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Association of body mass index and hypoglycemia with mortality rates among sepsis patients: A retrospective sub-analysis of the FORECAST study

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Abstract

Aim: Hypoglycemia at admission is associated with high mortality in sepsis patients. However, the influence of body mass index (BMI) on this association remains unknown. Therefore, this study assesses the association of hypoglycemia at admission with mortality in patients with sepsis according to BMI.

Methods: This was a secondary analysis of a multicenter, prospective cohort study of 59 intensive care units in Japan. We included 1184 patients (age ≥16 years) with severe sepsis and excluded those with missing data on glucose level, BMI, or survival at discharge. The initial blood glucose level of <70 mg/dL was defined as hypoglycemia. Patients were assigned to the hypoglycemia or non-hypoglycemia group as per BMI category (<18.5 [low], 18.5–24.9 [normal], and ≥25 [high] kg/m^2). The main outcome was in-hospital mortality. Multivariate logistic regression models were used to evaluate BMI category-by-hypoglycemia interactions.

Results: Overall, 1103 patients, including 65 with hypoglycemia, were analyzed. In the normal BMI group, patients with hypoglycemia had a higher in-hospital mortality rate (18/38, 47.4%) than those without (119/584, 20.4%). There was a significant interaction between normal BMI and hypoglycemia affecting in-hospital mortality; however, this effect was not observed for other BMI categories (odds ratio, 2.32; 95% confidence interval, 1.05–5.07; p-value for interaction = 0.0476).

Conclusion: The relationship between patients with sepsis and hypoglycemia on admission may differ according to BMI. Hypoglycemia on admission may be associated with high mortality in patients with normal BMI, but not in those with low or high BMI.

KEYWORDS
blood glucose, body mass index, hypoglycemia, mortality, sepsis

INTRODUCTION

Sepsis is a life-threatening syndrome characterized by organ dysfunction because of infection.[1,2] It is estimated that, annually, >10 million patients with sepsis die, and the number of deaths is increasing.[1,3] The association of body mass index (BMI) with sepsis-related mortality has also been investigated. Studies from North America and Europe have demonstrated that a higher BMI was associated with lower mortality rates, whereas a report from China has indicated that while a higher BMI was not associated significantly with lower mortality rates, a lower BMI was associated with a high risk of mortality.[4–7]

Although the association between BMI, hypoglycemic event rate, and mortality in patients admitted to the intensive care unit (ICU) has been investigated using large international clinical databases, the influence of BMI on the association of initial hypoglycemia with survival outcomes

among patients with sepsis remains unclear. Compared with those of the normal BMI group, the high BMI groups showed a reduced hypoglycemic rate, whereas the low BMI group showed an increased rate of hypoglycemia. Hypoglycemic events were associated with increased mortality in all BMI groups[8]; however, the impact of initial hypoglycemia at admission was not determined. Previous reports have shown an association between hypoglycemia at admission and a high mortality rate in patients with sepsis.[9–12]

Therefore, this study assesses the association between hypoglycemia at admission and mortality in patients with sepsis according to BMI.

METHODS

Design, setting, and participants

This was a retrospective secondary analysis of the Focused Outcomes Research in Emergency Care in Acute Respiratory Distress Syndrome, Sepsis, and Trauma (FORECAST) study, which described the incidence, clinical characteristics, and evolving management of sepsis in Japan. The FORECAST study was a multicenter, prospective cohort study of sepsis patients from 59 ICUs, conducted between January 2016 and March 2017.[13] The study included patients (age ≥16 years) diagnosed with severe sepsis based on the 2003 Sepsis-2 criteria[14] because the FORECAST study was planned before the announcement of the Sepsis-3 criteria. All the patients were admitted to the ICU. Severe sepsis was defined as a diagnosis or suspected new-onset infection based on the history of present illness, with at least two criteria for systemic inflammatory response syndrome[15] and one criterion for organ dysfunction. Patients with limited data on sustained life care or post-cardiopulmonary arrest resuscitation status at the time of sepsis diagnosis were excluded.

In this secondary analysis, we screened all the patients enrolled in the FORECAST study. We excluded those with missing data on initial blood glucose level, BMI, or survival at discharge. Because data were rarely missing, no assumptions were made for such.

