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ORIGINAL ARTICLE

Clinical profile of patients with diabetic ketoacidosis and hyperglycemic hyperosmolar syndrome in Japan: a multicenter retrospective cohort study

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Abstract

Introduction Diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar syndrome (HHS) are life-threatening complications of diabetes mellitus. Their clinical profiles have not been fully investigated.

Methods A multicenter retrospective cohort study was conducted in 21 acute care hospitals in Japan. Patients included were adults aged 18 or older who had been hospitalized from January 1, 2012, to December 31, 2016 due to DKA or HHS. The data were extracted from patient medical records. A four-group comparison (mild DKA, moderate DKA, severe DKA, and HHS) was performed to evaluate outcomes.

Results A total of 771 patients including 545 patients with DKA and 226 patients with HHS were identified during the study period. The major precipitating factors of disease episodes were poor medication compliance, infectious diseases, and excessive drinking of sugar-sweetened beverages. The median hospital stay was 16 days [IQR 10–26 days]. The intensive care unit (ICU) admission rate was 44.4% (mean) and the rate at each hospital ranged from 0 to 100%. The in-hospital mortality rate was 2.8% in patients with DKA and 7.1% in the HHS group. No significant difference in mortality was seen among the three DKA groups.

Conclusions The mortality rate of patients with DKA in Japan is similar to other studies, while that of HHS was lower. The ICU admission rate varied among institutions. There was no significant association between the severity of DKA and mortality in the study population.

Trial Registration This study is registered in the UMIN clinical Trial Registration System (UMIN000025393, Registered 23th December 2016).

Keywords Diabetes · Hyperglycemic emergencies · Hyperglycemic crisis · Intensive care · Epidemiology · Prognosis

Introduction

Hyperglycemic emergencies are serious acute complications of diabetes that include diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar syndrome (HHS) [1]. DKA is characterized by hyperglycemia, metabolic acidosis, and ketonemia while HHS presents with severe hyperglycemia, high serum osmolality, and dehydration [2], which require close monitoring of electrolytes and vital signs. Clinical characteristics of patients with hyperglycemic emergencies have been investigated in several studies, although not thoroughly described. Typically, DKA is common among young patients with type 1 diabetes while HHS often occurs in the elderly with type 2 diabetes. Common precipitating factors of hyperglycemic emergencies are infection, noncompliance, or acute conditions such as stroke, myocardial

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infarction, and trauma [3, 4]. Additionally, many drugs such as corticosteroids and antipsychotic medications have been reported to impair glucose tolerance [5]. These factors affect not only the pathophysiology of the hyperglycemic crisis but also the overall prognosis. Although these precipitating factors have been suggested, the actual prevalence of these factors in patients with hyperglycemic emergencies is unknown.

The epidemiology and management of patients with acute hyperglycemic emergencies vary among countries. The reported mortality rate of patients with DKA in developed countries ranges from 0.16% to 4.1% [6–8], whereas in developing countries it is higher [9, 10]. HHS-related mortality is reported to be 10–20%, approximately 10 times higher than that of DKA [3, 11]. Trends in the rate of hospitalization and use of intensive care for patients with DKA and HHS vary by country and variation exists even among institutions in the same region [12, 13]. Interestingly, these variations were reported not to affect the length of hospital stay or mortality of the patients [13]. Currently, there is no consensus regarding whether to use the ICU for the care of such patients, leaving optimal resource allocation in controversy [14]. Some consider that emergency departments or even general wards can provide an appropriate level of care with improved cost-effectiveness compared to admission to the intensive care unit (ICU) [15].

The aim of this study is to provide a detailed clinical profile of patients with DKA and HHS and the use of the ICU for these patients in Japan. We particularly focused on the patients' background, short-term outcomes, and medical resources used.

