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Diabetic ketoacidosis and hyperosmolar hyperglycemic state in diabetes patients with heart failure: insight from the National inpatient sample

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Abstract

Background Diabetic Ketoacidosis (DKA) and Hyperosmolar Hyperglycemic State (HHS) are acute, life-threatening hyperglycemic conditions in diabetes. We aim to assess in-hospital cardiovascular outcomes of DKA and HHS in type 2 diabetes (T2D) patients with heart failure (HF) and compare both complications.

Methods The National Inpatient Sample database was used to gather data on T2D patients admitted for HF (primary diagnosis) from 2008 to 2019. The secondary diagnoses were DKA or HHS. The outcomes investigated were mortality, ischemic stroke, acute renal failure, and cardiogenic shock.

Results Diabetes HF patients with DKA were younger than those without HHS-DKA, more likely to be females, and had a higher prevalence of coronary artery disease and chronic kidney disease. DKA was associated with higher adjusted risk of mortality (aOR = 2.75[2.42–3.13)], ischemic stroke (aOR = 2.51[1.80–3.49]), acute renal failure (aOR = 1.54[1.45–1.64]), and cardiogenic shock (aOR = 2.53[2.19–2.92]. Diabetes HF patients with HHS were also younger but had more comorbidities than those without HHS-DKA. However, HHS was only associated with an increased adjusted risk of acute renal failure (aOR = 1.59[1.49–1.70]. When both hyperglycemic groups were compared, DKA patients were younger and had fewer comorbidities. However, they had a higher adjusted risk of mortality (aOR = 2.90[2.22–3.79] and cardiogenic shock (aOR = 2.86 [2.13–3.83], but not acute renal failure or stroke.

Conclusions DKA and HHS are associated with worse cardiovascular outcomes in heart failure patients with type 2 diabetes. Further, when both conditions were compared, the mortality risk and cardiogenic shock were higher in DKA compared to HHS. Implementing tailored fluid and electrolyte management, optimizing insulin protocols, and enhancing monitoring with early intervention could be lifesaving for these high-risk patients.

Keywords Diabetic ketoacidosis, Hyperosmolar hyperglycemic state, Heart failure, Diabetes, Cardiology, Cardiovascular disease

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Introduction

Heart failure (HF) hospitalizations are a growing concern for healthcare systems worldwide due to the aging population, increased prevalence of comorbidities, and advancements in treatment that prolong life but do not eliminate the risk of HF. In 2017, it was estimated that 6.2 million patients in the United States had HF, and one-third to half of those had comorbid diabetes [1]. In a recent analysis of the National Readmission Database (NRD), an upward trend in HF hospitalizations from 2014 to 2021 and an increase in HF mortality from 2012 onwards were reported earlier this year [2]. This rising burden significantly strains healthcare resources through repeated hospital admissions, prolonged stays, and higher costs. For example, in the United States, HF is a leading cause of hospitalization among older adults, with annual costs projected to exceed $70 billion by 2030 [3].

Diabetic ketoacidosis (DKA) is a complication of type 1 and type 2 diabetes, considered an emergency and a primary cause of mortality. Recent data indicate that the incidence of DKA hospitalizations in the United States has increased [4]. The clinical picture of diabetic ketoacidosis is characterized by abnormally high blood glucose levels, elevated anion gap metabolic acidosis, and ketoacids in the urine [5]. Initially, it was thought to be associated only with type 1 diabetes. However, literature has shown that DKA also occurs in patients with type 2 diabetes who undergo stressful conditions such as acute cardiovascular conditions and infections [6]. In addition to DKA, diabetes patients might develop a similar metabolic complication known as Hyperglycemic Hyperosmolar State (HHS). The diagnostic criteria of HHS include increased plasma osmolality with glucose > 600 mg/dL and increased effective plasma osmolality > 320 mOsm/kg without ketoacidosis [7]. It is reported that HHS is diagnosed in < 1% of admitted patients, and its mortality varies from 10 to 20% [7]. Further, DKA and HHS may overlap, as reported in a recent analysis of patients admitted for acute hyperglycemia [8].

Individuals with diabetes are significantly more likely to develop heart failure than those without diabetes [9]. The underlying mechanisms involve hyperglycemia-induced oxidative stress, inflammation, and endothelial dysfunction, contributing to myocardial damage and impaired cardiac function [10]. Moreover, diabetes exacerbates existing heart failure by promoting adverse cardiac remodeling and increasing the likelihood of hospitalization and mortality [11]. Consequently, the prognosis of patients with diabetes is considerably worse compared to non-diabetic individuals [12].

