


# Characteristics of patients with emergency attendance for severe hypoglycemia and hyperglycemia in a general hospital in Japan

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## Abstract

Despite advances in treatments for diabetes mellitus (DM), severe acute glycemic crises still occur. In this study, the characteristics of patients who were transported to an emergency department due to acute glycemic crises were investigated.

We enrolled patients who were transported to our hospital by ambulance due to hypoglycemia or hyperglycemia during the period from January 2015 to December 2019. Initial glucose levels below 70 mg/dL and above 250 mg/dL were defined as hypoglycemia and hyperglycemia, respectively.

In the 5-year period, 16,910 patients were transported to our hospital by ambulance. Of those patients, 87 patients (0.51%) were diagnosed with hypoglycemia, 26 patients (0.15%) were diagnosed with hyperglycemia and 1 patient was diagnosed with lactic acidosis. Compared to patients with hypoglycemia, blood urea nitrogen, serum potassium and hemoglobin levels were higher in patients with hyperglycemia. Systolic blood pressure was lower and pulse rate was higher in patients with hyperglycemia, possibly reflecting dehydration in hyperglycemia. Patients with hyperglycemia were younger (63 vs 70 years old, median), more likely to be hospitalized (92.3% vs 23.0%) with poorer prognosis (23.1% vs 4.6%) than those with hypoglycemia. In 64 DM patients with hypoglycemia, 34 patients were treated with insulin and 24 patients were treated with sulfonylurea or glinide, and their medication was often inappropriate. Excessive alcohol intake and malnutrition were the main causes of hypoglycemia in 23 non-DM patients. The main reasons for hyperglycemia were interrupted treatment, forgetting insulin injection and infection.

To avoid acute glycemic crises, optimization of anti-DM therapy and education of patients are needed.

**Abbreviations:** BMI = body mass index, BP = blood pressure, BUN = blood urea nitrogen, DKA = diabetic ketoacidosis, DM = diabetes mellitus, DPP-4 = dipeptidyl peptidase-4, ED = emergency department, eGFR = estimated glomerular filtration rate, HHS = hyperosmolar hyperglycemic syndrome.

**Keywords:** acute glycemic crises, diabetes mellitus, hyperglycemia, hypoglycemia

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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## 1. Introduction

Several clinical studies have shown that intensive glycemic control did not reduce cardiovascular events but increased hypoglycemic events.<sup>[1,2]</sup> Severe hypoglycemia is known to be associated with increases in micro- and macro-vascular complications, cognitive impairment, falls, disturbed quality of life, and mortality in patients with diabetes mellitus (DM).<sup>[3–8]</sup> There has been a number of emergency department (ED) visits due to hypoglycemia, and 2.3% of all ED calls in the United States were due to DM-related conditions.<sup>[9]</sup> Aging, treatment with insulin and/or sulfonylurea, presence of comorbidities and a prior hypoglycemia-related ED visit have been shown to be associated with ED visits and hospitalizations due to hypoglycemia.<sup>[10]</sup> In the United States, however, ED visit rate for hypoglycemia declined by 22% from 2006 to 2011 possibly due to increased awareness of the importance of avoiding hypoglycemia after clinical trials.<sup>[11]</sup> On the other hand, the rate was unchanged from 2005 to 2013 in Japan, probably due to the rapid increase in the number of elderly patients with DM in Japan.<sup>[12]</sup> The proportion of patients treated with insulin and sulfonylurea among hypoglycemic patients remained unchanged between 2005 and 2013 in Japan.<sup>[12]</sup> A recent survey of severe hypoglycemia by the

Japan Diabetes Society revealed that the median age of patients who visited the ED due to hypoglycemia was 71.5 years and that 60.8% and 33.1% of the patients were treated with insulin and sulfonylurea, respectively.<sup>[13]</sup> In Japan, dipeptidyl peptidase-4 (DPP-4) inhibitors, which are less likely to cause hypoglycemia, were launched in 2009, and the current number of users has increased to more than half of DM patients.<sup>[14,15]</sup> Therefore, the number of hypoglycemic events may have decreased recently in Japan due to the increased use of dipeptidyl peptidase-4 (DPP-4) inhibitors. However, there have been few recent reports on ED visits caused by hypoglycemia in DM patients in Japan. Furthermore, a certain number of patients who visit the ED for hypoglycemia are non-DM patients, and these patients have a worse prognosis than that of DM patients.<sup>[16,17]</sup>