Methods

Study design

A retrospective cohort study was conducted to investigate the clinical characteristics of patients with hyperglycemic emergencies. Participating facilities included 21 acute care hospitals in Japan. This is a part of the CLORINE study (The effect of fluid therapy on kidney function in hyperglycemic emergencies, a multicenter retrospective study), registered in the UMIN clinical trial registration system (UMIN000025393).

Patients

Patients included in the study were adults aged 18 years or older admitted to the hospital due to DKA or HHS from January 1, 2012, to December 31, 2016. Individuals who received treatment in the emergency department were also included. Patients were initially identified according to ICD-10 coding. Subsequently, diagnoses were confirmed with laboratory data according to the criteria of the American Diabetes Association as follows:

DKA (meets all below)

- Serum glucose > 250 mg/dl
- pH of arterial blood gas (ABG) ≤ 7.30 or HCO_3 ≤ 18 mmol/L
- Positive urine or blood ketone

HHS (meets all below)

- Serum glucose > 600 mg/dl
- pH of ABG > 7.30 and HCO_3 > 18 mmol/L
- Negative or low positive urine/blood ketone

Patients with DKA were also classified into three groups: severe (ABG pH < 7.0 or HCO_3 < 10 mmol/L), mild (ABG pH > 7.25 and HCO_3 < 10 mmol/L), and moderate (neither mild nor severe) for analysis. Exclusion criteria were missing data necessary for diagnosis.

Outcomes and data collection

The primary outcome was in-hospital mortality from any cause. Secondary outcomes were serious complications including cardiovascular events, infection, length of hospital stay and ICU stay, and use of intensive therapy (ventilator, vasopressors, and renal replacement therapy).

Data were obtained through patient medical records in participating facilities. Data extraction for each patient included patient characteristics, type, duration, and treatment of diabetes, complications of diabetes, precipitating factors for hyperglycemic emergencies (including factors associated with patient behavior, acute medical events, and medications affecting diabetes), admission route and type of ward, complications during hospitalization, and requirement for intensive therapy. Medications affecting diabetes were defined as corticosteroids, atypical antipsychotics, thiazides, quinolones, and phenytoin. Complications were limited to newly diagnosed adverse events during hospitalization, excluding comorbidities that existed prior to admission. For patients who died, causes of death were also recorded.

Statistical analysis

Continuous variables were presented with a mean (± SD: standard deviation) and median (IQR: interquartile range) as appropriate. Categorical variables were expressed with percentages. Clinical features and outcomes were compared among the four groups (HHS and the 3 groups of DKA stratified by severity). The precipitating factors prior to

hyperglycemic emergencies were also compared between the patients with known diabetes and new-onset diabetes. The type of admission ward is aggregated by each institution. On the basis of the normality of the data, continuous variables were analyzed with the ANOVA or the Kruskal–Wallis test for four-group comparisons. For categorical data, the chi-square test was used. *P* value < 0.05 was considered statistically significant. All analyses were performed using R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

During the study period, 771 patients were admitted to participating hospitals with DKA (545 patients) and HHS (226 patients). Among patients with DKA, 19% (n = 104) were mild, 23.7% (n = 129) were moderate, and 57.2% (n = 312) were severe. The mean age of the patients was 58.3 years (SD 19.3) and the proportion of males was 54.7%. Table 1 shows the baseline characteristics of the patients. Compared with the DKA groups, patients with HHS were older (52.7 years vs. 71.9 years, $p < 0.001$) and had more comorbidities, including hypertension (31.9% vs. 57.2%, $p < 0.001$), ischemic heart disease (4.9% vs. 16.1%, $p < 0.001$), chronic heart failure (3.6% vs. 18.0%, $p < 0.001$), and stroke (5.8% vs. 25.0%, $p < 0.001$).

The duration of diabetes varied among the patients. While the proportion of new onset diabetes was 23.6%, 32.9% of the patients had been treated for more than 10 years. Type 2 diabetes was prevalent in the HHS group (81.8%) and type 1 diabetes was most frequent in the severe DKA group (52.5%). Regarding treatment before admission, the proportion of patients receiving insulin therapy is higher in DKA groups, while oral medication was common in the HHS group. A total of 284 (36.8%) patients had taken no medications to treat diabetes mellitus prior to hospital admission.