Hyperglycemia on admission of patients with heart failure increases the risk of mortality, even in non-diabetes patients [13, 14]. One critical clinical gap that needs to be addressed is the limited understanding of how DKA and HHS influence the in-hospital outcomes of heart failure in patients with type 2 diabetes. Despite the known associations between diabetes, HF, and acute metabolic complications, there is a lack of large-scale comparative data on the prognostic differences between DKA and HHS in this high-risk population. This study aims to examine the in-hospital outcomes of DKA and HHS in type 2 diabetes patients with HF and compare both complications using a large database.

Patients and methods

Database

The National Inpatient Sample Database (NIS) was used to gather patient information from 2008 to 2019. This database collects data about hospitalized patients admitted to the United States and has collective information on seven million hospitalized patients. NIS was initiated in 1998 as part of the Healthcare Cost and Utilization Project (HCUP) and funded by the Agency of Healthcare Research and Quality (AHRQ) [15]. The database includes information such as race, sex, age, mortality, income, charges at the hospital, patient demographics, and outcomes [16]. Income is classified into four quartiles based on the median household income of the patients' residential ZIP code. The lowest quartile includes patients from areas where the median household income falls within the bottom 25% nationally. The low-middle quartile represents individuals from regions with median incomes between the 25th and 50th percentiles. In contrast, the high-middle quartile includes those residing in areas with median incomes between the 50th and 75th percentiles. The highest quartile comprises patients from ZIP codes, and the median household income ranks in the top 25% nationwide. The research complied with the Helsinki Declaration. Data extracted from the NIS was de-identified. The study received administrative approval from Weill Cornell Medicine-Qatar's Institutional Review Board (IRB) (determination number 18 – 00017). The same IRB committee waived patient consent. Clinical trial number: not applicable.

Diagnosis and outcomes

All diagnoses and outcomes were identified using the International Classification of Disease, Ninth Revision (ICD-9-CM) till 2014 and the 10th edition (ICD-10). The primary diagnosis was heart failure (ICD-9: 428.9, ICD-10: I50.9) with type 2 diabetes (ICD-9: 250. X, ICD-10: E11.2, E11.3:

E11.4, E11.5, E11.6, E11,7, E11.8, E11.9). The secondary diagnoses were either DKA (ICD-9: 250 – 10 and 250.12, ICD-10: E11.10, E11.11) or HHS (ICD-9: 250.20, 25022, ICD-10: E11.00, E11.01). The primary outcome was in-hospital mortality. Secondary outcomes consisted of acute renal failure, ischemic stroke, and cardiogenic

shock. All patients less than 18 years of age or with missing age, gender, and outcomes were excluded.

Plan of analysis and statistics

After merging all data for the corresponding observation period and excluding patients with missing data, we compared (i) diabetes patients with HF who develop DKA to those without DKA and (ii) patients with HHS to those without HHS. Lastly, we compared both groups. Patient-level discharge trend weights consisted of applying the DISCWT variable before 2012 and the TRENDWT variable from 2012 to 2019 to generate national estimates from sampled discharge data. These weights adjust for the sampling design, ensuring discharges represent the broader population. By applying these weights, we extrapolated the sample data to estimate the total number of discharges across the United States (as recommended by the AHRQ [17]). Variables are presented as means with standard deviation and numbers with percentages as appropriate. Comparisons of groups were performed using an independent t-test or chi-square test as deemed appropriate. Binary logistic regression was used to assess the unadjusted odds ratios, and multivariate regression analysis was used to determine the adjusted odds ratios. In every comparison, the outcomes were adjusted for baseline characteristics and comorbidities that were statistically significant between both groups, including categorical and non-categorical variables.

Further, we performed propensity score (PS) matching as a sensitivity analysis. The propensity scores were matched using the following variables: age, race, obesity, hypertension, and dyslipidemia, and were used using the 1:1 nearest neighbor matching method with a tolerance level of 0.005. The standardized mean difference (SMD) was used to assess covariate balance before and after PS matching. Further adjustment was made for all variables not included in the PS matching. SPSS® Statistics (Version 27.0, International Business Machine Corporation®, 2020) was used to analyze the data. The significance level was 5% for all the analyses.

Results

Participants

From 2008 to 2019, the NIS database recorded 1,161,015 patients with type 2 diabetes and heart failure. After excluding patients with missing data, the final study population consisted of 1,122,300 diabetic patients with heart failure (Fig. 1). Of those patients, only 5,375 developed DKA (0.47%), and 4,809 (0.43%) developed HHS.

Diabetic Ketoacidosis in diabetic heart failure

- Comparison of demographics between diabetes patients with heart failure who developed DKA and those who did not develop HHS-DKA.

Patients with DKA were younger (Table 1), where approximately 40% of patients with DKA were younger than 55 years of age, compared to only 11.7% of non-HHS-DKA patients ($p < 0.001$). More females and African Americans were in the DKA group ($p < 0.001$). DKA patients had a higher prevalence of hypertension, CAD, and chronic kidney disease (CKD) ($p < 0.001$ for all). However, the prevalence of obesity, dyslipidemia, and smoking was significantly higher in non-H HHS-DDK patients.