The FORECAST study protocol was approved by the ethics committees/institutional review boards (IRBs) of all the participating institutes in the Japanese Association for Acute Medicine Study Group, Japan (IRB number 014-0306, Hokkaido University, the representative of FORECAST). Data collection was performed as part of routine clinical workup without any interventions, and data management and statistical analyses were processed anonymously. Hence, the need for informed consent was waived by the ethics committees/IRBs.

Data collection

Data were compiled by the FORECAST investigators and obtained from the FORECAST database. We collected data on patient characteristics, admission source, pre-existing comorbidities assessed using the Charlson comorbidity index, activities of daily living, suspected sites of infection, organ dysfunction, sepsis-related severity scores, duration of mechanical ventilation and ICU stays, and survival information at 28 days post ICU admission and at hospital discharge. The Sequential Organ Failure Assessment (SOFA)[16] and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores[17] were calculated using physiological and laboratory data obtained at the initial examination as part of the routine medical workup. The blood glucose levels at the time of admission were measured using a blood gas analyzer, as recommended in the international sepsis guidelines,[18] and not using a glucometer.

Variable definitions

The patients were divided into three groups based on their initial BMI, according to the definition of the Japan Society for the Study of Obesity: <18.5 kg/m^2 (low BMI), 18.5–24.9 kg/m^2 (normal BMI), and ≥25 kg/m^2 (high BMI).[19] The patients in each group were further divided into two groups depending on their initial blood glucose levels: <70 mg/dL (hypoglycemia) or ≥70 mg/dL (non-hypoglycemia). Although not universally defined, blood glucose levels of <70 mg/dL are widely accepted as the definition of hypoglycemia.[20] In the subgroup analysis, 28-day and in-hospital mortality were assessed in patients with or without diabetes mellitus (DM). Septic shock and organ dysfunction were defined using the Sepsis-2 criteria.[14] The Charlson comorbidity index was classified into four groups as previously defined: 0 (none), 1–2 (low), 3–4 (moderate), and ≥5 (high) points.[21]

Outcome

The primary outcome was in-hospital mortality.

Statistical analyses

Descriptive statistics included counts (proportions) for categorical variables and medians (interquartile ranges) for continuous variables, given that not all variables followed a normal distribution. The categorical variables were compared using the χ^2 test, and the continuous variables were compared using the Mann–Whitney U test between patients with initial blood glucose levels of <70 mg/dL and those with ≥70 mg/dL in each BMI category. To examine the heterogeneity of the association of hypoglycemia with in-hospital mortality across each BMI category, we performed a multivariable logistic regression analysis with the interaction term between the BMI category and hypoglycemia in each BMI category group. In this multivariable logistic regression analysis, the outcome variable was in-hospital mortality, and explanatory variables were blood glucose levels of

<70 mg/dL or not, age, SOFA score, and Charlson comorbidity index. Statistical significance was defined as *p*-values of <0.05 and statistical analyses were performed using JMP 15 (SAS Institute).

RESULTS

The FORECAST study registered 1184 patients; however, 81 were excluded because of missing data on their initial blood glucose level, BMI, or survival information at hospital discharge. Finally, we analyzed the data of 1103 patients with severe sepsis. The patients were divided into three groups according to their BMI categories: 223 patients with low BMI, 622 with normal BMI, and 258 with high BMI. Furthermore, patients in each BMI category were divided according to hypoglycemia or non-hypoglycemia. Patients in the low BMI category were divided as follows: 13/1103 (1% of all included patients) with hypoglycemia and 210/1103 (19%) with non-hypoglycemia. Patients in other BMI categories were divided as follows: 38/1103 (2%) and 584/1103 (53%) in the normal BMI category and 14/1103 (1%) and 244/1103 (22%) in the high BMI category with hypoglycemia and non-hypoglycemia, respectively (Figure 1).

