09)	4.70 (2.25, 9.81)

Hypokalemia: defined as potassium level <2.5 mEq/dL; acute kidney injury defined as an elevation of creatinine in 0.5 mg/dL from baseline.

[a]Model 1: adjusted for age, gender, BMI, race

[b]Model 2: model 1 + hyperglycemic crises category, glucose on admission, anion gap, HCO3, osmolality, admission sodium level.

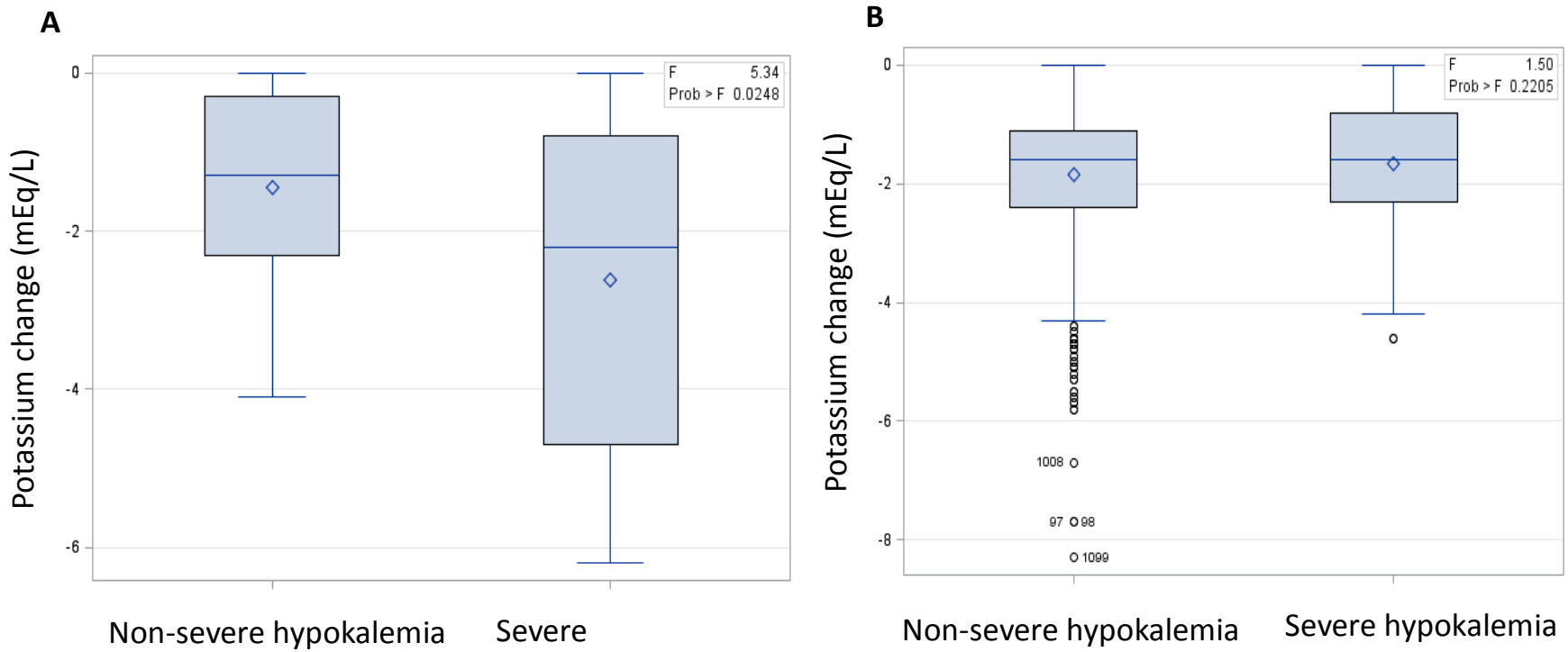

Figure 1. Change in Potassium Levels from Baseline Among Survivors and non-Survivors. A) Non-survivors. B) Survivors. Potassium change represents change from admission to lowest potassium level during admission. The magnitude of the drop was more significant among non-survivors, p=0.02.