- Comparison of cardiovascular events between diabetes patients with heart failure who developed DKA and those who did not develop HHS-DKA.

Patients with DKA had increased adjusted odds of death (aOR = 2.75[2.42–3.13]), acute renal failure (aOR = 1.54 [1.45–1.64]), cardiogenic shock (aOR = 2.53[2.19–2.92]), and ischemic stroke (aOR = 2.51[1.80–3.49]) compared to patients without HHS-DKA (Table 2).

Hyperglycemic hyperosmolar state in diabetic heart failure

- Comparison of demographics between diabetes patients with heart failure who developed HHS and those who did not develop HHS-DKA.

Patients who developed HHS were younger (Table 3). The age group most frequently admitted with HHS was 55–64 years, comprising 28.9% of HHS patients, while the age group admitted the most without HHS-DKA was 75–84 years, at 27.2% ($p < 0.001$ for all). African Americans, females, and those with a low income were most frequent in the HHS group ($p < 0.001$ for all). Patients admitted with HHS had a higher prevalence of CKD but a lower prevalence of CAD (60.9% vs. 54.1%, 26.4% vs. 34%, HHS vs. no HHS-DKA, respectively) ($p < 0.01$ for all). In contrast, non-HHS-DKA patients had higher rates of dyslipidemia (53.4% vs. 47%), PVD (12.0% vs. 10.1%), and hypertension (51.7% vs. 45.6%).

- Comparison of cardiovascular events between diabetes patients with heart failure who developed HHS and those who did not develop HHS-DKA.

There was no difference in the risk of mortality between both groups (aOR = 1.00[0.81–1.24]) nor in the risk of cardiogenic shock (aOR = 1.05[0.84–1.32]) and ischemic

