Association of Body Mass Index and Hypoglycaemia with Mortality Rates Among Sepsis Patients: A Retrospective Sub-Analysis of the FORECAST Study

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Research

Keywords: Blood glucose, body mass index, mortality, sepsis

Posted Date: June 28th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-615999/v1

Abstract

Background: Hypoglycaemia at admission is associated with high mortality in sepsis patients. The association of hypoglycaemia and body mass index (BMI) with mortality in sepsis patients has not been clarified. We aimed to assess the influence hypoglycaemia at admission on mortality in sepsis patients according to BMI categories.

Methods: This was a secondary analysis of a multicentre, prospective cohort study of 59 intensive care unit in Japan. The study included 1,184 patients (age ≥16 years) with severe sepsis; the diagnosis was made based on the Sepsis-2 criteria. After excluding patients with missing data of glucose level, BMI, or survival at discharge, patients were divided into groups according to the initial blood glucose level, <70 (hypoglycaemia) or ≥70 (non-hypoglycaemia) mg/dL, and according to BMI categories, <18.5 (low), 18.5–24.9 (normal), and ≥25 (high) kg/m^2. The main outcome measure was in-hospital mortality. A multivariate logistic regression model was used to examine the association between hypoglycaemia and in-hospital mortality. BMI category-by-hypoglycaemia interactions were evaluated to assess the heterogeneity of the impact of hypoglycaemia on in-hospital mortality across BMI categories.

Results: In total, 1,103 patients, including 65 patients with hypoglycaemia, were analysed. Among patients with hypoglycaemia, 13 had low, 38 had normal, and 14 had high BMI. Patients with hypoglycaemia showed higher in-hospital mortality (18/38, 47.4%) than those without hypoglycaemia (119/584, 20.4%) in the normal BMI group but not in the low and high BMI groups. In the multivariate logistic regression model, hypoglycaemia was not significantly associated with higher mortality in all patients (odds ratio [OR] 1.41; 95% confidence interval [CI] 0.77–2.58). However, there was a significant interaction between patients with normal BMI and hypoglycaemia on in-hospital mortality but not between patients with low or high BMI and hypoglycaemia (OR 2.32, 95% CI 1.05–5.07), and *p* for interaction: 0.0476).

Conclusions: Hypoglycaemia at admission in sepsis patients was associated with high mortality in patients with normal BMI, but not in those with low or high BMI. This association may be used as a prognostic marker in sepsis patients.

Background

Sepsis is a life-threatening syndrome characterised by organ dysfunction due to infection [1, 2]. It is estimated that more than 10 million sepsis patients die each year, and the number of deaths is increasing [1, 3].

Previous reports showed that hypoglycaemia at admission is associated with a high mortality in sepsis patients [4–7]. The association of body mass index (BMI) with sepsis-related mortality has also been investigated. Studies from North America and Europe demonstrated that higher BMI was associated with lower mortality rates, while a report from China indicated that higher BMI was not significantly associated with lower mortality rates, but lower BMI was associated with a high risk of death [8–11].

In addition to these inconsistent results, it remained unclear whether hypoglycaemia is associated with survival outcomes regardless of BMI or only for a particular BMI category. This study aimed to assess the association between hypoglycaemia at admission and mortality in sepsis patients according to BMI categories.

Methods

Design, setting, and participants

This is 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 multicentre, prospective cohort study of sepsis patients at 59 intensive care units (ICUs), and it was conducted between January 2016 and March 2017 [12]. The subjects were patients (age ≥ 16 years) diagnosed with severe sepsis based on the Sepsis-2 criteria in 2003 [13] 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 [14], and at least one criterion for organ dysfunction. Exclusion criteria included the limitation of sustained life care or post-cardiopulmonary arrest resuscitation status at the time of sepsis diagnosis.

In this secondary analysis, we screened all patients included in the FORECAST study. We excluded patients with missing data of initial blood glucose level, BMI, or survival at discharge. Because only few data were missing, we did not make any assumptions for missing data.

