Original Article

Sepsis-associated hypoglycemia on admission is associated with increased mortality in intensive care unit patients

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Aim: Hyperglycemia is a common response to acute illness, but it is not often seen in critical conditions. The frequency and cause of hypoglycemia in septic patients have not been well elucidated. In this study, we focused on sepsis-associated hypoglycemia in the early phase and evaluated the impact of hypoglycemia on mortality.

Methods: We performed a retrospective review of 265 patients with sepsis admitted to a tertiary medical center. Blood glucose levels on admission were evaluated and analyzed by a Cox proportional hazard model.

Results: We categorized patients with sepsis into five groups according to blood glucose levels. Seven patients (2.6%) were admitted with severe hypoglycemia (≤40 mg/dL), 19 (7.2%) with mild hypoglycemia (41–70 mg/dL), 103 (38.9%) with euglycemia (71–140 mg/dL), 58 (21.9%) with mild hyperglycemia (141–180 mg/dL), and 78 (29.4%) with hyperglycemia (>180 mg/dL). There was a significant difference in 28-day mortality between those with severe hypoglycemia and euglycemia (71.4% versus 8.7%; $P < 0.05$). We analyzed the hazard ratios for the groups (relative to the reference of euglycemia) adjusted for sex, age, and Acute Physiology and Chronic Health Evaluation II and Sequential Organ Failure Assessment scores on admission. The hazard ratios for 28-day mortality in patients with severe hypoglycemia and mild hypoglycemia compared with that in patients with euglycemia were 8.18 (95% confidence interval [CI], 2.39–27.96; $P = 0.001$) and 7.56 (95% CI, 2.96–19.35; $P < 0.001$), respectively.

Conclusion: Septic patients with severe hypoglycemia had significantly higher mortality compared with patients with euglycemia.

Key words: Hypoglycemia, mortality, sepsis

INTRODUCTION

ABNORMAL BLOOD GLUCOSE concentration is related to mortality in critical illness. Hyperglycemia is a common response to acute illness, but hypoglycemia, both spontaneous and iatrogenic, is not so often seen in critical conditions. Admission hypoglycemia is reported to be a risk factor in patients with pneumonia or critically ill patients.[1,2] Regarding sepsis, there are only few reports about hypoglycemia on admission.

Glycemic control for hyperglycemia is often needed along with insulin control. Since the Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study, hypoglycemia is now recognized as a critical factor in glycemic control.[3] In a subsequent analysis of this study, hypoglycemia in the "absence of insulin treatment" was also evaluated, which showed that the mortality rate of patients with moderate hypoglycemia (blood glucose 41–70 mg/dL) in the absence of insulin treatment was 36% (136/378), and that of those with severe hypoglycemia (blood glucose ≤40 mg/dL) in the absence of insulin treatment was 59% (22/37). In fact, the fatal hypoglycemic event happened in the absence of insulin treatment.[4] In particular, in the group of patients with distributive shock, the hazard ratio was higher in patients

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with hypoglycemia than in those without hypoglycemia.[5] In this study, we focused on patients with sepsis, a typical disease of distributive shock, and retrospectively evaluated the association between hypoglycemia and mortality.

METHODS

Patients

THIS WAS A retrospective study that comprised 265 patients with sepsis admitted to a single tertiary care center from June 2008 to January 2018. Sepsis and septic shock were defined according to Sepsis-1.[6] Antibiotics were administered under the same policy during the entire study period.[7,8] This study was approved by the Institutional Review Board of Osaka University (approval no. 14186). The board waived the need for informed consent because this was a retrospective study using clinical data.

Methods

Blood glucose and levels of oxygen, carbon dioxide, pH, bicarbonate, base excess, and lactate were measured by arterial blood gas analysis immediately after hospital arrival. Patients were categorized into five groups based on their glucose levels on the first measurement as follows: severe hypoglycemia, ≤40 mg/dL; mild hypoglycemia, 41–70 mg/dL; euglycemia, 71–140 mg/dL; mild hyperglycemia, 141–180 mg/dL; and severe hyperglycemia, >180 mg/dL. This categorization of blood glucose levels is based on the NICE-SUGAR study.[3]

Statistical analysis

Results are expressed as the mean ± standard deviation and median with interquartile range. Statistical analysis was performed with an unpaired Student *t*-test for normally distributed variables and Wilcoxon rank-sum test for non-normally distributed variables. For comparison between multiple groups, a parametric test was performed with analysis of variance and a nonparametric test with the Kruskal–Wallis test.