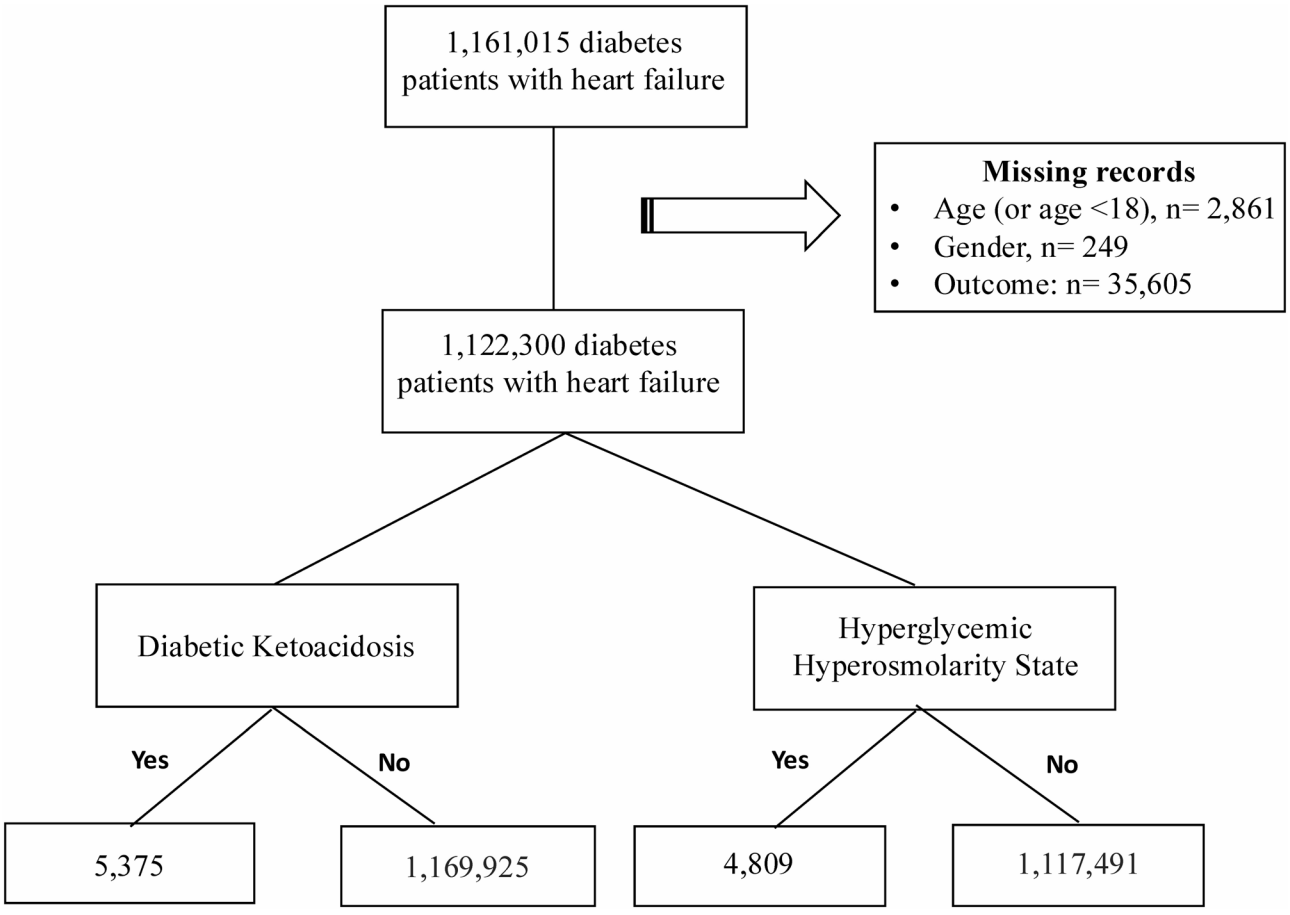

Fig. 1 Flow chart of the study

strokes (aOR = 1.45[0.88–2.39]) (Table 4). However, patients with HHS had higher odds of developing acute renal failure (aOR = 1.59[1.49–1.70]).

Comparison of DKA to HHS in diabetic heart failure

- Comparison of characteristics and outcomes between diabetes patients with heart failure who developed DKA and those who developed HHS.

Patients with DKA were younger than those with HHS (Table 5). However, patients with HHS were more likely to be African American, have a low income, and have a higher prevalence of obesity and dyslipidemia ($p < 0.001$ for all). However, the prevalence of hypertension, PVD, CKD, and CAD was higher in DKA patients ($p < 0.001$ for all). The adjusted risk of mortality (aOR = 2.90[2.22–3.79]) and cardiogenic shock (aOR = 2.86[2.13–3.83]) were higher in the DKA group (Table 6). The two groups had no significant difference in the development of acute renal failure. The odds of developing an ischemic stroke were higher in patients with DKA, but the statistical significance disappeared after adjustment, which could be due to the low number of events (aOR = 1.72[0.90–3.30]).

- Propensity score matching:

The comparison of both groups after PS matching showed that all variables included in the PS were balanced with a standardized mean difference of < 0.1 and an overall C-statistic of 67% (Table 7). Outcomes after PS matching also showed that DKA was associated with a higher risk of mortality (Propensity OR Prop OR = 2.84[1.45–5.54]) and cardiogenic shock (Prop OR = 2.22[1.08–4.58]). Further adjustment on variables that were still different after PS matching confirmed the detrimental impact of DKA as it was associated with a higher risk of mortality (adjusted propensity score aProp OR = 2.67[1.34–5.32] and cardiogenic shock (aProp OR = 2.29[1.08–4.84]).

Discussion

Long-standing diabetes has been established to affect blood vessels detrimentally, leading to microvascular and macrovascular complications [18]. Further, acute hyperglycemia and hypoglycemia are also associated with

Table 1 Comparison of demographics between diabetes patients with heart failure who developed DKA and those who did not develop HHS-DKA

		DKA *n* = 5,375	No HHS-DKA *n* = 1,169,925	*p*-value
Age	Mean (SD)	58.5 (16.0)	70.6 (12.8)	< 0.001
	< 55	2,122 (39.5%)	655,518 (11.7%)	< 0.001
	55–64	1,247 (23.2%)	1,069,493 (19.1%)	
	65–74	1,009 (18.8%)	1,510,322 (27.0%)	
	75–84	764 (14.2%)	1,520,327 (27.2%)	
	> 84	232 (4.3%)	830,868 (14.9%)	
Gender	Male	2,433 (45.3%)	2,850,455 (51.0%)	< 0.001
	Female	2,942 (54.7%)	2,736,072 (49.0%)	
Race	White	2,809 (54.6%)	3,245,426 (61.9%)	< 0.001
	African American	1,463 (28.4%)	1,176,767 (22.4%)	
	Hispanic	547 (10.6%)	530,598 (10.1%)	
	Asian	149 (2.9%)	119,600 (2.3%)	
	Native American	35 (0.7%)	33,472 (0.6%)	
	Not Specified	139 (2.7%)	136,548 (2.6%)	
Income	Low	1,981 (37.7%)	1,954,617 (35.7%)	0.140
	Low-Mid	1,336 (25.5%)	1,460,947 (26.7%)	
	High-Mid	1,118 (21.3%)	1,210,325 (22.1%)	
	High	814 (15.5%)	854,597 (15.6%)	
Comorbidities	Obesity	928 (17.3%)	1,625,815 (29.1%)	< 0.001
	Smoking	1,324 (24.6%)	1,469,904 (26.3%)	0.005
	Dyslipidemia	2,238 (41.6%)	2,984,568 (53.4%)	< 0.001
	Hypertension	3,200 (59.5%)	2,889,604 (51.7%)	< 0.001
	PVD	681 (12.7%)	668,018 (12.0%)	0.107
	VHD	203 (3.8%)	535,119 (9.6%)	< 0.001
	CKD	3,413 (63.5%)	3,021,530 (54.1%)	< 0.001
	CAD	2,136 (39.7%)	1,897,671 (34.0%)	< 0.001