Compared with hypoglycemia, ED visits for hyperglycemia is clinically important because it was shown that patients with severe hyperglycemia were more likely to be hospitalized and had a worse prognosis than patients with hypoglycemia.<sup>[11,18]</sup> In contrast to hypoglycemia, ED visit rate for hyperglycemia remained unchanged or rather increased in the United States, though the incidence was lower than that for hypoglycemia.<sup>[11,19,20]</sup> In-hospital mortality attributed to diabetic ketoacidosis (DKA) was decreased to less than 1% in 2014 in the United States, but it was 2% to 6% in Taiwan and Japan.<sup>[21–24]</sup> Mortality rates for hyperosmolar hyperglycemic syndrome (HHS) have recently been reported to be up to 20%.<sup>[23,25]</sup> In Japan, the lifespan of DM patients has been extended by 3 to 4 years over the past 10 years according to survey on causes of death.<sup>[26]</sup> Mortality caused by hyperglycemia- and hypoglycemia-induced coma has also decreased, but a certain number of patients still die from acute glycemic crises.<sup>[26]</sup>

There are many reports on patients who visited the ED for severe hypoglycemia, but there are few reports on patients with hyperglycemia in Japan.<sup>[12,13,24,27–30]</sup> Most of the studies on hypoglycemic events, including the survey by the Japan Diabetes Society, were carried out in DM-specialized facilities,<sup>[13,28,29]</sup> possibly reflecting the trend in a specific, but not general, cohort of diabetic patients. Furthermore, there have been few reports in which the characteristics of hypoglycemic and hyperglycemic patients are compared in the same period of time in a single region. We therefore conducted a study of ED attendance for both patients with hypoglycemia and patients with hyperglycemia in a general hospital.

## 2. Methods

This study was conducted in strict adherence with the principles of the Declaration of Helsinki and was approved by the Clinical Investigation Ethics Committee of Oji General Hospital (OGH2020–24). Informed consent for this retrospective study was obtained via the study information publicized in the Internet.

We retrospectively analyzed data for consecutive patients who were transported to our hospital by ambulance for acute glycemic crises during the period from January 1, 2015 to December 31, 2019. East Iburi district consists of Tomakomai City and 4 towns with a population of approximately 210,000 and area of 2340 km<sup>2</sup>. Tomakomai City has a population of 170,000, accounting for 80% of the total population in East Iburi district. The proportion of the population over 65 years of age in Tomakomai City is 29.4%, which is the same as the average population structure in Japan. Therefore, East Iburi district is a standard area consisting of a core city (Tomakomai City), which is mainly an

industrial area, and surrounding towns, which are mainly agricultural areas, though the average income in the district is relatively low in Japan. In this district, all emergency patients have been handled by 2 hospitals, one of which is our hospital. Our hospital has accepted all emergency patients on even days and the other general hospital has accepted all emergency patients on odd days, and the analysis conducted in this study would thus reflect the general trend in emergency medical care in this area. Hypoglycemia was defined as venous plasma glucose level at arrival in our hospital being less than 70 mg/dL. Patients who had glucose levels in the hospital above 70 mg/dL due to glucose ingestion were excluded, even if they had typical symptoms and/or unconsciousness when an ambulance was called. Hyperglycemia was defined as venous plasma glucose level being higher than 250 mg/dL. Diagnosis of DKA and HHS was made by the judgment of the attending physician. DKA was diagnosed by the presence of hyperglycemia, arterial blood pH < 7.3 and blood bicarbonate < 18 mmol/L, since blood ketone levels were not always examined at the ED in our hospital. HHS was diagnosed when glucose level and serum osmolality were above 600 mg/dL and 320 mOsm/kg, respectively, without severe acidemia. Data from ambulance records were used for the degree of consciousness disorder evaluated by the Japan Coma Scale, blood pressure and pulse rate. We used data obtained from a blood examination at the time of an emergency visit, but HbA1c was used when data were available within a week before and after the visit. Patients who died or had some sequelae were defined as patients with a poor prognosis.

Variables are shown as medians and interquartile ranges (25th–75th percentiles), since the Shapiro–Wilk test showed that these were not normally distributed. The Chi Squared test was used to compare proportions between 2 groups and the Mann–Whitney *U* test was used to compare non-normal distributions between 2 groups. The Kruskal–Wallis test was used to examine differences among 3 groups, and Bonferroni correction was used to test all detected differences for significance. Differences were considered to be significant if the *P* value was less than .05.

## 3. Results

In the 5-year period, 16,910 patients were transported to our hospital by ambulance. Of those patients, 90 were diagnosed with hypoglycemia, 26 were diagnosed with hyperglycemia and 1 patient was diagnosed with lactic acidosis. Three patients with hypoglycemia were excluded because pre-arrival glucose intake resulted in blood glucose levels being above 70 mg/dL at the time of testing in our hospital. Therefore, 87 patients with hypoglycemia and 26 patients with hyperglycemia were included in the analysis.