Patient characteristics and clinical outcomes

The patient characteristics are shown in Table 1 (detailed characteristics are shown in Table S1). The median patient age was 73 (64–81) years, and the median BMI was 21.7 (19.0–24.7) kg/m^2. Of the 1038 patients, 23.3% were diagnosed with DM before admission. The proportion of patients with pre-existing DM was similar between patients with and without hypoglycemia in all the BMI categories. The most suspected site of infection was the lungs (31.1%), followed by the abdomen (25.7%). The SOFA scores, APACHE II scores, and lactate levels tended to be higher in patients with hypoglycemia than in those without hypoglycemia in all the BMI categories. The clinical outcomes of the patients are shown in Table 2 (results of the outcome measures are listed in Table S2). In all patients, the in-hospital and 28-day mortality rates were 253/1103 (22.9%) and 200/1093 (18.3%), respectively, which were higher among those with hypoglycemia than in those without hypoglycemia in the normal BMI group (18/38 [47.4%] vs. 119/584 [20.4%], *p* = 0.0001, and 16/38 [42.1%] vs. 89/577 [15.4%], *p* < 0.0001, respectively). However, these rates were similar in the low and high BMI groups. In patients without DM in the normal BMI group, in-hospital and 28-day mortality were higher in patients with hypoglycemia than in those without. In patients with DM in the normal BMI group, for patients with and without hypoglycemia, in-hospital and 28-day mortality showed similar tendencies, with no significant differences (Table S3).

Interaction between hypoglycemia and BMI category for in-hospital mortality

There was a significant interaction between normal BMI and hypoglycemia on in-hospital mortality (odds ratio, 2.32; 95% confidence interval, 1.05–5.07; *p*-value for interaction = 0.0476), whereas no similar interaction was found between low or high BMI and hypoglycemia (age, SOFA score, and Charlson comorbidity index were adjusted in the multivariate logistic regression model) (Figure 2). Overall, hypoglycemia was not significantly associated with increased mortality (Table S4).
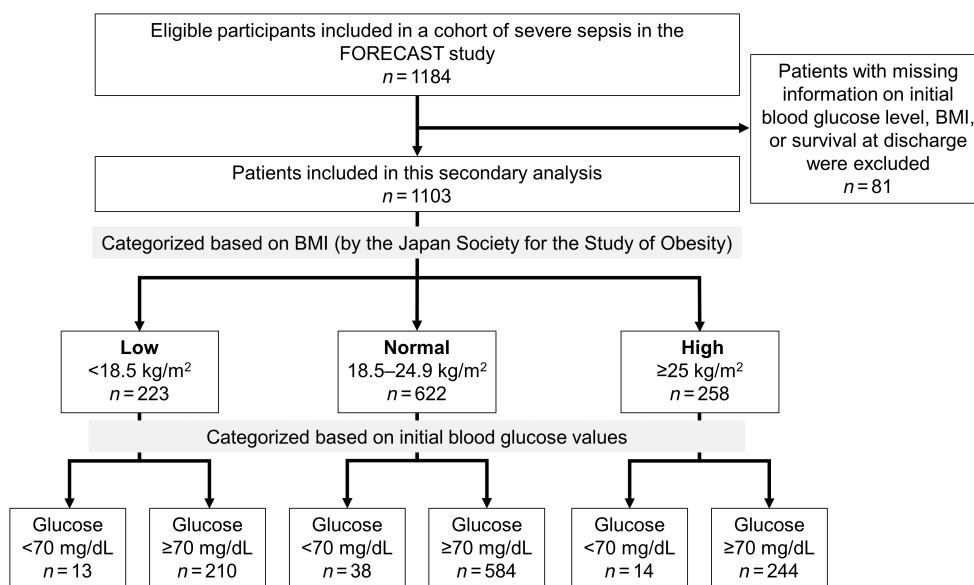

FIGURE 1 Flowchart of the patient selection process. BMI, body mass index; FORECAST study, Focused Outcomes Research in Emergency Care in Acute Respiratory Distress Syndrome, Sepsis, and Trauma study.

TABLE 1 Characteristics of patients classified by BMI category and glucose levels on admission.