CAD = coronary artery disease, CKD = chronic kidney disease, PVD = peripheral vascular disease, VHD = valvular heart disease

Table 2 Comparison of cardiovascular events between diabetes patients with heart failure who developed DKA and those who did not develop HHS-DKA

	No HHS-DKA *n* (%)	DKA *n* (%)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
Mortality				
No	5,454,399 (97.6%)	5,126 (95.4%)	Ref	Ref
Yes	132,129 (2.4%)	249 (4.6%)	2.00 (1.76–2.28)	2.75 (2.42–3.13)
Acute renal failure				
No	3,975,556 (71.2%)	3,312 (61.6%)	Ref	Ref
Yes	1,610,972 (28.8%)	2,063 (38.4%)	1.54 (1.46–1.62)	1.54 (1.45–1.64)
Cardiogenic shock				
No	5,513,720 (98.7%)	5,155 (95.9%)	Ref	Ref
Yes	72,808 (1.3%)	219 (4.1%)	3.22 (2.81–3.69)	2.53 (2.19–2.92)
Ischemic stroke				
No	5,572,490 (99.7%)	5,339 (99.3%)	Ref	Ref
Yes	14,037 (0.3%)	36 (0.7%)	2.65 (1.91–3.69)	2.51 (1.80–3.49)

*Adjusted for age (categorical), gender, race, obesity, smoking, dyslipidemia, hypertension, peripheral vascular disease, valvular heart disease, chronic kidney disease, and coronary artery disease

adverse cardiovascular outcomes [19–21]. In this study, we showed that DKA was associated with a higher risk of mortality, ischemic stroke, acute renal failure, and cardiogenic shock in HF and type 2 diabetes. In contrast, HHS was only associated with an increased risk of acute renal failure.

While all studies reported an increased risk of death in patients who develop HHS or DKA, the rates of mortality are discordant. In a retrospective, hospital-based

Table 3 Comparison of demographics between diabetes patients with heart failure who developed HHS and those who did not develop HHS-DKA

		HHS *n* = 4,809	No HHS *n* = 1,117,491	*p*-value
Age	Mean (SD)	64.1 (13.1)	70.6 (12.8)	< 0.001
	< 55	1,101 (22.9%)	656,539 (11.8%)	< 0.001
	55–64	1,391 (28.9%)	1,069,349 (19.1%)	
	65–74	1,274 (26.5%)	1,510,057 (27.0%)	
	75–84	717 (14.9%)	1,520,374 (27.2%)	
	> 84	326 (6.8%)	830,774 (14.9%)	
Gender	Male	2,367 (49.2%)	2,850,522 (51.0%)	0.013
	Female	2,442 (50.8%)	2,736,571 (49.0%)	
Race	White	2,192 (47.6%)	3,246,043 (61.9%)	< 0.001
	African American	1,499 (32.6%)	1,176,730 (22.4%)	
	Hispanic	643 (14.0%)	530,503 (10.1%)	
	Asian	113 (2.5%)	119,636 (2.3%)	
	Native American	15 (0.3%)	33,492 (0.6%)	
	Not Specified	141 (3.1%)	136,545 (2.6%)	
Income	Low	1,891 (40.0%)	1,954,707 (35.7%)	< 0.001
	Low-Mid	1,217 (25.8%)	1,461,067 (26.7%)	
	High-Mid	1,050 (22.2%)	1,210,393 (22.1%)	
	High	565 (12.0%)	854,846 (15.6%)	
Comorbidities	Obesity	1,448 (30.1%)	1,625,295 (29.1%)	0.120
	Smoking	1,248 (25.9%)	1,469,980 (26.3%)	0.572
	Dyslipidemia	2,260 (47.0%)	2,984,546 (53.4%)	< 0.001
	Hypertension	2,194 (45.6%)	2,890,610 (51.7%)	< 0.001
	PVD	484 (10.1%)	668,215 (12.0%)	< 0.001
	VHD	487 (10.1%)	534,835 (9.6%)	0.192
	CKD	2,931 (60.9%)	3,022,012 (54.1%)	< 0.001
	CAD	1,268 (26.4%)	1,898,485 (34.0%)	< 0.001

CAD = coronary artery disease, CKD = chronic kidney disease, PVD = peripheral vascular disease, VHD = valvular heart disease

Table 4 Comparison of cardiovascular events between diabetes patients with heart failure who developed HHS and those who did not develop HHS-DKA