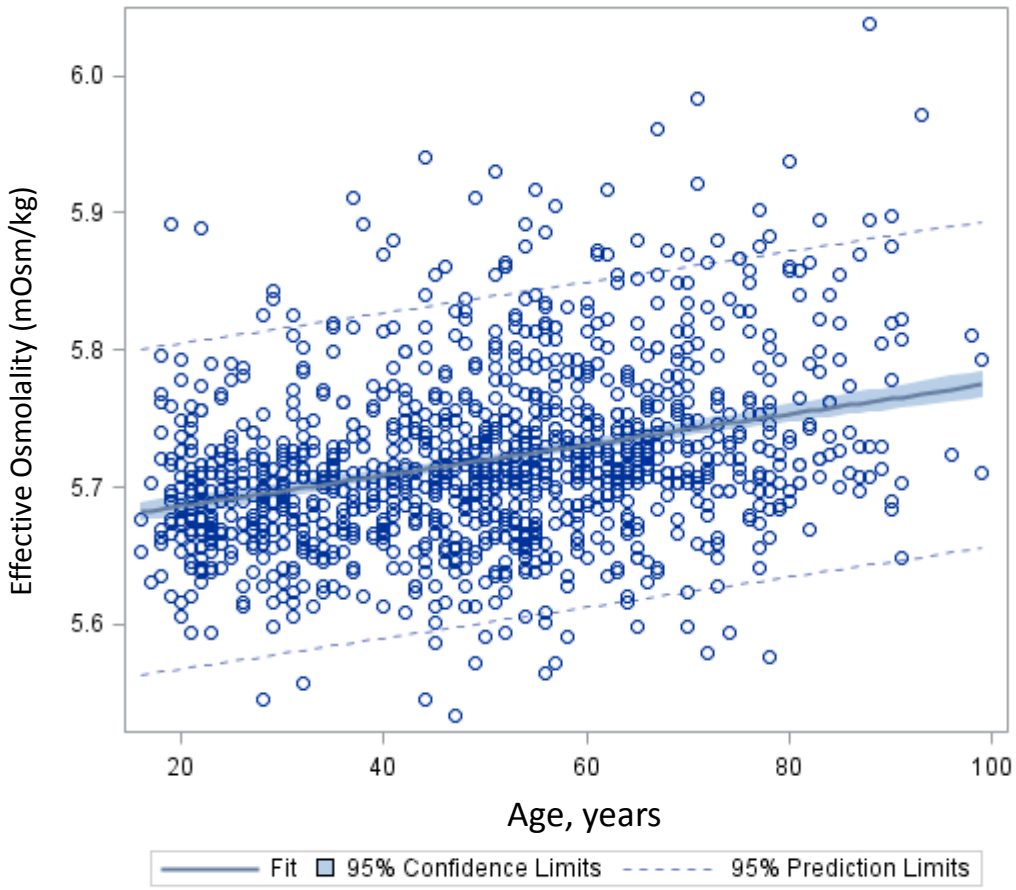

Figure 2. Association of Effective Osmolality and Age in Patients Admitted with Hyperglycemic Crises