Table 1 shows the clinical characteristics of patients with hypoglycemia and patients with hyperglycemia. Patients with hypoglycemia were older than patients with hyperglycemia (70 vs 63 years old, median, Fig. 1A and B). Median blood glucose and HbA1c levels in hypoglycemic cases were 28 mg/dL and 6.6%, respectively, and those in hyperglycemic cases were 593 mg/dL and 9.6%, respectively, but there is a wide variation in HbA1c values in both patients with hypoglycemia and patients with hyperglycemia (Fig. 1C and D). Blood urea nitrogen (BUN), serum potassium and hemoglobin levels were higher in patients with hyperglycemia compared than in patients with hypoglycemia (Fig. 1G and H). Furthermore, systolic blood pressure (BP) was lower and pulse rate was higher in patients with

**Table 1**  
**Characteristics of patients with hypoglycemia and with hyperglycemia.**

	Hypoglycemia	No. of inspected	Hyperglycemia	No. of inspected
Events, n	87		26	
Age, y	70 (62, 81)		63 (52, 75) *	
Male, n (%)	48 (55.2)		19 (73.1) *	
Type of DM, n				
type 1	11		5	
type 2	51		20	
other	2		1	
non-DM, n	23		0	
BMI	22.3 (18.7, 23.6)	57	20.2 (18.6, 23.1)	21
Glucose level, mg/dL	28 (20, 37)	87	593 (475, 721) *	26
HbA1c, %	6.6 (5.5, 7.7)	40	9.6 (8.3, 13.2) *	23
BUN, mg/dL	18.2 (12.9, 29.7)	69	35.0 (18.5, 60.0) *	26
eGFR, mL/min/1.73m <sup>2</sup>	61.4 (36.6, 88.0)	69	46.9 (26.7, 80.9)	26
Na, mmol/L	138 (134, 141)	67	132 (126, 135) *	26
K, mmol/L	3.5 (3.2, 4.2)	67	4.4 (3.9, 5.2) *	26
ALT, IU/L	23 (14, 34)	71	21 (11, 31)	25
Hb, g/dL	11.4 (10.0, 12.9)	71	13.2 (11.4, 14.6) *	26
SBP, mmHg	155 (125, 168)	85	118 (101, 150) *	26
DBP, mmHg	77 (62, 87)	85	72 (55, 91)	25
PR, bpm	75 (65, 93)	85	108 (80, 126) *	25
Admission, n (%)	20 (23.0)		24 (92.3) *	
Poor prognosis, n (%)	4 (4.6)		6 (23.1) *	

Data are presented as number of events with percentage or median with interquartile range (25th, 75th percentiles).

\*  $P < .05$  vs hypoglycemia.

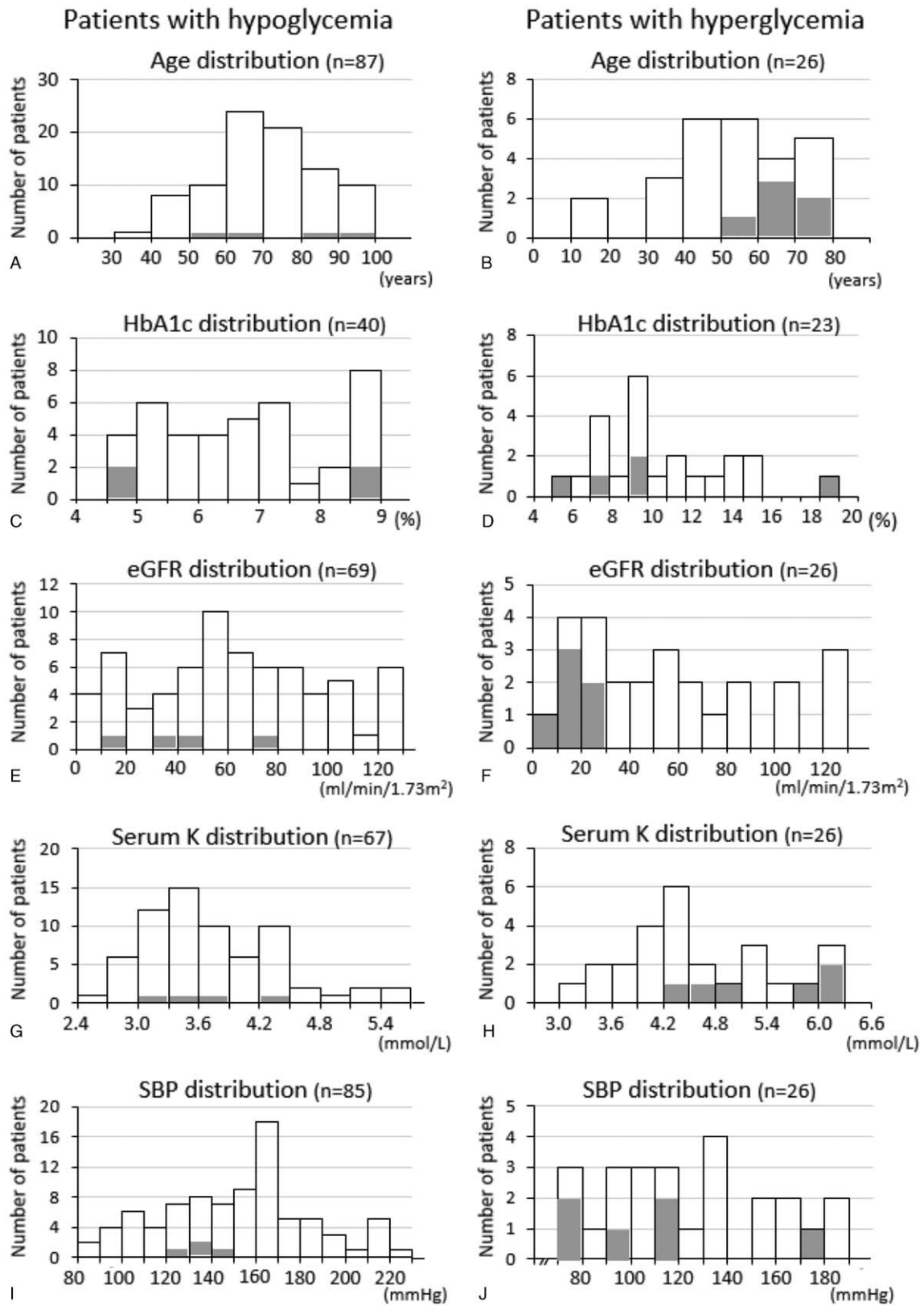
ALT = alanine transaminase, BMI = body mass index, bpm = beats per minute, BUN = blood urea nitrogen, DBP = diastolic blood pressure, DM = diabetes mellitus, eGFR = estimated glomerular filtration rate, Hb = hemoglobin, PR = pulse rate, SBP = systolic blood pressure.