Severity of disease on admission was evaluated with the following scoring systems: the Acute Physiology and Chronic Health Evaluation II (APACHE II), with scores ranging from 0 to 71 and higher scores indicating more severe illness, and the Sequential Organ Failure Assessment (SOFA), with scores ranging from 0 to 4 for each organ system and higher scores indicating more severe organ dysfunction. Sepsis and septic shock were defined according to Sepsis-1. Acute kidney injury was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline.[9]

The outcome was overall survival followed up to 28 days. The variables of the other groups were compared with the euglycemia group, which was set as the reference. Survival rates of groups were calculated using a Kaplan–Meier method. To assess whether blood glucose levels on admission were correlated with outcome, we conducted a Cox proportional hazard model analysis with adjustment for sex, age, and APACHE II and SOFA baseline scores. To assess the continuous associations between the blood glucose levels and outcome with this hazard model, we generated piecewise linear splines with knots corresponding to the blood glucose level cut-off points used in this study. We also implemented restricted cubic splines to obtain a smoother fit to the data.

A significance level of a two-sided $P < 0.05$ was used for statistical inferences. All statistical analyses were performed using JMP 13 (SAS Institute Inc., Cary, NC, USA) and R statistical software, version 3.5.1. (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

WE ENROLLED 265 patients with sepsis in this study (Fig. 1). The study group comprised 168 men and 97 women with a median age of 71 years. The median APACHE II and SOFA scores of all patients were 17 and 5, respectively. The 28-day mortality rate of all patients was 15.1%.

Among the five groups categorized according to blood glucose levels, 7 patients (2.6%) were admitted with severe hypoglycemia (≤40 mg/dL), 19 (7.2%) with mild hypoglycemia (41–70 mg/dL), 103 (38.9%) with euglycemia

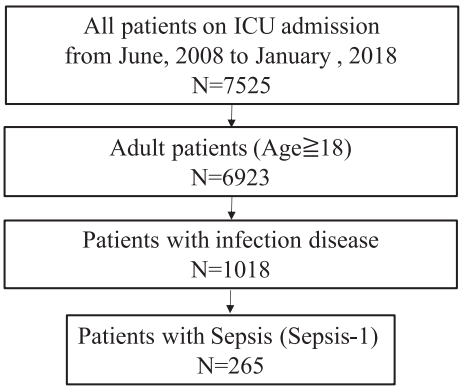


Fig 1. Flow diagram of the study population. ICU, intensive care unit.