In terms of factors precipitating a hyperglycemic emergency, poor adherence to treatment, infectious diseases, and excessive intake of sugar-sweetened beverages were major factors (Table 2). Poor adherence was most prevalent in the DKA groups (47.7%) and infectious diseases were the most frequent factor in the HHS group (42.7%). Some patients took medications that could increase the severity of diabetes. Corticosteroids were prescribed for 6.2% of patients with HHS, and the proportion was higher than in patients with DKA. As shown in Supplemental Table, excessive drinking of sugar sweetened beverages was seen more frequently in new-onset diabetes cases in comparison with known diabetics (41.7% vs. 19.0%, $p < 0.001$). Whereas infectious disease is more prevalent in known diabetics (26.1% vs. 37.8%, $p = 0.007$).

Outcomes during hospital admission are shown in Table 3. The median hospital stay was 16 days [IQR 10–26 days] and was longer in the HHS group compared to the DKA groups (19.5 days vs. 15 days, $p < 0.001$). The ICU admission rate was 44.4% on average and highest in the severe DKA group (55.1%), with a p value of < 0.001. ICU admission rate in each hospital ranged from 0 to 100% (Fig. 1). The median ICU stay was 3 days, the same for all groups.

With regard to intensive therapy, 52 (6.7%) patients were mechanically ventilated, 68 (8.8%) were treated with vasopressors, and 24 (3.1%) required RRT. Six (0.7%) patients needed maintenance dialysis on discharge. Overall, patients in the severe DKA group required mechanical ventilation more frequently compared to the other groups ($p < 0.001$).

In the entire cohort, 31 (4%) patients died during admission. The in-hospital mortality rate was 2.8% in patients with DKA and 7.1% in the HHS group, respectively. No significant difference was seen among the DKA groups ($p = 0.94$). The most common complication was infection (18%), followed by pulmonary edema (2.7%), stroke (2.1%), ventricular arrhythmia (1.6%), and deep vein thrombosis (1%). Figure 2 shows in-hospital events (mortality + complications) according to the groups. The rate of events was higher in the HHS group than in other groups and was similar among the 3 DKA groups (not proportional to severity).

The causes of mortality are presented in Table 4. Twenty (65%) of 31 deaths were due to infection. Other causes included stroke, pulmonary edema, acute coronary syndrome, and ventricular arrhythmia.

Discussion

The present study describes the clinical characteristics of patients with hyperglycemic crises using data obtained from multiple institutions in Japan. The mortality rate of patients with DKA and HHS was 2.8% and 7.1%, respectively. No linear relationship was found between the severity of DKA and mortality. Major precipitating factors of acute episodes were poor adherence to treatment regimens, infections, and intake of excessive sugar-sweetened beverages. The rate of ICU admission varied among institutions.

The mortality rate of patients with DKA and HHS varies among countries and has changed over time. In recent publications, the mortality rate of patients with DKA has been reported from 0.16% to 4.1% [6–8], whereas that of HHS was between 10 and 20% [3, 11]. The results of the present study are similar to previous reports for DKA, but the mortality rate of patients with HHS in the present study was lower. The reason for this difference is unclear but could be explained by global trends in improving diabetes