hyperglycemia, possibly reflecting dehydration in hyperglycemia (Fig. 1I and J). The rate of hospitalization and the rate of poor outcome were higher in patients with hyperglycemia than in patients with hypoglycemia. Two non-DM patients with hypoglycemia due to malnutrition died 15 days and 18 days after admission. Two patients with hypoglycemia (1 patient with type 1 DM and 1 patient with type 2 DM) did not completely recover consciousness. These 2 patients were found unconscious (Japan coma scale 300) by a family member, and it is therefore likely that prolonged hypoglycemia had occurred before ED attendance. Six patients with hyperglycemia (4 patients with DKA and 2 patients with HHS) died 1 to 28 days after admission. One patient with type 1 DM did not eat or take insulin for 4 days due to pneumonia and died on the day he visited the emergency room after developing DKA. Of the 3 patients with type 2 DM who died of DKA, 2 had treatment interruptions and one had an infection as the cause of their DKA. One of the HHS patients had treatment interruption as the cause of onset, and one was a traveler and unspecified. A type 2 DM female patient on metformin treatment developed lactic acidosis under the condition of dehydration (lactate, 16.7 mmol/L) but recovered without sequelae after intensive treatment.

Table 2 shows a comparison of the clinical characteristics of hypoglycemic patients with type 1 DM (n=11), type 2 DM (n=51), and non-DM (n=23). All DM patients had already been diagnosed and treated at one of the hospitals. The median age of type 2 DM patients was older than the ages of type 1 DM and non-DM patients, though body mass index (BMI) and estimated glomerular filtration rate (eGFR) were not significantly different between type 1 and type 2 patients. All type 1 DM patients were on insulin therapy, and the most common cause of hypoglycemia was inappropriate diet and/or dietary timing. Considering the

drug use among DM patients in Japan,<sup>[14,15]</sup> many of the type 2 DM patients who experienced hypoglycemia were treated with insulin or sulfonylurea/glinide, and relatively few patients were treated with metformin or DPP-4 inhibitors in the present study. Only 2 patients who experienced hypoglycemia were treated with glucagon-like peptide-1 receptor agonists. Overdose or misuse of drugs in addition to inappropriate diet was the cause of hypoglycemia in the type 2 DM patients. Although the HbA1c value was measured in only 23 (45.1%) of the 51 patients with type 2 DM, it was lower than that in patients with type 1 DM. Furthermore, the HbA1c value was below 6.5% in 10 patients, 9 of whom were treated with insulin, sulfonylurea or glinide (Fig. 2B and E). Twenty three non-DM patients were transported to our hospital by ambulance. Since the main causes of hypoglycemia in those patients were excessive alcohol intake and malnutrition, they had low BMI and liver dysfunction (Table 2). One patient with pancreatic DM (79-year-old female) experienced episodes of hypoglycemia twice, but the reason was not clearly determined.