Characteristics	All patients (n=1103)	Low BMI (n=223)			Normal BMI (n=622)			High BMI (n=258)		
		Glucose <70 mg/dL (n=13)	Glucose ≥70 mg/dL (n=210)	p-value	Glucose <70 mg/dL (n=38)	Glucose ≥70 mg/dL (n=584)	p-value	Glucose <70 mg/dL (n=14)	Glucose ≥70 mg/dL (n=244)	p-value
Age (years)	73 (64–81)	71 (58.0–79.5)	75 (67–83)	0.224	74 (69.5–80)	73 (64–82)	0.297	68 (64–72.5)	69 (61–80)	0.581
Sex (male)	664 (60.2)	6 (46.2)	114 (54.3)	0.568	19 (50.0)	368 (63.0)	0.109	6 (42.8)	151 (61.9)	0.156
BMI (kg/m²)	21.7 (19.0–24.7)	15.6 (14.9–17.4)	16.8 (15.2–17.8)	0.429	21.2 (19.7–23.2)	21.5 (19.9–23.1)	0.722	29.8 (26.4–31.8)	27.0 (25.8–30.4)	0.123
Glucose (mg/dL)	136 (104–188)	40 (25.5–61)	133.5 (105–179)	<0.0001	51.5 (36–63)	139 (110–192)	<0.0001	59 (47–53)	146.5 (116.5–199)	<0.0001
SOFA score	9 (6–11)	10 (7–14)	9 (6–11)	0.177	11 (9–14.5)	8 (6–11)	<0.0001	12 (10–13)	8 (5–12)	0.00168
APACHE II score	22 (17–29)	26 (20–31)	22 (17–30)	0.433	29 (21–38)	22 (17–29)	0.0003	30 (23–36)	22 (16–30)	0.087
Pre-existing DM	257 (23.3)	2 (15.4)	34 (15.7)	0.975	7 (18.4)	129 (22.1)	0.596	4 (28.6)	82 (33.6)	0.698
CCI	1 (0–2)	1 (0–2)	1 (0–2)	0.710	1 (0–2)	1 (0–2)	0.629	1 (0–3.5)	1 (0–2)	0.947
Septic shock	684 (62.0)	11 (84.6)	137 (65.2)	0.151	31 (81.6)	359 (61.5)	0.0130	12 (85.7)	134 (54.9)	0.0238

Note: Number of patients with missing data: SOFA score, 158; APACHE II score, 112; other variables, 0.

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; BMI, body mass index; CCI, Charlson Comorbidity Index; DM, diabetes mellitus; SOFA, Sequential Organ Failure Assessment.

TABLE 2 Clinical outcomes of patients with or without hypoglycemia classified by BMI.

Outcomes	All patients (n=1103)	Low BMI (n=223)			Normal BMI (n=622)			High BMI (n=258)		
		Glucose <70 mg/dL (n=13)	Glucose ≥70 mg/dL (n=210)	p-value	Glucose <70 mg/dL (n=38)	Glucose ≥70 mg/dL (n=584)	p-value	Glucose <70 mg/dL (n=14)	Glucose ≥70 mg/dL (n=244)	p-value
In-hospital mortality	253/1103 (22.9)	3/13 (23.1)	53/210 (25.2)	0.862	18/38 (47.4)	119/584 (20.4)	0.0001	3/14 (21.4)	57/244 (23.4)	0.868
Twenty-eight-day mortality	200/1093 (18.3)	3/13 (23.1)	43/209 (20.6)	0.829	16/38 (42.1)	89/577 (15.4)	<0.0001	3/14 (21.4)	46/242 (19.0)	0.823
ICU-free days	19 (11–24)	16.5 (10–24)	20 (13–25)	0.355	17 (9.5–22)	19 (10–24)	0.437	13 (4–20)	20 (11–24)	0.097
Length of hospital stay	24 (12–46)	22 (6–40)	24 (14–45)	0.524	27 (4–44)	26 (13–47)	0.260	24 (19–52)	21 (11–46)	0.200

Note: Number of missing data: 28-day mortality, 10; ICU-free days, 210; length of hospital stay, 0.