The FORECAST study protocol was reviewed and approved by the ethics committee of all participating institutes in the Japanese Association for Acute Medicine (JAAM) Study Group, Japan (IRB number 014–0306, Hokkaido University the presentative for FORECAST). Data collection was performed as a 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 committee/institutional review board.

Data collection

Data were compiled by the FORECAST investigators and obtained from the FORECAST database. We collected data of patient characteristics, admission source, pre-existing comorbidities assessed using the Charlson comorbidity index, activities of daily living (ADL), suspected sites of infection, organ dysfunction, sepsis-related severity scores, duration of mechanical ventilation and ICU stays, and survival information 28 days after ICU admission and at hospital discharge. The Sequential Organ Failure Assessment (SOFA) score [15] and the Acute Physiology and Chronic Health Evaluation II (APACHE II) score [16] were calculated using physiological and laboratory data on the initial examination as part of the routine medical workup. Blood glucose levels were measured using a blood gas analyser, as recommended by the international sepsis guidelines [17], and not using a glucometer. All glucose levels were measured before corticosteroid administration, if possible.

Date definitions

Patients were divided into two groups depending on their initial blood glucose levels: <70 mg/dL (hypoglycaemia) or ≥ 70 mg/dL (non-hypoglycaemia). Although not universally defined, blood glucose levels of < 70 mg/dL are widely accepted as the definition of hypoglycaemia [18].

BMI classification was made based on the definition of the Japan Society for the Study of Obesity [19]: <18.5 kg/m^2 (low BMI), 18.5–24.9 kg/m^2 (normal BMI), and ≥ 25 kg/m^2 (high BMI). Septic shock and organ dysfunction were defined using Sepsis-2 criteria [13]. The Charlson comorbidity index was classified into four groups as previously defined: 0 (none), 1–2 (low), 3–4 (moderate), and ≥ 5 (high) points [20].

Outcome

The primary outcome was in-hospital mortality.

Statistical analysis

Descriptive statistics included counts (proportions) for categorical variables and medians (interquartile range, IQR) for continuous variables, as not all variables had normal distribution. Categorical variables were compared using chi-square tests, and continuous variables were compared using the Mann-Whitney U test. We performed a multivariable logistic regression analysis using in-hospital mortality as the objective variable and blood glucose level of < 70 mg/dL or not, three BMI category groups, age, SOFA score, and Charlson comorbidity index, as explanatory variables. To examine the heterogeneity of the impact of hypoglycaemia on in-hospital mortality across each BMI category, we performed a multivariable logistic regression analysis including the interaction term between BMI category and hypoglycaemia in each BMI category group. Statistical significance was defined as $p < 0.05$, and statistical analyses were performed using JMP® 15 (SAS Institute Inc., Cary, NC, USA).

Results

The FORECAST study registered 1,184 patients. Eighty-one patients were excluded because of missing data of the initial blood glucose level, BMI, or survival information at hospital discharge. Finally, we analysed data from 1,103 patients with severe sepsis.

The patients were divided into two groups according to blood glucose levels: 65 patients with hypoglycaemia and 1,038 patients without hypoglycaemia. Furthermore, patients with hypoglycaemia were divided according to BMI categories: 13/1,103 (1% of all included patients) with low BMI, 38/1,103 (2%) with normal BMI, and 14/1,103 (1%) with high BMI. Patients without hypoglycaemia were also divided: 210/1,103 (19%), 584/1,103 (53%), and 244/1,103 (22%), respectively (Fig. 1).

Patient characteristics and clinical outcomes

Patient characteristics are shown in Table 1 (detailed characteristics are shown in **Supplemental Table 1**). Median patient age was 73 (64–81) years, and BMI was 21.7 kg/m^2 (19.0–24.7). Of the 1,038 patients, 23.3% were diagnosed with DM before admission. The proportion of patients with pre-existing DM was similar between patients with and without hypoglycaemia in all BMI categories. The most suspected site of infection was the lung (31.1%), followed by the abdomen (25.7%). SOFA score, APACHE II score, and lactate levels tended to be higher in patients with hypoglycaemia than those without hypoglycaemia in all BMI categories.