Table 3 shows hyperglycemia-associated characteristics by type of DM. A 57-year-old male was diagnosed with pancreatic DM after the onset of DKA, but the other 25 patients were either being treated for or had previously been diagnosed with DM. The median age of type 1 DM patients (45 years old, n=5) with hyperglycemia was younger than that of type 2 DM patients (66 years old, n=20), though BMI and eGFR were not different between type 1 and type 2 patients. Glucose and serum potassium levels were higher in type 1 DM patients than in type 2 DM patients, but HbA1c levels were not different. Fifteen patients (4 patients with type 1 DM and 10 patients with type 2 DM) developed DKA, and 3 patients with type 2 DM developed HHS. One DKA patient taking a sodium-glucose cotransporter 2



**Figure 1.** Distribution of age (A), HbA1c (C), eGFR (E), serum potassium (G) and systolic blood pressure (I) in patients with hypoglycemia and those with hyperglycemia (B, D, F, H, J). Gray bars show the individual number of patients with poor prognosis.

**Table 2**  
**Comparison of characteristics and factors associated with hypoglycemia by type of DM.**

	All	Type 1 DM	Type 2 DM	Non-DM
Events, n	87	11	51	23
Age, y	70 (62, 81)	62 (62, 64)	74 (67, 85) *	59 (52, 75) #
BMI	22.3 (18.7, 23.6)	23.1 (20.7, 23.1)	22.3 (20.0, 24.1)	17.7 (16.0, 19.0) *,#
Glucose level, mg/dL	28 (20, 37)	24 (21, 32)	30 (22, 37)	23 (15, 36)
HbA1c, %	6.6 (5.5, 7.7)	8.6 (8.3, 8.9)	6.5 (6.1, 7.1) *	5.0 (4.9, 5.0) *,#
eGFR, mL/min/1.73m <sup>2</sup>	61.4 (36.6, 88.0)	51.6 (42.1, 59.8)	56.6 (29.7, 81.0)	69.6 (38.7, 90.5)
ALT, IU/L	23 (14, 34)	17 (11, 20)	18 (12, 27)	36 (27, 45) *,#
SBP, mmHg	155 (125, 168)	172 (164, 187)	159 (128, 168)	136 (110, 155) *,#
Factors of hypoglycemia				
Inappropriate diet/dietary timing	28	9	19	0
Drug overdose/ misuse	23	0	23	0
Excessive alcohol intake	14	0	1	13
Malnutrition	8	0	0	8
Other/Unknown	14	2	8	2
Therapy				
Insulin	34	11	21	0
GLP-1RA	2	0	2	0
Sulfonylurea	20	0	20	0
Glinide	4	0	4	0
Metformin	12	0	12	0
DPP-4 inhibitor	21	0	21	0
α-GI	15	0	15	0
Thiazolidine	4	0	4	0
SGLT2 inhibitor	1	0	1	0
No use of insulin/SU/glinide	26	0	3	23
Unknown	6	0	6	0
JCS, n (%)				
0	7 (8.0)	0	4	3
1–3	34 (39.1)	3	20	9
10–30	20 (23.0)	5	9	6
100–300	26 (29.9)	3	18	5

Data are presented as number of events or median with interquartile range (25th, 75th percentiles).

\*  $P < .05$  vs type 1 DM.

#  $P < .05$  vs type 2 DM.

α-GI = α-glucosidase inhibitor, ALT = alanine transaminase, BMI = body mass index, DPP-4 = dipeptidyl peptidase-4, eGFR = estimated glomerular filtration rate, GLP-1RA = glucagon-like peptide-1 receptor agonist, JCS = Japan Coma Scale, SBP = systolic blood pressure, SGLT2 = sodium-glucose cotransporter 2, SU = sulfonylurea.

Two events from 1 patient with pancreatic diabetes are not listed separately.

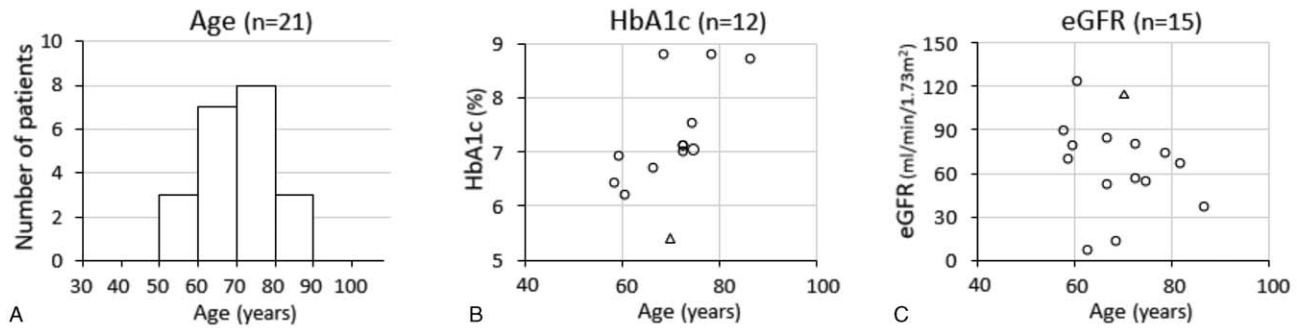
inhibitor showed a condition close to that of euglycemic DKA with a glucose level of 265 mg/dL. The other 8 patients were transferred to our hospital in a poor general condition due to hyperglycemia (median glucose level of 479 mg/dL). Interrupted treatment, forgetting insulin injection and infection were the major causes of hyperglycemia. Nine patients were not treated with insulin or sulfonylureas. The causes of hyperglycemia in those patients were interrupted treatment in 3 patients, infection in 3 patients and steroid usage in 1 patient, with no obvious cause in the remaining 2 patients.