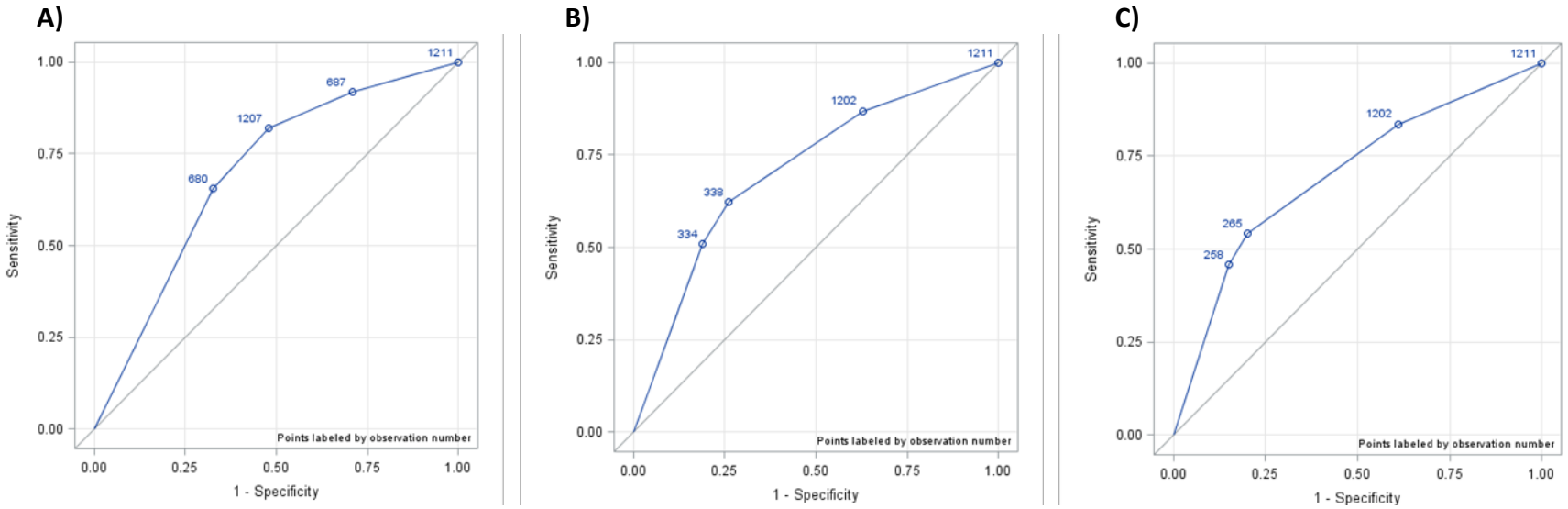

Figure 3. Age and Hyperosmolality as Predictors of Case Fatalities in Patients with Hyperglycemic Crises. A) Age > 50 and Effective Osmolality ≥ 300 mOsm/kg (c-statistic: 0.70); B) Age > 60 and Effective Osmolality ≥ 300 mOsm/kg (c-statistic: 0.71); Age > 65 and Effective Osmolality ≥ 300 mOsm/kg (c-statistic: 0.71).

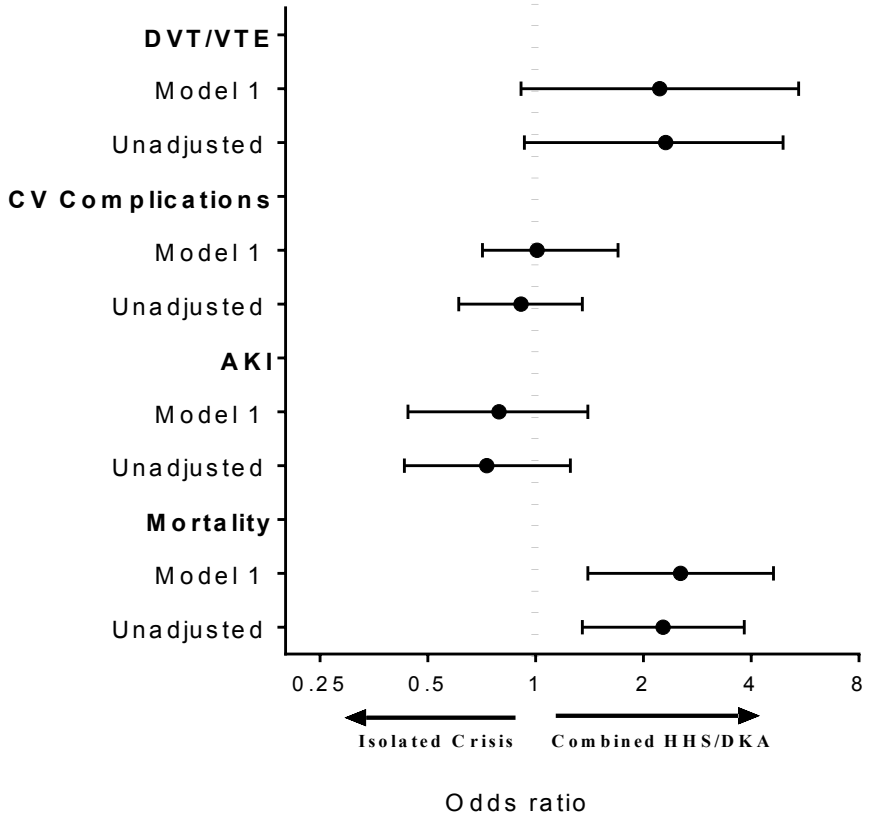

Figure 4. Forest Plot Showing Odds ratios for the Comparison of Combined DKA-HHS with Isolated Hyperglycemic Crises on Hospital Outcomes . DVT/VTE deep venous thrombosis/venous thromboembolism; **CV** cardiovascular; **AKI** acute kidney injury: defined as an elevation of creatinine of 0.5 mg/dL; **Mortality** death occurring within 30 days from admission.