Table 1 Patient baseline characteristics

	Mild DKA (n = 104)	Moderate DKA (n = 129)	Severe DKA (n = 312)	HHS (n = 226)	*P* value
Age, years, mean (SD)	56.0 (18.8)	56.3 (18.7)	49.9 (17.1)	71.9 (14.9)	< 0.001
Female gender, n (%)	47 (45.2)	60 (46.5)	141 (45.2)	103 (45.6)	0.99
Body-mass index, mean (SD)	23.3 (6.1)	22.1 (5.0)	21.9 (4.8)	21.6 (4.7)	0.04
Diabetic retinopathy, n (%)	20 (27.8)	26 (28.6)	40 (18.4)	37 (28.9)	0.07
Diabetic nephropathy, n (%)	32 (41.6)	25 (26.6)	75 (32.1)	50 (35.0)	0.20
Diabetic neuropathy, n (%)	22 (31.0)	20 (22.0)	68 (30.9)	26 (20.5)	0.10
Hypertension, n (%)	44 (45.8)	43 (35.8)	73 (25.9)	123 (57.2)	< 0.001
Dyslipidemia, n (%)	26 (27.1)	34 (29.3)	62 (21.7)	56 (27.2)	0.32
Ischemic heart disease, n (%)	4 (4.3)	8 (7.1)	12 (4.2)	33 (16.1)	< 0.001
Chronic heart failure, n (%)	3 (3.2)	4 (3.5)	11 (3.8)	37 (18.0)	< 0.001
Stroke, n (%)	11 (11.7)	8 (7.1)	10 (3.5)	52 (25.0)	< 0.001
Peripheral artery disease, n (%)	3 (3.3)	2 (1.8)	4 (1.4)	2 (1.0)	0.54
Mental disorder, n (%)	16 (15.4)	21 (16.3)	51 (16.3)	20 (8.8)	0.07
Duration of diabetes, n (%)					< 0.001
New onset	29 (28.2)	34 (26.6)	79 (25.3)	40 (17.8)	
< 1 year	2 (1.9)	8 (6.2)	10 (3.2)	8 (3.6)	
1–5 years	9 (8.7)	11 (8.6)	47 (15.1)	12 (5.3)	
5–10 years	9 (8.7)	14 (10.9)	38 (12.2)	19 (8.4)	
> 10 years	39 (37.9)	39 (30.5)	98 (31.4)	78 (34.7)	
Unknown	15 (14.6)	22 (17.2)	40 (12.8)	68 (30.2)	
Fulminant type 1 diabetes, n (%)	4 (3.9)	8 (6.2)	25 (8.2)	1 (0.4)	0.001
Type of diabetes, n (%)					< 0.001
Type 1	37 (35.9)	54 (42.2)	163 (52.2)	24 (10.7)	
Type 2	62 (60.2)	71 (55.5)	126 (40.4)	184 (81.8)	
Others	2 (1.9)	2 (1.6)	12 (3.8)	7 (3.1)	
Unknown	2 (1.9)	1 (0.8)	11 (3.5)	10 (4.4)	
Treatment before admission, n (%)					< 0.001
Insulin	29 (27.9)	50 (38.8)	120 (38.6)	31 (13.8)	
Oral medications	18 (17.3)	19 (14.7)	30 (9.6)	79 (35.3)	
Insulin + Oral medications	12 (11.5)	12 (9.3)	47 (15.1)	28 (12.5)	
No medication	45 (43.3)	46 (35.7)	110 (35.4)	83 (37.1)	
Unknown	0 (0.0)	2 (1.6)	4 (1.3)	3 (1.3)	
Admission route, n (%)					0.17
Emergency department	77 (74.0)	101 (78.3)	252 (80.8)	179 (79.2)	
General outpatient	13 (12.5)	18 (14.0)	24 (7.7)	29 (12.8)	
Transfer from other hospitals	14 (13.5)	10 (7.8)	36 (11.5)	18 (8.0)	

DKA Diabetic ketoacidosis, *HHS* Hyperosmolar hyperglycemic syndrome, *SD* Standard deviation

P values are results of the ANOVA or the Kruskal–Wallis test for four-group comparisons

care. Although there have been few studies on the prognosis of HHS recently, a report based on a US national survey showed that the mortality rate of patients with DKA was decreasing while hospitalization was increasing [7]. This improvement might be attributed to increased awareness of the disease and adaption of established guidelines for the treatment of patients with hyperglycemic crises.