#### 4. Discussion

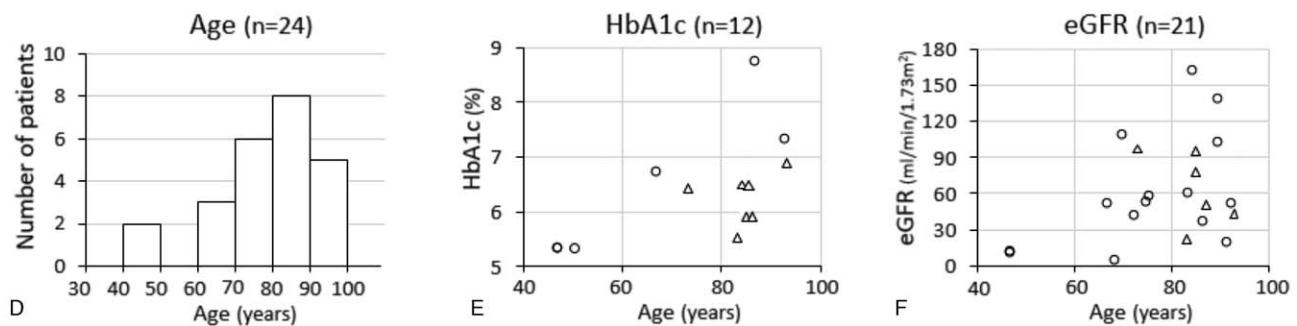
In this retrospective study, we investigated and compared the incidences of hypoglycemia and hyperglycemia and characteristics of patients who visited the ED due to severe hypoglycemia or hyperglycemia during the same period. Out of a total of 16,910 patients transported by ambulance to our hospital during the period 2015 to 2019, 0.38% were DM patients with severe hypoglycemia. Tsujimoto et al. reported that 0.62% of 59,602 patients transported to the ED by ambulance between 2006 and 2012 were DM patients with hypoglycemia,<sup>[29]</sup> and Takahashi

et al. reported that 0.77% of 37,044 patients transported to the ED between 2005 and 2009 were DM patients with hypoglycemia.<sup>[16]</sup> Morikawa et al. reported that the ED visit rates for DM patients with hypoglycemia were not different in 2006 (0.77%) and in 2013 (0.79%) in the same institute.<sup>[12]</sup> A more recent survey by the Japan Diabetes Society conducted in 2014 to 2015 showed that 0.34% of ED visits were due to hypoglycemia, the incidence being almost the same as that in the present study.<sup>[13]</sup> Therefore, the number of ED visits due to severe hypoglycemia in DM patients in Japan did not change greatly, but may have decreased in the past few years. The recent reduction in hypoglycemic events in DM patients may be largely due to the development of new anti-DM medication in addition to efforts to avoid hypoglycemia. Unlike in Europe and the United States, metformin was used in only about 30% of patients in Japan, and the use of sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide-1 receptor agonists was not high during this study period.<sup>[14,15]</sup> On the other hand, the increased use of DPP-4 inhibitors, which were launched in 2009, and the decreased use of sulfonylurea may have led to a decrease in the incidence of hypoglycemia.<sup>[14,15]</sup> However, it remains a fact that sulfonylurea and insulin are used in some patients and

## Type 2 DM patients with hypoglycemia treated with insulin



## Type 2 DM patients with hypoglycemia treated with sulfonylurea/glinide



**Figure 2.** Distributions of age (A), HbA1c (B) and eGFR (C) in type 2 DM patients treated with insulin and those (D, E, F) in type 2 DM patients treated with sulfonylurea or glinide. The triangles indicate individuals whose HbA1c levels were below the lower limit of HbA1c recommended for elderly patients in the Japanese Clinical Practice Guideline for Diabetes.<sup>[38]</sup>

hypoglycemic crises in these patients are common. From 2015 to 2019, 0.15% of the ED visits by ambulance in our hospital were due to hyperglycemia, which was 30% of the total incidence of hypoglycemia and was 41% of hypoglycemic events in DM patients. Although there has been no report in which the incidences of hypoglycemia and hyperglycemia are compared at the same time in Japan, fewer ED visits due to acute hyperglycemia than due to hypoglycemia were similar to the results of previous studies by Wang et al. (42%–62% in the US)<sup>[11]</sup> and by Andreano et al. (30% in Italy).<sup>[18]</sup>