Table 1
Characteristics of patients classified by body mass index category and glucose levels on admission

	All patients	**BMI low (n = 223)**			**BMI normal (n = 622)**			**BMI high (n = 258)**		
	(n = 1103)	Glucose <70 mg/dL	Glucose ≥ 70 mg/dL	*p* value	Glucose < 70 mg/dL	Glucose ≥ 70 mg/dL	*p* value	Glucose < 70 mg/dL	Glucose ≥ 70 mg/dL	*p* value
		(n = 13)	(n = 210)		(n = 38)	(n = 584)		(n = 14)	(n = 244)	
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/m^2)	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)	< .0001	51.5 (36–63)	139 (110–192)	< .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)	< .0001	12 (10–13)	8 (5–12)	0.00168
APACHE II score	22 (17–29)	26 (20–31)	22 (17–30)	0.433	29 (21–38.5)	22 (17–29)	0.0003	29.5 (23–35.5)	22 (16–30)	0.087
Pre-existing diabetes mellitus	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
Charlson Comorbidity Index	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
Number of patients with missing data: SOFA score, 158; APACHE II score, 112										
APACHE, acute physiology and chronic health evaluation; BMI, body mass index; SOFA, sequential organ failure assessment										

The clinical outcomes are shown in Table 2 (detailed results of outcome measures are shown in **Supplemental Table 2**). In all patients, the in-hospital and 28-day mortality rates were 253/1103 (22.9%) and 200/1093 (18.3%), respectively. The in-hospital and 28-day mortality rates were higher in patients with hypoglycaemia than those without hypoglycaemia 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%], $p < .0001$, respectively). However, these rates were similar in low and high BMI groups.

Table 2
Clinical outcomes in patients with or without hypoglycaemia classified by body mass index.

	All patients	**BMI low (n = 223)**			**BMI normal (n = 622)**			**BMI high (n = 258)**		
	(n = 1103)	Glucose < 70 mg/dL	Glucose ≥ 70 mg/dL	*p* value	Glucose < 70 mg/dL	Glucose ≥ 70 mg/dL	*p* value	Glucose < 70 mg/dL	Glucose ≥ 70 mg/dL	*p* value
		(n = 13)	(n = 210)		(n = 38)	(n = 584)		(n = 14)	(n = 244)	
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
28-day mortality	200/1093 (18.3)	3/13 (23.1)	43/209 (20.6)	0.829	16/38 (42.1)	89/577 (15.4)	< .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 (5.5–40)	24 (14–45)	0.524	27 (4–44)	25.5 (13–47)	0.260	23.5 (19–52.5)	21 (11–46)	0.200
Number of missing data: 28-day mortality, 10; ICU-free days, 210										
BMI, body mass index; ICU, intensive care unit										

Interaction between hypoglycaemia and BMI category for in-hospital mortality

In the multivariate logistic regression model, hypoglycaemia was not significantly associated with higher mortality in all patients (Table 3). However, there was a significant interaction between patients with normal BMI and hypoglycaemia on in-hospital mortality (OR 2.32, 95% CI 1.05–5.07, *p* value for interaction = 0.0476), whereas there was no interaction between patients with low or high BMI and hypoglycaemia (Fig. 2).

Table 3
Odds ratios for in-hospital mortality.

Variables	**Odds ratio**	**95% CI**	***p*-value**
Glucose level < 70 mg/dL	1.41	0.77–2.58	0.268
BMI low vs. normal	1.19	0.78–1.81	0.407
BMI high vs. normal	1.09	0.73–1.62	0.662
BMI high vs. low	0.92	0.56–1.50	0.724
Age	1.02	1.00–1.03	0.0189
SOFA	1.18	1.13–1.23	< 0.0001
Charlson Comorbidity Index	1.22	1.12–1.34	< 0.0001
BMI, body mass index; CI, confidence interval; SOFA, sequential organ failure assessment			

Discussion

We found that hypoglycaemia at admission in sepsis patients was associated with high mortality in patients with normal BMI but not in those with low and high BMI. To the best of our knowledge, this is the first study to examine the association between hypoglycaemia at admission and mortality in sepsis patients according to BMI categories.