	No HHS-DKA *n* (%)	HHS *n* (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Mortality				
No	5,454,813 (97.6%)	4,712 (98.0%)	Ref	Ref
Yes	132,281 (2.4%)	97 (2.0%)	0.85 (0.69–1.03)	1.00 (0.81–1.24)
Acute renal failure				
No	3,976,024 (71.2%)	2,844 (59.1%)	Ref	Ref
Yes	1,611,069 (28.8%)	1,965 (40.9%)	1.70 (1.61–1.81)	1.59 (1.49–1.70)
Cardiogenic shock				
No	5,514,152 (98.7%)	4,723 (98.2%)	Ref	Ref
Yes	72,942 (1.3%)	86 (1.8%)	1.37 (1.11–1.69)	1.05 (0.84–1.32)
Ischemic stroke				
No	5,573,036 (99.7%)	4,793 (99.7%)	Ref	Ref
Yes	14,057 (0.3%)	16 (0.3%)	1.23 (0.79–2.13)	1.45 (0.88–2.39)

*Adjusted for age (categorical), gender, race, income, dyslipidemia, hypertension, valvular heart disease, chronic kidney disease, and coronary artery disease

cohort, Pasquel et al. reported that in-hospital mortality for HHS patients was 5%, and that of DKA was 3% [22]. A different study at a tertiary teaching hospital in Brazil showed that the DKA-related mortality rate was 5.8% in patients with DKA [23]. It was also found that the degree of severity of DKA was directly proportional to mortality. Furthermore, in a retrospective pilot study that involved 1527 patients with DKA, the mortality rate in moderate and severe DKA was 13.3% and 26%, respectively [24]. In the United States, the mortality of hospitalized patients with a primary diagnosis of HHS was reported to be 1.44% in 2008, which was significantly higher than in the

Table 5 Comparison of characteristics between diabetes patients with heart failure who developed DKA and those who developed HHS

		DKA *n* = 5,375	HHS *n* = 4,809	*p*-value
Age	Mean (SD)	58.5 (16.0)	64.1 (13.1)	< 0.001
	< 55	2,102 (39.7%)	1,101 (22.9%)	< 0.001
	55–64	1,222 (23.1%)	1,391 (28.9%)	
	65–74	990 (18.7%)	1,274 (26.5%)	
	75–84	754 (14.2%)	717 (14.9%)	
	> 84	232 (4.4%)	326 (6.8%)	
Gender	Male	2,389 (45.1%)	2,367 (49.2%)	< 0.001
	Female	2,911 (54.9%)	2,442 (50.8%)	
Race	White	2,785 (55.0%)	2,192 (47.6%)	< 0.001
	African American	1,418 (28.0%)	1,499 (32.6%)	
	Hispanic	542 (10.7%)	643 (14.0%)	
	Asian	149 (2.9%)	113 (2.5%)	
	Native American	35 (0.7%)	15 (0.3%)	
	Not Specified	139 (2.7%)	141 (3.1%)	
Income	Low	1,936 (37.4%)	1,891 (40.0%)	< 0.001
	Low-Mid	1,327 (25.6%)	1,217 (25.8%)	
	High-Mid	1,098 (21.2%)	1,050 (22.2%)	
	High	814 (15.7%)	565 (12.0%)	
Comorbidities	Obesity	908 (17.1%)	1,448 (30.1%)	< 0.001
	Smoking	1,309 (24.7%)	1,248 (25.9%)	0.148
	Dyslipidemia	2,209 (41.7%)	2,260 (47.0%)	< 0.001
	Hypertension	3,146 (59.4%)	2,194 (45.6%)	< 0.001
	PVD	676 (12.8%)	484 (10.1%)	< 0.001
	VHD	203 (3.8%)	487 (10.1%)	< 0.001
	CKD	3,353 (63.3%)	2,931 (60.9%)	0.016
	CAD	2,107 (39.7%)	1,268 (26.4%)	< 0.001

CAD = coronary artery disease, CKD = chronic kidney disease, PVD = peripheral vascular disease, VHD = valvular heart disease

Table 6 Comparison of cardiovascular events between diabetes heart failure patients who developed DKA and those who developed HHS