In this study, we compared the clinical characteristics, including hemodynamics, of patients with acute severe hypoglycemia and those with acute severe hyperglycemia (Table 1). Systolic BP was lower and pulse rate was higher in patients with hyperglycemia than in patients with hypoglycemia. Hypoglycemia results in increased BP due to elevated sympathetic nerve activity and secretion of insulin-antagonistic hormones such as epinephrine and norepinephrine.<sup>[31,32]</sup> On the other hand, in patients with hyperglycemia, dehydration may be the cause of hypotension and tachycardia.<sup>[30,33]</sup> Fourteen (22%) of the 64 DM patients in the present study who developed hypoglycemia had severe hypertension with systolic BP higher than 180 mmHg, and these responses of BP to hypoglycemia were similar to those reported by Tsujimoto et al.<sup>[28]</sup> Among the patients with hypoglycemia, systolic BP was lower in non-DM patients than in DM patients, though blood glucose levels were similar (Table 2). Since non-DM patients were lean and had hypoglycemic events due to malnutrition and excessive alcohol intake, these

conditions may be the reason for an inadequate increase in BP. Serum potassium concentration in patients with hypoglycemia was lower than that in patients with hyperglycemia (Table 1) and was also lower than the concentrations in type 2 DM patients without acute glycaemic crises and in the general population.<sup>[34]</sup> This may be due to insulin action and increased secretion of catecholamines in patients with hypoglycemia.<sup>[35]</sup> Hypokalemia is known to increase the risk of lethal arrhythmias, and an electrocardiogram should therefore be examined in patients with hypoglycemia. Indeed, more than half of the patients with hypoglycemia had prolonged QTc,<sup>[28]</sup> a pathological consequence of hypokalemia to increase the risk of lethal arrhythmia.

Patients with hyperglycemia were more likely to be hospitalized (92.3% vs 23.0%) with poorer prognosis (23.1% vs 4.6%) than those with hypoglycemia. Two non-DM patients with malnutrition-induced hypoglycemia died after admission in our hospital. Since the main causes of hypoglycemia in non-DM patients were excessive alcohol intake and malnutrition, the prognosis of those patients is known to be poor as previously reported.<sup>[16,17,29]</sup> It has been reported that several factors including elderly age, renal dysfunction, co-morbidity and sepsis are predictors of mortality in patients urgently hospitalized for hyperglycemia.<sup>[23,24,36]</sup> In our study, 6 patients with severe hyperglycemia died 1 to 28 days after admission. All of those 6 patients had severe renal dysfunction at the ED visit (BUN, 96.6 mg/dL; creatinine, 4.23 mg/dL; eGFR, 11.9 mL/min/1.73m<sup>2</sup>; K, 5.4 mmol/L; medians,  $P < .05$ ) compared with survivors (BUN, 22.1 mg/dL; creatinine, 0.81 mg/dL; eGFR, 61.3 mL/min/1.73m<sup>2</sup>;

**Table 3**  
**Comparison of characteristics and factors associated with hyperglycemia by type of DM.**

	All	Type 1 DM	Type 2 DM
Events, n	26	5	20
Age, y	63 (52, 75)	45 (45, 63)	66 (56, 79) *
BMI	20.2 (18.6, 23.1)	20.2 (20.2, 21.1)	19.7 (18.6, 23.6)
Glucose level, mg/dL	593 (475, 721)	722 (625, 1171)	544 (457, 685) *
HbA1c, %	9.6 (8.3, 13.2)	9.3 (8.3, 10.2)	9.8 (8.1, 13.5)
eGFR, mL/min/1.73m <sup>2</sup>	46.9 (26.7, 80.9)	40.5 (13.1, 65.9)	46.9 (27.6, 79.2)
K, mmol/L	4.4 (3.9, 5.2)	5.4 (5.2, 5.7)	4.3 (3.9, 4.8) *
Type of hyperglycemia			
DKA	15	4	10
HHS	3	0	3
Other	8	1	7
Factors of hyperglycemia			
Interrupted treatment	7	0	7
Forgetting insulin injection	6	3	3
Infection	6	0	6
Excessive alcohol intake	3	1	2
Other/Unknown	4	1	2
Therapy			
Insulin	12	5	7
GLP-1RA	1	0	1
Sulfonylurea	4	0	4
Metformin	6	0	6
DPP-4 inhibitor	11	0	11
$\alpha$ -GI	3	0	3
Thiazolidine	2	0	2
SGLT2 inhibitor	4	1	3
No use of insulin/sulfonylurea	10	0	9
Unknown	6	0	5
JCS, n (%)			
0	6 (23.1)	0	6
1–3	9 (34.6)	0	8
10–30	7 (26.9)	4	3
100–300	4 (15.4)	1	3

Data are presented as number of events or median with interquartile range (25th, 75th percentiles).