It is unclear if severity of DKA correlates with mortality or not. While some studies indicated an association between them [8, 16], other studies found that other factors were more important than DKA severity. For example, a previous study of a prediction model for the prognosis of patients with DKA concluded that coexisting severe diseases are the most significant predictor for mortality [17]. Another study suggested that advanced age and altered levels of consciousness were important predictors of mortality as well as electrolyte disturbances [18]. In the present study, the severe DKA group was younger and the prevalence of comorbidities such as stroke was lower compared with the other DKA groups. Considering the findings of the present study and previous

Table 2 Precipitating factors identified in patients with DKA and HHS

	Mild DKA	Moderate DKA	Severe DKA	HHS	*P* value
	(n = 104)	(n = 129)	(n = 312)	(n = 226)	
Precipitating factors					
Poor adherence	39 (39.0)	65 (51.2)	156 (51.7)	71 (32.1)	< 0.001
Excessive sugar sweetened beverages	25 (25.3)	33 (26.2)	69 (23.2)	47 (21.4)	0.74
Excessive alcohol beverages	6 (5.9)	15 (11.7)	32 (10.7)	4 (1.8)	< 0.001
Cessation of diabetes medication by treating physician	3 (2.9)	1 (0.8)	5 (1.6)	11 (4.9)	0.057
Infectious disease	38 (36.9)	39 (31.0)	108 (35.2)	96 (42.7)	0.14
Ischemic heart disease	0 (0.0)	2 (1.6)	4 (1.3)	3 (1.3)	0.69
Heart failure	0 (0.0)	0 (0.0)	3 (1.0)	7 (3.1)	0.03
Stroke	6 (5.8)	3 (2.3)	1 (0.3)	4 (1.8)	0.004
Pancreatitis	2 (1.9)	3 (2.4)	15 (4.8)	2 (0.9)	0.048
Trauma	3 (2.9)	3 (2.3)	2 (0.6)	8 (3.5)	0.12
Surgery	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0.49
Medications					
Corticosteroids	1 (1.0)	4 (3.1)	4 (1.3)	14 (6.2)	0.006
Thiazides	0 (0.0)	1 (0.8)	3 (1.0)	6 (2.7)	0.16
Beta blockers	0 (0.0)	0 (0.0)	2 (0.6)	4 (1.8)	0.19
Olanzapine	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.4)	0.44
Quetiapine	1 (1.0)	1 (0.8)	2 (0.6)	1 (0.4)	0.95
Clozapine	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA
Asenapine	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA
Quinolones	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA
Phenytoin	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA

All data are presented as number (%)

DKA Diabetic ketoacidosis, *HHS* Hyperosmolar hyperglycemic syndrome

P values are results of the ANOVA or the Kruskal–Wallis test for four-group comparisons

reports, the severity of DKA may be less important than other factors such as patient age or comorbidities.

Treatment in the ICU has been considered appropriate for patients with hyperglycemic crises for decades as noted in the guidelines which were published by American Diabetes Association in 2009 [19]. The essentials of treatment for hyperglycemic crises are fluid resuscitation, electrolyte replacement, and insulin infusion, which require close monitoring of vital signs, electrolytes, and blood glucose levels. However, recent studies have shown that DKA can be safely managed in the emergency department [20] or even in general wards [21]. We found that ICU utilization for these patients by institution was quite varied, ranging from 0 to 100%. Such a discrepancy may reflect variations in practice and setting of each hospital. A study including 159 hospitals in the United States also reported ICU admission rates from 2.1 to 87.7%, but no association was found between the rates of ICU utilization and mortality or length of hospital stay [13]. Another large retrospective study involving 15,022 patients with DKA showed that institutions that utilized ICUs more frequently had higher costs but no improvement in-hospital mortality [22]. As far as proper triage and management are provided, where care is provided for these patients could be less important. Nevertheless, it should be emphasized that patients who need organ support or have severe comorbidities are suitable for management in the ICU [14]. As the present study suggests, a considerable number of patients required mechanical ventilation, vasopressor use, and renal replacement therapy. Patient profile and conditions also affect prognosis, which should be considered. Past reports suggested that older age, sepsis, coma and lower levels of activity of daily living, and severe comorbidities were risk factors for mortality [17, 23]. Accordingly, the use of organ support as well as patient background should be taken into account for the selection of providing care in the ICU.