Table 1. Characteristics of patients based on blood glucose levels

	Severe hypoglycemia ≤40 mg/dL	Mild hypoglycemia 41–70 mg/dL	Euglycemia 71–140 mg/dL	Mild hyperglycemia 141–180 mg/dL	Hyperglycemia >180 mg/dL	All patients	*P* value
Variables							
Patients, *n* (%)	7 (2.6)	19 (7.2)	103 (38.9)	58 (21.9)	78 (29.4)	265	—
Demographics							
Age (years), median (IQR)	64 (61–77)	67 (61–77)	69 (55–81)	73 (60–82)	73 (63–79)	71 (59–81)	0.788
Sex, male, *n* (%)	5 (71.4)	8 (42.1)	64 (62.1)	39 (67.2)	53 (67.9)	168 (63.4)	0.321
Body mass index, median (IQR)	19.6 (19.1–21.9)	20.4 (18–23.9)	20.2 (18.8–22.6)	21.4 (18.7–23.3)	20.8 (18.4–23.7)	20.7 (18.6–2.2)	0.809
Chronic comorbidity, *n* (%)							
Cardiovascular compromise	0	2 (10.5)	15 (14.6)	9 (15.5)	14 (17.9)	40 (15.1)	0.871
Chronic obstructive pulmonary disease	0	3 (15.8)	12 (11.7)	8 (13.8)	7 (9.0)	30 (11.3)	0.774
Diabetes	2 (28.6)	6 (31.6)	27 (26.2)	14 (24.1)	20 (25.6)	69 (26.0)	0.964
Hypertension	2 (28.6)	6 (31.6)	26 (25.2)	24 (41.4)	31 (39.7)	89 (33.6)	0.169
Immunocompromise	1 (14.3)	3 (15.8)	17 (16.5)	11 (19.0)	13 (16.7)	45 (17.0)	0.993
Malignancy	2 (28.6)	3 (15.8)	20 (19.4)	8 (13.8)	12 (15.4)	45 (17.0)	0.744
Renal insufficiency	1 (14.3)	3 (15.8)	4 (3.9)	6 (10.3)	8 (10.3)	22 (8.3)	0.137
Infection site, *n* (%)							
Respiratory	0 (0)	8 (42.1)	39 (37.9)	25 (43.1)	31 (39.7)	103 (38.9)	0.264
Abdomen	2 (28.6)	3 (15.8)	26 (25.2)	12 (20.7)	18 (23.1)	61 (23.0)	0.883
Skin/soft issue	2 (28.6)	5 (26.3)	12 (11.7)	9 (15.5)	16 (20.5)	44 (16.6)	0.43
Urinary tract	2 (28.6)	1 (5.3)	11 (10.7)	5 (8.6)	6 (7.7)	25 (9.4)	0.233
Central nervous system	0 (0)	0 (0)	8 (7.8)	1 (1.7)	2 (2.6)	11 (4.2)	0.335
Unknown or others	1 (14.3)	2 (10.5)	11 (10.7)	6 (10.3)	6 (7.7)	26 (9.8)	0.87
Blood culture positive, *n* (%)	5 (71.4)	11 (57.9)	45 (43.7)	23 (40.0)	39 (50.0)	122 (46.0)	0.348
Severity of disease on admission							
APACHE II, median (IQR)	25 (19–28)	23 (14.5–26.5)	16 (12–23)	14 (9.5–22)	18 (13–25)	17 (12–24)	0.021
SOFA, median (IQR)	10 (8.5–10.5)	9 (4.5–12)	5 (2–8)	4.5 (1.3–7)	5.5 (3–8.8)	5 (3–9)	0.003
Septic shock, *n* (%)	6 (85.7)	10 (52.6)	33 (32.0)	13 (22.4)	29 (37.2)	91 (34.3)	0.005
Acute kidney injury, *n* (%)	6 (85.7)	11 (57.9)	36 (35.0)	9 (15.5)	25 (32.1)	87 (32.8)	<0.001
Mechanical ventilation, *n* (%)	6 (85.7)	17 (89.5)	66 (64.1)	32 (55.2)	61 (78.2)	182 (68.7)	0.007

APACHE, Acute Physiology and Chronic Health Evaluation; IQR, interquartile range; SOFA, Sequential Organ Failure Assessment.

Table 2. Blood examination

Blood examination, median (IQR)	Severe hypoglycemia ≤40 mg/dL	Mild hypoglycemia 41–70 mg/dL	Euglycemia 71–140 mg/dL	Mild hyperglycemia 141–180 mg/dL	Hyperglycemia >180 mg/dL	All patients	*P* value
White blood cells (×1,000/μL)	11.3 (6.8–16.5)	7.3 (2.1–24.7)	3.2 (1.6–12.1)	11.3 (7.1–16.2)	11.0 (7.1–15.7)	13.3 (7.9–17.8)	0.015
Hemoglobin (g/dL)	11.3 (9.8–12.9)	11.6 (11.1–12.4)	9.7 (8.3–11.5)	11.2 (9.9–13.1)	11.8 (10.4–13.1)	11.3 (9.6–12.9)	0.015
Platelets (10,000/μL)	16.2 (9.7–24.4)	5.7 (4.8–9.7)	8.6 (4.6–20.8)	16 (9.4–22.5)	18.3 (12.4–26.3)	16.4 (12.4–24.8)	0.012
Glucose (mg/dL)	21 (13.5–27.5)	57 (52–61.5)	113 (99–125.5)	158.5 (148.3–171)	237.5 (200–298)	142 (109–192)	<0.001
Arterial pH	7.16 (7.09–7.23)	7.36 (7.15–7.42)	7.44 (7.33–7.49)	7.43 (7.38–7.49)	7.39 (7.26–7.45)	7.42 (7.31–7.45)	<0.001
Lactate (mg/dL)	45 (28.5–108.5)	52 (17.5–98)	16 (10.5–44)	21 (14–33.5)	27.5 (14–50)	22 (12–48)	0.005

IQR, interquartile range.