	DKA *n* (%)	HHS *n* (%)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)	Propensity score adjusted OR† (95% CI)
Mortality					
No	5,052 (95.3%)	4,712 (98.0%)	Ref	Ref	Ref
Yes	249 (4.7%)	97 (2.0%)	2.40 (1.89–3.05)	2.90 (2.22–3.79)	2.67 (1.34–5.32)
Acute renal failure					
No	3,263 (61.6%)	2,844 (59.1%)	Ref	Ref	Ref
Yes	2,037 (38.4%)	1,965 (40.9%)	0.90 (0.83–0.98)	1.08 (0.98–1.18)	1.02 (0.81–1.28)
Cardiogenic shock					
No	5,081 (95.9%)	4,723 (98.2%)	Ref	Ref	Ref
Yes	219 (4.1%)	86 (1.8%)	2.38 (1.85–3.07)	2.86 (2.13–3.83)	2.29 (1.08–4.84)
Ischemic stroke					
No	5,265 (99.3%)	4,793 (99.7%)	Ref	Ref	Ref
Yes	36 (0.7%)	16 (0.3%)	2.07 (1.14–3.76)	1.72 (0.90–3.30)	1.73 (0.41–7.22)

* Adjusted on age (categorical), gender, race, income, obesity, dyslipidemia, hypertension, peripheral vascular disease, valvular heart disease, chronic kidney disease, and coronary artery disease

† Propensity score matching on the following variables: age(categorical), race, obesity, hypertension, and dyslipidemia. Further adjustment was made on gender, income, smoking, coronary artery disease, valvular heart disease, chronic kidney disease, and coronary artery disease

Table 7 Comparison of characteristics between diabetes patients with heart failure who developed DKA and those who developed HHS after propensity score matching

		DKA *n* = 694	HHS *n* = 694	*p*-value	SMD
Age	< 55	200 (28.8%)	196 (28.2%)	0.987	0.011
	55–64	191 (27.5%)	187 (26.9%)		0.011
	65–74	165 (23.8%)	169 (24.4%)		-0.011
	75–84	102 (14.7%)	102 (14.7%)		0.000
	> 84	36 (5.2%)	40 (5.8%)		-0.012
Gender	Male	407 (58.6%)	348 (50.1%)	0.001	
	Female	287 (41.4%)	346 (49.9%)		
Race	White	349 (50.3%)	353 (50.9%)		0.010
	Black	232 (33.4%)	227 (32.7%)		-0.012
	Hispanic	79 (11.4%)	79 (11.4%)		0.000
	Asian	17 (2.4%)	16 (2.3%)		-0.005
	Native American	17(2.5%)	19 (2.7%)		0.000
	Not Specified	17 (2.4%)	15 (2.2%)		
Income	Low	254 (37.6%)	278 (40.8%)	0.078	
	Low-Mid	178 (26.3%)	171 (25.1%)		
	High-Mid	136 (20.1%)	154 (22.6%)		
	High	108 (16.0%)	79 (11.6%)		
Comorbidities	Obesity	148 (21.3%)	140 (26.5%)	0.596	0.022
	Smoking	174 (25.1%)	184 (26.5%)	0.540	
	Dyslipidemia	315 (45.4%)	307 (44.2%)	0.666	0.020
	Hypertension	377 (54.3%)	377 (54.3%)	0.999	0.000
	PVD	100 (14.4%)	75 (10.8%)	0.043	
	VHD	26 (3.7%)	65 (9.4%)	< 0.001	
	CKD	448 (64.6%)	413 (59.5%)	0.053	
	CAD	283 (40.8%)	205 (29.5%)	< 0.001	

CAD = coronary artery disease, CKD = chronic kidney disease, PVD = peripheral vascular disease, VHD = valvular heart disease, SMD = standardized mean difference

general population [25]. Additionally, from 2008 to 2018, hospitalization rates with HHS have increased, with people of the white race comprising the majority of admissions [25]. These findings are consistent with our results, which showed that people from the white race were admitted the most over the 12 years of the study period.

When comparing the two groups in the context of heart failure and diabetes, mortality risk and cardiogenic shock were higher in patients with DKA than in those with HHS. This indicates that cardiovascular triggers may play a less significant role in the elevated mortality rate observed in HHS compared to DKA. Although the exact mechanisms remain unclear, the higher mortality in DKA could be attributed to profound acidosis, more severe electrolyte imbalances, and the complexities of fluid management in the context of heart failure [26]. Additionally, limited data exist on the impact of heart failure on the management of DKA, and current guidelines provide no specific recommendations for this scenario. Furthermore, the acute and dramatic presentation of DKA hospitalizations may lead clinicians to underestimate the influence of a patient's history of heart failure on the outcomes of their DKA episode. As a result, managing patients with a history of heart failure who develop DKA requires meticulous care, particularly with cautious and closely monitored fluid administration.

Using the same database and a single University hospital cohort, Agarwal et al. recently showed that nearly 4% of patients with DKA and HHS have heart failure on admission. Further, the odds of in-hospital mortality almost doubled in those patients [27], concordant with our results. Heart failure and DKA or HHS are interconnected through complex pathophysiological mechanisms. DKA and HHS can precipitate HF due to their profound effects on fluid balance, electrolyte homeostasis, and metabolic status [28, 29]. In DKA, severe dehydration and electrolyte imbalances, particularly hypokalemia, can exacerbate underlying heart conditions and lead to worsening of HF [30]. HHS, characterized by extreme hyperglycemia and dehydration without significant ketosis, can also strain the cardiovascular system, leading to HF exacerbations due to increased blood viscosity and subsequent increased cardiac workload [29]. Conversely, HF can increase the risk of DKA and HHS by impairing renal function, which complicates glucose regulation, and by promoting systemic inflammation, which can trigger metabolic decompensation in diabetic patients [31].