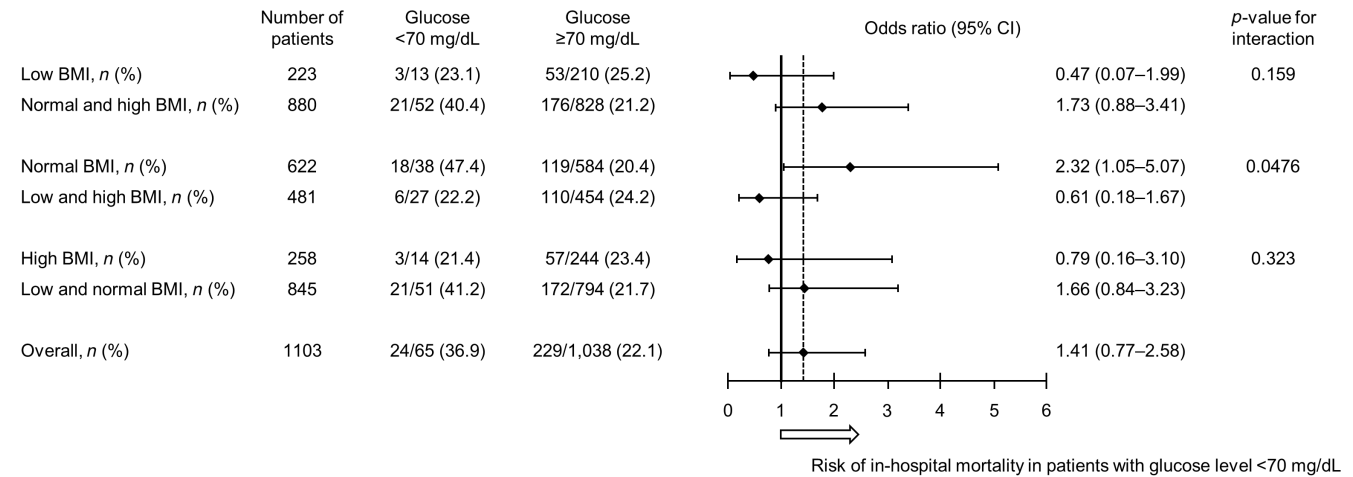Abbreviations: BMI, body mass index; ICU, intensive care unit.

	Number of patients	Glucose <70 mg/dL	Glucose ≥70 mg/dL	Odds ratio (95% CI)	p-value for interaction
Low BMI, n (%)	223	3/13 (23.1)	53/210 (25.2)	0.47 (0.07–1.99)	0.159
Normal and high BMI, n (%)	880	21/52 (40.4)	176/828 (21.2)	1.73 (0.88–3.41)	
Normal BMI, n (%)	622	18/38 (47.4)	119/584 (20.4)	2.32 (1.05–5.07)	0.0476
Low and high BMI, n (%)	481	6/27 (22.2)	110/454 (24.2)	0.61 (0.18–1.67)	
High BMI, n (%)	258	3/14 (21.4)	57/244 (23.4)	0.79 (0.16–3.10)	0.323
Low and normal BMI, n (%)	845	21/51 (41.2)	172/794 (21.7)	1.66 (0.84–3.23)	
Overall, n (%)	1103	24/65 (36.9)	229/1,038 (22.1)	1.41 (0.77–2.58)	

Risk of in-hospital mortality in patients with glucose level <70 mg/dL

FIGURE 2 Interaction between body mass index (BMI) category and hypoglycemia for in-hospital mortality. Row 1: odds ratios of hypoglycemia for in-hospital mortality in patients with low body mass index (BMI). Row 2: odds ratios of hypoglycemia for in-hospital mortality in patients with normal and high BMI. Row 3: odds ratios of hypoglycemia for in-hospital mortality in patients with normal BMI. Row 4: odds ratios of hypoglycemia for in-hospital mortality in patients with low and high BMI. Row 5: odds ratios of hypoglycemia for in-hospital mortality in patients with high BMI. Row 6: odds ratios of hypoglycemia for in-hospital mortality in patients with low and normal BMI. Row 7: odds ratios of hypoglycemia for in-hospital mortality in all patients. The odds ratios and 95% confidence intervals (CIs) were obtained using a multivariable logistic regression model. Squares indicate odds ratios. Horizontal bars indicate 95% CIs. The dotted vertical line indicates the odds ratio of hypoglycemia for in-hospital mortality in all patients. Rows 1 and 2, 3 and 4, and 5 and 6 show the interaction between patients in a BMI group and the others. In rows 3 and 4, the interaction was significant (p-value for interaction = 0.0476) between odds ratios 2.32 (1.05–5.07) for in-hospital mortality of hypoglycemia in patients with normal BMI and odds ratios 0.61 (0.18–1.67) for in-hospital mortality of hypoglycemia in patients with low and high BMI. In rows 1 and 2, and 5 and 6, the interactions were not significant. These results indicate that hypoglycemia was associated with increased in-hospital mortality in only the normal BMI group. Low BMI, <18.5 kg/m^2; normal BMI, 18.5–24.9 kg/m^2; high BMI, ≥25 kg/m^2.