(71–140 mg/dL), 58 (21.9%) with mild hyperglycemia (141–180 mg/dL), and 78 (29.4%) with hyperglycemia (>180 mg/dL; Table 1). There was a significant difference in the severity of disease between patients with severe hypoglycemia and those with euglycemia. The median APACHE II scores were 25 versus 16 ($P = 0.021$) and those of SOFA were 10 versus 5 ($P = 0.003$). The infection sites mostly included respiratory and abdominal sites.

The results of the blood examinations are shown in Table 2. There were no significant differences in complete blood counts between the groups. The median levels of lactate in the two hypoglycemia groups were significantly higher than those in the euglycemia group, with that in the severe hypoglycemia group being 45 mg/dL compared with 16 mg/dL in the euglycemia group ($P < 0.05$). The median pH in the hypoglycemia group indicated more severe acidosis compared with that in the euglycemia group (7.16 versus 7.44; $P < 0.001$; Table 2).

Patients with severe hypoglycemia tended to have higher rates of positive blood cultures, and there was a difference in the rate of positive blood cultures between groups. However, there was no significant difference in bacterial species

Table 3. Bloodstream isolates

Pathogens	Isolates, *n* (%)
Gram-positive cocci	
Staphylococcus sp.	41 (15.5)
Streptococcus sp.	14 (5.3)
Enterococcus sp.	6 (2.3)
Peptostreptococcus sp.	1 (0.4)
Gram-positive rods	
Corynebacterium sp.	6 (2.3)
Bacillus sp.	5 (1.9)
Propionibacterium acnes	5 (1.9)
Actinomyces sp.	2 (0.8)
Clostridium tertium	1 (0.4)
Anaerobic Gram-positive rods	2 (0.8)
Gram-negative rods	
Escherichia coli	18 (6.8)
Klebsiella sp.	8 (3.0)
Pseudomonas aeruginosa	4 (1.5)
Bacteroides sp.	3 (1.1)
Serratia marcescens	1 (0.4)
Proteus mirabilis	1 (0.4)
Aeromonas sp.	1 (0.4)
Achromobacter xylosoxidans	1 (0.4)
Anaerobic Gram-negative rods	1 (0.4)
Fungi	
Candida albicans	2 (0.8)

collected from blood cultures between groups (Table 3). In all groups, the largest numbers of microorganisms collected from blood cultures were *Streptococcus* spp. among Gram-positive cocci and *Escherichia coli* among Gram-negative rods.

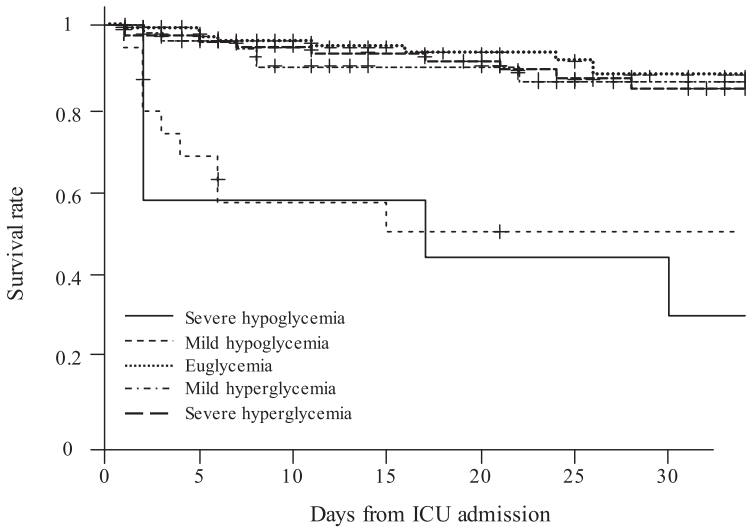
The Kaplan–Meier estimate of the probability of survival followed up to 28 days was lower in patients with severe and mild hypoglycemia than in those with euglycemia ($P < 0.05$; Fig. 2). Moreover, there was a significant difference in intensive care unit mortality between the severe hypoglycemia and euglycemia groups (71.4% versus 8.7%; $P < 0.05$; Table 4). We analyzed the hazard ratios for the groups (relative to the reference of euglycemia) adjusted for sex, age, and APACHE II and SOFA scores on admission, and the hazard ratios for 28-day mortality in patients with severe hypoglycemia and mild hypoglycemia as compared with that in the euglycemia group were 8.18 (95% confidence interval [CI], 2.39–27.96; $P = 0.001$) and 7.56 (95% CI, 2.96–19.35; $P < 0.001$), respectively (Table 5).[6,9] Figure 3 depicts the hazard ratio curves based on blood glucose level after adjustment for age, sex, and SOFA and APACHE II scores. Patients with lower blood glucose levels had a significantly higher risk of mortality into duration until 28 days rather than those with blood glucose levels of 140 mg/dL.