DKA has been associated with acute renal failure and could lead to long-term complications such as diabetic nephropathy [32]. Consistent with that, our results show that patients with DKA are at an increased risk of acute renal failure. Acute renal failure was also strongly associated with HHS, which is also consistent with our results that showed the odds of developing acute renal failure are higher in patients with HHS and underlying heart failure than in patients without HHS [33]. Compared to males, females were admitted more than males with DKA and HHS in Emory hospitals from 2005 to 2015 (53% in DKA and 50% in HHS). This is also consistent with our results, which show that females were admitted more in both groups [22].

We acknowledge the limitations of this study. The NIS represents all hospital admissions in the United States, so conclusions cannot be generalized to the rest of the world. Diagnoses and outcomes rely on the ICD-10 coding systems; hence, the possibility of erroneous coding or misclassification, particularly those of DKA or HHS, cannot be ruled out. A recent study that assessed the diagnostic accuracy of the ICD-10 code of DKA found a positive predictive value of almost 70%, which might be even lower in patients with HHS [34]. Further, DKA and HHS may overlap by about 38% in acute life-threatening hyperglycemia [8]. Additionally, only selecting patients with a primary diagnosis of HF may underestimate the number of HF admissions since many patients could be coded with a primary diagnosis of other cardiac and pulmonary diseases, such as pneumonia, for example, but have concomitant acute heart failure [35]. Missing data were not imputed, which could affect the precision of the results as it decreases the statistical power. One of the limitations of our study is the absence of patients' medications at admission or during their hospital stay. Other important parameters, such as HBA_{1C}, duration of diabetes, the ejection fraction, and the etiology of heart failure, were also unavailable. These factors act as potentially major confounding variables in our analysis. Finally, and probably most importantly, causality could not be established without randomized clinical trials; hence, our study only shows an association between acute life-threatening hyperglycemia and worse cardiovascular outcomes. On the other hand, this study provides outcome data that has been collected under strict and specific standards across different hospitals in the US. After weighting, the data fairly represents the US population, thus providing a very large sample for analyzing rare conditions such as DKA and HHS.

The burden of diabetes on the healthcare system poses a need to investigate associations with adverse outcomes in acute cardiac conditions to facilitate targeted interventions and minimize morbidity and mortality. Our analysis could benefit healthcare workers who would pay close attention to patients hospitalized with DKA and HHS and underlying heart failure and to warning signs and prevention methods of those acute complications. Since this study only looked at in-hospital patients, a future direction would be to consider the etiology and outcome of readmission from HHS and DKA patients in follow-up heart failure studies. Treatment strategies could include tailored fluid and electrolyte management, optimized insulin protocols, and enhanced monitoring and early intervention. Further research is needed to elucidate the pathophysiological mechanisms linking acute life-threatening hyperglycemia with increased mortality in heart failure. Investigations might focus on how acid-base imbalances, electrolyte shifts, and inflammatory responses interact with myocardial stress and arrhythmogenic potential. Randomized controlled trials may be warranted to test modified treatment protocols for those hyperglycemic conditions in the context of heart failure. This could include evaluating different fluid regimens, insulin dosing strategies, or the early use of cardioprotective agents to see if these adjustments improve survival rates.

Conclusion

Our analysis demonstrates that both Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic State are linked to worse cardiovascular outcomes in heart failure patients with type 2 diabetes. However, when comparing the two conditions, DKA is associated with a higher risk of mortality and cardiogenic shock than HHS.

Abbreviations

CVD Cardiovascular disease
DKA Diabetic ketoacidosis
HF Heart failure
HHS Hyperosmolar Hyperglycemic State

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Author contributions

CAK conceived the study concept and design. HA acquired data and performed statistical analyses with SD and ZM. HA, AJ, JAS, and CAK analyzed and interpreted data. HA wrote the first draft and conducted the literature search. All authors contributed to the critical revision of the manuscript. CAK is the guarantor of this work and, as such, has full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript.

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Data availability

Analyzed data are available upon reasonable request from the corresponding author.

Declarations

Ethics approval and consent to participate
The research complied with the Helsinki Declaration. Data extracted from the NIS was de-identified. The study received administrative approval from Weill Cornell Medicine- Qatar's Institutional Review Board (IRB) (determination number 18 – 00017). The same IRB committee waived patient consent. Clinical trial number: not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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