In the present study, more than 20% of the patients reported excessive consumption of sugar-sweetened beverages prior to hyperglycemic emergencies. Both patients' behavior and medical illnesses are important triggers for hyperglycemic emergencies [24, 25]. Previous reports identified poor adherence and infection as common precipitants [2, 26, 27]. Recent studies demonstrated that increased consumption of sweet soft drinks worsens insulin resistance and impairs pancreatic beta-cell function [28, 29], which is

Table 3 Outcomes

	Mild DKA	Moderate DKA	Severe DKA	HHS	*P* value
	(n = 104)	(n = 129)	(n = 312)	(n = 226)	
In-hospital mortality, n (%)	3 (2.9)	3 (2.3)	9 (2.9)	16 (7.1)	0.05
Infection, n (%)	17 (16.3)	13 (10.1)	57 (18.3)	52 (23.0)	0.02
Acute coronary syndrome, n (%)	1 (1.0)	1 (0.8)	0 (0.0)	1 (0.4)	0.45
Pulmonary edema, n (%)	2 (1.9)	2 (1.6)	7 (2.2)	10 (4.4)	0.30
Ventricular arrhythmia(%)	2 (1.9)	2 (1.6)	2 (0.6)	6 (2.7)	0.31
Stroke, n (%)	3 (2.9)	1 (0.8)	8 (2.6)	4 (1.8)	0.60
Deep vein thrombosis, n (%)	1 (1.0)	1 (0.8)	3 (1.0)	3 (1.3)	0.96
Hospital stay, days, median [IQR]	16 [10, 26]	15 [8, 22.5]	16 [10, 24]	19.5 [12, 31]	0.001
ICU admission, n (%)	28 (26.9)	53 (41.1)	172 (55.1)	89 (39.4)	< 0.001
ICU stay, days, median [IQR]	3 [2, 5]	3 [2, 4]	3 [2, 5]	3 [2, 5]	0.19
HCU admission, n(%)	31 (29.8)	39 (30.2)	106 (34.0)	51 (22.6)	0.04
HCU stay, days, median [IQR]	3 [2, 4]	3 [2, 5]	3 [2, 5]	4 [2, 7]	0.41
SOFA score on admission, median [IQR]	0 [0, 2]	0.5 [0, 3]	2 [0, 4]	2.5 [0, 5]	< 0.001
Organ support					
Mechanical ventilation, n (%)	6 (5.8)	3 (2.3)	34 (10.9)	9 (4.0)	0.001
Vasopressor use, n (%)	3 (2.9)	3 (2.3)	42 (13.5)	20 (8.8)	< 0.001
Renal replacement therapy, n (%)	1 (1.0)	2 (1.6)	16 (5.1)	5 (2.2)	0.06
Renal replacement therapy on discharge, n (%)	0 (0.0)	1 (0.8)	2 (0.6)	3 (1.3)	0.62

DKA Diabetic ketoacidosis, *HHS* Hyperosmolar hyperglycemic syndrome, *GCS* Glasgow coma scale, *SBP* Systolic blood pressure, *SOFA* sequential organ failure assessment, *ICU* Intensive care unit, *HCU* High care unit, *IQR* Interquartile range

P values are results of the ANOVA or the Kruskal–Wallis test for four-group comparisons