DISCUSSION

IN THIS STUDY, we found that septic patients who had severe hypoglycemia (blood glucose level ≤ 40 mg/dL) on admission had significantly higher mortality, significantly more severe acidosis as indicated by blood pH level, and significantly higher blood lactate level compared with those who had euglycemia.

Blood glucose level is maintained within normal range by various hormones such as cortisol, adrenaline, glucagon, growth hormone, and thyroid hormone. Although hyperglycemia is common in patients with sepsis due to increased insulin resistance, hypoglycemia has rarely been described as a clinical sign of severe bacterial sepsis.[10] Prevention and treatment of hypoglycemia in sepsis are important because hypoglycemia has been associated with mortality.

Regarding hypoglycemia, Ssekitoleko *et al.*[11] reported in a large prospective observational study in Uganda that septic patients with hypoglycemia on admission have a poor prognosis. The most common organisms causing sepsis are human immunodeficiency virus, *Mycobacterium tuberculosis*, and *Salmonella*, which are very different from the causative factors in the present study. However, because blood glucose monitoring is very simple and easily available, it



Number at risk

Severe hypoglycemia	7	4	4	4	3	3	3
Mild hypoglycemia	19	12	8	8	7	6	6
Euglycemia	103	93	77	64	53	50	43
Mild hyperglycemia	58	48	37	28	28	20	17
Severe hyperglycemia	78	71	57	52	46	37	33

Fig 2. Kaplan–Meier survival curves for patients with sepsis in the five categories of blood glucose levels. Mortality of patients with severe and mild hypoglycemia was significantly higher than that in patients with euglycemia ($P < 0.05$ by log-rank test). ICU, intensive care unit.

Table 4. Patients outcome based on blood glucose levels

	Severe hypoglycemia >180 mg/dL	Mild hypoglycemia >180 mg/dL	Euglycemia >180 mg/dL	Mild hyperglycemia >180 mg/dL	Hyperglycemia >180 mg/dL	All patients	*P* value
Disease course							
Length of ICU stay, median days (IQR)	5 (2–12)	6 (2–16)	13 (8–25)	9 (5–17)	16 (8–28)	13 (6–22)	0.008
Outcome, *n* (%)							
28-day mortality	5 (71.4)	9 (47.4)	9 (8.7)	7 (12.1)	10 (12.8)	40 (15.1)	<0.001

ICU, intensive care unit; IQR, interquartile range.

Table 5. Cox proportional hazards regression analysis of 28-day mortality based on blood glucose levels

	Hazard ratio	95% Confidence interval	*P* value
Severe hypoglycemia (≤40 mg/dL)	8.18	2.39–27.96	0.001
Mild hypoglycemia (41–70 mg/dL)	7.56	2.96–19.35	<0.001
Euglycemia (71–140 mg/dL)	1 (reference)	—	—
Mild hyperglycemia (141–180 mg/dL)	1.59	0.58–4.34	0.365
Hyperglycemia (>180 mg/dL)	1.3	0.53–3.21	0.568

Hazard ratios were adjusted for sex, age, and Acute Physiology and Chronic Health Evaluation II and Sequential Organ Failure Assessment baseline scores.

may be very useful in routine clinical practice for predicting mortality in septic patients. Kushimoto *et al*.[12] focused on blood glucose abnormalities in patients with sepsis and showed that patients with hypoglycemia (blood glucose level ≤70 mg/dL) without a history of diabetes had a higher mortality rate than those with euglycemia. In the present study, we focused on a group of patients with lower blood glucose level (≤40 mg/dL) than that in previous studies and showed that their mortality was higher. Patients with severe hypoglycemia were associated with severe metabolic acidosis and elevated lactate level, and had higher rates of positive blood culture and septic shock. Thus, hypoglycemia may be a marker for the early detection of severe clinical manifestations.