DISCUSSION

In this study, we found that the relationship between patients with sepsis and hypoglycemia on admission may differ according to BMI, and that hypoglycemia on admission may be associated with high mortality in patients with normal BMI, but not in those with low or high BMI.

Previous studies showed that hypoglycemia was associated with a high mortality rate in sepsis patients and those who were critically ill.[8,10–12] A multicenter observational study of sepsis patients in Japan suggested that hypoglycemia was related to increased mortality in patients with sepsis.[10] However, the BMI category was not adjusted in this study and hypoglycemia was not associated with increased mortality when adjusted for BMI categories (Table S4).

The secondary analysis of the large databases indicated that the BMI category may influence hypoglycemic events; low BMI was associated with increased hypoglycemic event rate, whereas high BMI was associated with reduced hypoglycemic event rate in critically ill patients.[8] Therefore, adjusting for the BMI category might be needed when assessing the impact of hypoglycemia on outcomes. To the best of our knowledge, this is the first study to examine the association between hypoglycemia at admission and mortality in sepsis patients according to BMI categories.

One study reported that patients with sepsis with hypoglycemia at admission are at risk of high mortality in all BMI groups.[10] Meanwhile, we found that only patients with sepsis with hypoglycemia and normal BMI were associated with high mortality. The reason low and high BMIs were not associated with worse mortality in patients with hypoglycemia remains to be determined. Adipose tissue and lipoproteins are related to BMI,[22] and the amount of adipose tissue and lipoproteins is possibly related to the robustness of the host defense system.[23,24] Therefore, the amount may affect the host defense of patients with sepsis and hypoglycemia. High BMI with plenty of adipose tissue and lipoproteins and low BMI with a low amount of adipose tissue and lipoproteins may be associated with robust and relatively vulnerable host defensive potentials, respectively.[25] Although hypoglycemia has been shown to be associated with high mortality and disease severity in patients with sepsis, disease severity may not significantly influence mortality in patients with low or high BMI showing different defense potentials. Further studies are warranted to elucidate the biological response of adipose tissue and lipoproteins to hypoglycemia in patients with sepsis. Further studies are warranted to elucidate the biological reaction of adipose tissue and lipoproteins to hypoglycemia in patients with sepsis.

Limitations

This study has some limitations. First, because these data were collected before the Sepsis-3 criteria were published, the definition of sepsis used in this study differed from the latest definition. Second, the number of patients with hypoglycemia was too small to be assessed with sufficient statistical power. Third, all participants were Japanese; therefore, generalizability might be limited to East Asians. Fourth,

only a few explanatory variables in the multivariate analysis were considered because not many patients died. Fifth, whether mortality in patients with hypoglycemia was affected by DM treatment (insulin or antidiabetic drugs) before admission was not elucidated because the database did not include information on DM treatment. However, in patients either with or without DM in the normal BMI group, mortality in patients with hypoglycemia was high compared with those without hypoglycemia. Therefore, the influence of DM treatment on mortality may not be significant.

CONCLUSION

Our findings suggest that the relationship between patients with sepsis and hypoglycemia on admission may differ according to BMI, and that hypoglycemia on admission is associated with high mortality in patients with normal BMI, but not in those with low or high BMI. The presence of hypoglycemia in patients with sepsis, especially those with normal BMI, may warrant increased attention on admission. Our findings remain to be confirmed in larger cohort studies.

CONFLICT OF INTEREST STATEMENT
The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT
Research data are not shared.

ETHICS STATEMENT
Approval of the research protocol: The study protocol was reviewed and approved by the ethics committee of all participating institutes in the JAAM study group, Japan (IRB No. 015-0021 on Hokkaido University, the representative for FORECAST).
Informed consent: N/A.
Registry and the registration no. of the study/trial: The University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR ID: UMIN000019702), Date of registration: 11/09/2015, https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000022760.
Animal studies: N/A.

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SUPPORTING INFORMATION

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