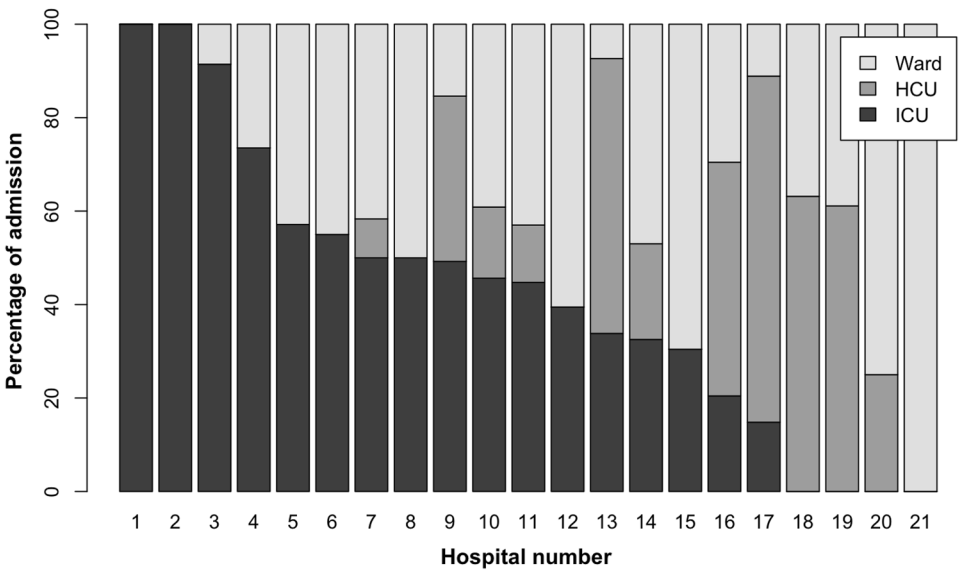

Fig. 1 Percentage of admission wards by hospital. Each bar-chart represents a hospital. Intensive care unit (ICU), high care unit (HCU), or general ward (Ward) displayed in black, gray or white, respectively

related to the pathophysiology of decompensated hyperglycemia. Although the exact prevalence was not documented in previous studies, the results of the present study suggest that excessive consumption of sugar-sweetened beverages may be a significant trigger for developing DKA and HHS.

The present study shows the proportion of patients who were taking medications that could worsen diabetes. Several types of medication, e.g., corticosteroids [30], beta blockers [31], anti-psychotics [32], thiazides [33], quinolones [34], and phenytoin [5], have been reported to be associated with deterioration of diabetes control. Although the overall prevalence of drug-induced diabetes is unknown, approximately 15–50% of patients taking corticosteroids and 10% of people taking anti-psychotic

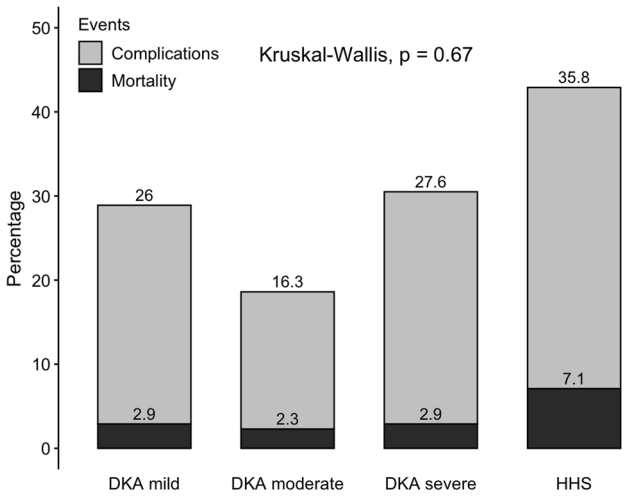

Fig. 2 Percentage of mortality and complications by group. Each bar-chart represents a group of diabetic ketoacidosis (DKA) or hyperglycemic hyperosmolar syndrome (HHS). Mortality and complications are combined and expressed with black and gray, respectively

medications develop diabetes [35, 36]. Some studies have also described patients with drug-induced DKA and HHS [37, 38]. We reviewed prescriptions for the patients with diabetes requiring emergency admission and found that a few patients were taking such medications. Although corticosteroids were prescribed in 6% of patients with HHS, only a small number of patients were taking other medications which could affect diabetes. Given that other precipitating factors are more frequent, the impact of these drugs may be less important in the context of the overall acute critical episodes.