\*  $P < .05$  vs type 1 DM.

$\alpha$ -GI =  $\alpha$ -glucosidase inhibitor, BMI = body mass index, DKA = diabetic ketoacidosis, DPP-4 = dipeptidyl peptidase-4, eGFR = estimated glomerular filtration rate, GLP-1RA = glucagon-like peptide-1 receptor agonist, HHS = hyperosmolar hyperglycemic syndrome, JCS = Japan Coma Scale, SGLT2 = sodium-glucose cotransporter 2.

One event from patient with pancreatic diabetes is not listed separately.

K, 4.3 mmol/L; medians) as shown by the gray part of the bars in Figure 1, though blood glucose and HbA1c levels were similar. Recently, Nishikawa et al. reported that sepsis and coagulation disorders were the most common causes of death in Japanese patients with hyperglycemic crises.<sup>[37]</sup> In their study, serum potassium and eGFR were not significantly different between survivors and deceased patients. Although we cannot clearly explain the differences between our study and that of Nishikawa et al,<sup>[37]</sup> our data support the notion that complications and/or comorbidities such as renal dysfunction, rather than blood glucose levels, are the primary factors determining the prognosis of patients with hyperglycemic crises.

It has been shown that advanced age, renal dysfunction, usage of sulfonylurea and/or insulin and a prior hypoglycemia-related ED visit are risks for hypoglycemia.<sup>[10–13]</sup> In this study, 40 and 25 of the 51 type 2 DM patients were  $\geq 65$  years and  $\geq 75$  years of age, respectively, and 82% of the type 2 DM patients were treated with insulin, sulfonylurea or glinide. Furthermore, the median age of type 2 DM patients who were treated with sulfonylurea or glinide was 84 years, which was older than patients treated with insulin (Fig. 2A and D). The causes of hypoglycemia in most patients were thought to be overdose or misuse of drugs in

addition to inappropriate diet. Recently, blood glucose targets and their lower limits have been set to ensure patient-centered care including prevention of hypoglycemia in elderly DM patients in Japan.<sup>[38]</sup> Among insulin users and patients taking sulfonylurea or glinide, there were patients whose HbA1c levels were below the lower limit recommended in the guidelines, especially among patients taking sulfonylurea or glinide (Fig. 2B and E). Some of them were patients with reduced renal function (Fig. 2C and F). There were 9 patients who visited the ED multiple times. Those patients included 1 type 1 DM patient on insulin, 1 type 2 DM patient on insulin, 5 type 2 DM patients on sulfonylurea therapy, and 2 non-DM patients with alcohol dependence. Thus, DM patients treated with insulin or sulfonylurea need to be aware of the risk of repeated hypoglycemia. On the other hand, the proportion of patients with severe hypoglycemia who were using metformin and DPP-4 inhibitors in the present study was lower than the proportion of Japanese DM patients who were using those agents.<sup>[14,15]</sup> Interrupted treatment, forgetting insulin injection and infection, well-known precipitating factors for the development of DKA and HHS,<sup>[39]</sup> were the major causes of hyperglycemia in the present study. It has also been reported that prior ED attendance, treatment with insulin and chronic renal

failure are associated with ED attendance for hyperglycemia.<sup>[18]</sup> In the present study, however, none of the 26 patients visited multiple times due to hyperglycemia during the 5-year period. Since only a few patients were being treated in our hospital, it was difficult to investigate renal function before the ED visits.

There are several limitations in the present study. First, some patients, especially those who visited the ED due to hypoglycemia, returned home just after confirmation of improvement in blood glucose level and recovery of consciousness. Therefore, there are missing data, which may have influenced the results and statistical analysis. Second, more than half of the patients had not been treated at our hospital. Therefore, it was impossible to clarify the clinical parameters and treatment status before ED admission and prognosis after returning home from the hospital in some of those patients. Third, patients who visited the ED by themselves were excluded. Relatively mild hypoglycemia and hyperglycemia are not included in the analysis, and therefore, this study does not reflect all acute glycemic crises.

## 5. Conclusions

Despite recent improvements in treatment of DM, some patients still die due to acute glycemic crises. We confirmed that many DM patients who visited the ED due to hypoglycemia were being treated with insulin and/or sulfonylurea, and their medication was often inappropriate. The main reasons for ED visits due to hyperglycemia were interrupted treatment, forgetting insulin injection and infection. Therefore, optimization of DM treatment and patient education are important to avoid acute glycemic crises and subsequent unfortunate outcomes.

## Author contributions

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