There are several possible mechanisms that may lead to hypoglycemia in septic patients. One such mechanism could be a lack of the hormones cortisol and adrenaline, which are essential for maintaining blood glucose level.[13,14] Critical illness is often accompanied by hypercortisolemia and hyperglycemia.[15] Sam *et al*.[16] reported that a high serum cortisol level in septic patients was associated with significantly higher mortality. Another potential mechanism of hypoglycemia in septic patients could be alteration in glucose metabolism. The first mechanism is failure of gluconeogenesis in

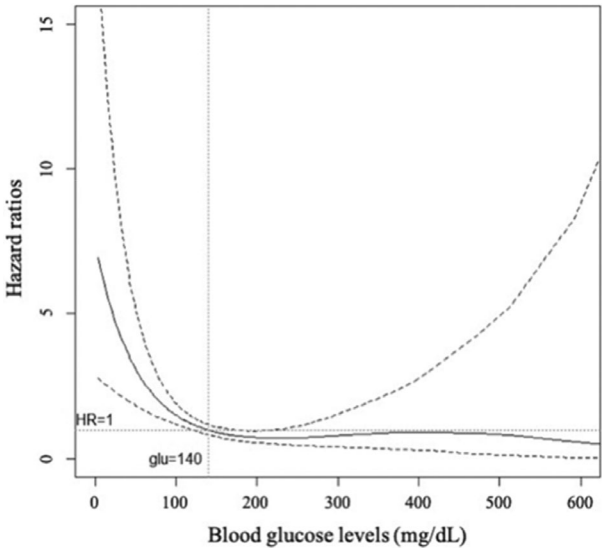


Fig 3. Hazard ratio (HR) curves based on blood glucose level after adjusting for age, sex, and SOFA and APACHE II scores. Patients with blood glucose levels of <140 mg/dL had a significantly higher risk of 28-day mortality compared with those with blood glucose levels of ≥140 mg/dL. APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment.

the liver. The final step of the gluconeogenesis pathway is catalysis by glucose-6-phosphatase (G6Pase), which hydrolyzes glucose to glucose-6-phosphate.[17] The other mechanism could be an increase in glucose consumption in peripheral tissues.[18] A shortage of glucose for cellular respiration can lead to a shortage of adenosine triphosphate and subsequent energy failure. In the present study, we did not evaluate these metabolic factors, but additional supplementation of these adrenal hormones and gluconeogenesis-related factors might be a treatment strategy to avoid severe hypoglycemia in addition to glucose administration.

The main pathogens from blood cultures of septic patients consist of *Staphylococcus aureus* among Gram-positive bacteria and *E. coli* and *Pseudomonas aeruginosa* among Gram-negative bacteria.[19] In the present study, the numbers of *P. aeruginosa* were not high, but the numbers of the other pathogens were similar to those of previous reports.

Low blood glucose levels in intensive care unit patients in the very early phase of sepsis have already been shown to be significantly related to mortality before using insulin.[4] Hypoglycemia on admission in patients with sepsis is also a critical prognosticator of mortality. In critically ill patients, decreased glycogen stores, failure of gluconeogenesis, and increased peripheral glucose utilization could lead to hypoglycemia.[20] The appropriate treatment based on the pathophysiology might lead to better outcomes in the future.

Limitations

There are some limitations to this study. This study was observed in a single center, so we did not analyze enough numbers of patients with hypoglycemia. Our results will need to be confirmed in a larger prospective study in the future. There may be unknown confounding factors that influenced the relationship between hypoglycemia and 28-day mortality. In addition, we could not investigate the mechanism of hypoglycemia, such as cortisol and glucagon.

CONCLUSION

IN CONCLUSION, SEPTIC patients who had severe hypoglycemia had significantly higher mortality compared with patients with euglycemia. Hypoglycemia occurring in the early phase of sepsis could be a critical prognosticator of mortality, and further study is needed to elucidate its pathophysiology and appropriate treatment.

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DISCLOSURE

APPROVAL OF THE research protocol with approval No. and committee Name: This study was approved by the Institutional Review Board of Osaka University (approval no.14186).

Informed Consent: N/A.

Registry and the Registration No. of the study/trial: N/A.

Animal Studies: N/A.

Conflict of Interest: None.

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