To the best of our knowledge, this is one of the largest and most detailed epidemiological studies of hyperglycemic crises in the medical literature. The strengths of this study are the large sample size and comprehensive description of patient characteristics including precipitating factors, medical resources used, and complications during hospitalization. However, the present study has also acknowledged limitations. First, multivariable regression analysis could not be conducted due to the low incidence of mortality. As a result, predictors of mortality or association between ICU admission and outcomes were not investigated. Considering the low mortality rate, studies with a much larger population such as a nationwide database will be needed to conduct multivariable regression analysis. Second, since the inclusion criteria included hyperglycemia, the present study did not enroll patients with euglycemic DKA which is currently an emerging problem [39]. However, this may be a minor issue because most of the study period was before the widespread use of sodium-glucose cotransporter 2 inhibitors which are a major trigger for euglycemic DKA [40]. Third, this study lacks data regarding the healthcare provider's specialty (e.g. endocrinologist or general practitioner), history of diabetes education or referrals to a dietician, and prior hospitalizations for diabetes. These factors may have impacted the incidence and outcomes of hyperglycemic crises, which should be investigated in future studies.

Conclusions

The present study describes the clinical profile of patients with DKA and HHS in acute care hospitals in Japan. The mortality rate of patients with DKA was similar while that of HHS was lower compared to previous studies. No significant association was seen between the severity of DKA and mortality, which suggests that other factors are more important for prognosis. We found excessive consumption of sugar-sweetened beverages as a new precipitating factor of hyperglycemic crises. This risky behavior should be noted in future educational guides for the dietary habits of patients with diabetes. The indications for ICU admission should be based not only on the severity of disease but also on patient

Table 4 Causes of mortality

	Mild DKA	Moderate DKA	Severe DKA*	HHS*	*P* value
	(n = 3)	(n = 3)	(n = 9)	(n = 16)	
Infection	1 (33.3)	1 (33.3)	5 (55.6)	13 (81.2)	0.19
Stroke	1 (33.3)	1 (33.3)	0 (0.0)	0 (0.0)	0.03
Acute coronary syndrome	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0.47
Pulmonary edema	0 (0.0)	0 (0.0)	0 (0.0)	2 (12.5)	0.57
Ventricular arrhythmia	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.2)	0.81
Pulmonary embolism	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0.47
Others	1 (33.3)	1 (33.3)	4 (44.4)	2 (12.5)	0.35

All data are presented as number numbers (%)

DKA Diabetic ketoacidosis, *HHS* Hyperosmolar hyperglycemic syndrome

*Some patients with severe DKA and HHS had multiple causes

P values are results of the ANOVA or the Kruskal–Wallis test for four-group comparisons

background and the need for organ support. Further studies are needed regarding the epidemiology of acute diabetic emergencies as it changes over time.

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Author contributions KT collected and analyzed the data and wrote the manuscript. NU designed the study and collected and analyzed the data. MS designed and directed the project. SU analyzed the data and supervised the manuscript. NY, TT, NN, HK, SO, KY, HY, SK, HT, NF, TK, TI, TK, KE, TM, TO, MH, AH, TM, YM, AY, TW, TU, TK, and TS collected and analyzed the data. AKL supervised the manuscript and provided a reliable edit to correct English language errors. All authors checked and approved the final version of the manuscript.

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Data availability The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest None.

Ethical approval and consent to participate The study design was approved by the ethics committee of Jichi Medical University (ID: RINS17-023. Registered 4th September 2017) and each institution with a waiver of informed consent prior to collecting the data. The study was performed in accordance with the Declaration of Helsinki.

Informed consent Due to the nature of the retrospective study, informed consent is waived, which was approved by the ethics commitiy in each institution. Instead, we kept all data completely anonymous and provided opportunities for opting out of the study.

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