Hypoglycaemia is associated with a high mortality rate in sepsis patients and critically ill patients [5–7]. The NICE-SUGAR study demonstrated that hypoglycaemia was associated with an increased risk of death, especially among patients with distributive shock [6]. Patients with both septic shock and hypoglycaemia on the day of enrolment had a 2.5-fold higher mortality rate than those without septic shock and hypoglycaemia in a multicentre observational study of sepsis patients in Japan [5].

The proportion of BMI in the population varies widely across countries and regions. A population-based study of adults was conducted in 200 countries in 2014, and it revealed that the proportions of high BMI (BMI ≥ 25), normal BMI, and low BMI (BMI < 18.5) were 50–60%, 30%, and < 5%, respectively, in Western countries, and 30%, 50%, and 10–20%, respectively, in East Asian countries [20]. Observational studies in sepsis patients of Western countries showed that the population with high BMI accounted for more than 50% and that of low BMI accounted for less than 10%, and sepsis patients with high BMI had better survival outcomes, suggesting “obesity paradox” [8–10]. By contrast, a study conducted in China reported that low BMI was an independent factor associated with reduced 90-day survival [11]. In addition, a retrospective observational study using two cohorts in Japan (including the FORECAST study) showed that patients with low BMI had a significantly higher 28-day mortality than those without low BMI [21]. However, previous studies did not address the association between hypoglycaemia at admission and mortality in sepsis patients according to BMI categories.

The mechanism by which low and high BMIs were not associated with worse mortality in patients with hypoglycaemia was not clear. Adipose tissue and lipoproteins are related to BMI [22], and adipose tissue and lipoproteins are associated with inflammation [23, 24]. The amount of adipose tissue and lipoproteins may depend on the host defence of patients with sepsis and hypoglycaemia. Further studies should be conducted to elucidate the mechanism of the biological reaction of adipose tissue and lipoproteins to hypoglycaemia in sepsis patients.

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 was different from the latest definition. Second, the number of patients with hypoglycaemia was too small to be assessed with sufficient statistical power. Third, all of our participants were Japanese; thus, generalisability might be limited to East Asians. Fourth, we could use a few explanatory variables in the multivariate analysis because not many patients died.

Conclusions

Hypoglycaemia at admission in sepsis patients was associated with high mortality in patients with normal BMI, but not in those with low and high BMI. This association may be used as a prognostic marker in sepsis patients. In the future, larger cohort studies are needed to confirm this finding.

Abbreviations

ADL
Activities of daily living
APACHE II
Acute Physiologic Assessment and Chronic Health Evaluation II
BMI
Body mass index
CCI
Charlson Comorbidity Index
DM

Diabetes mellitus
FORECAST
Focused Outcomes Research in Emergency Care in Acute Respiratory Distress Syndrome, Sepsis, and Trauma
ICU
Intensive care unit
IQR
Interquartile range
SOFA
Sequential Organ Failure Assessment

Declarations

Ethics approval and consent to participate

The study protocol was reviewed and approved by the ethics committee of all participating institutes in the Japanese Association for Acute Medicine (JAAM) Study Group, Japan. (IRB number 014–0306 Hokkaido University, the representative for FORECAST). Data collection was performed as a 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 committee/institutional review board.

Consent for publication

Not applicable.

Availability of data and materials

The dataset of the FORECAST study is not publicly available, based on the decision made by the Japanese Association for Acute Medicine.

Competing interests

The authors declare that they have no competing interests.

Funding

This work was supported by JSPS KAKENHI Grant Number JP 19H03755 for language editing.

Authors' contributions

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by AT and DK. Statistical analyses were reviewed by DK and HO. The first draft of the manuscript was written by AT. The manuscript was reviewed and edited by DK and SK, and all authors commented on the previous versions of the manuscript. All authors read and approved the final manuscript.

Acknowledgements

We thank the core investigators of the FORECAST study (Appendix) for providing the dataset. We are grateful to all investigators involved in the FORECAST study for contributing to data collection and assessment.

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Figures

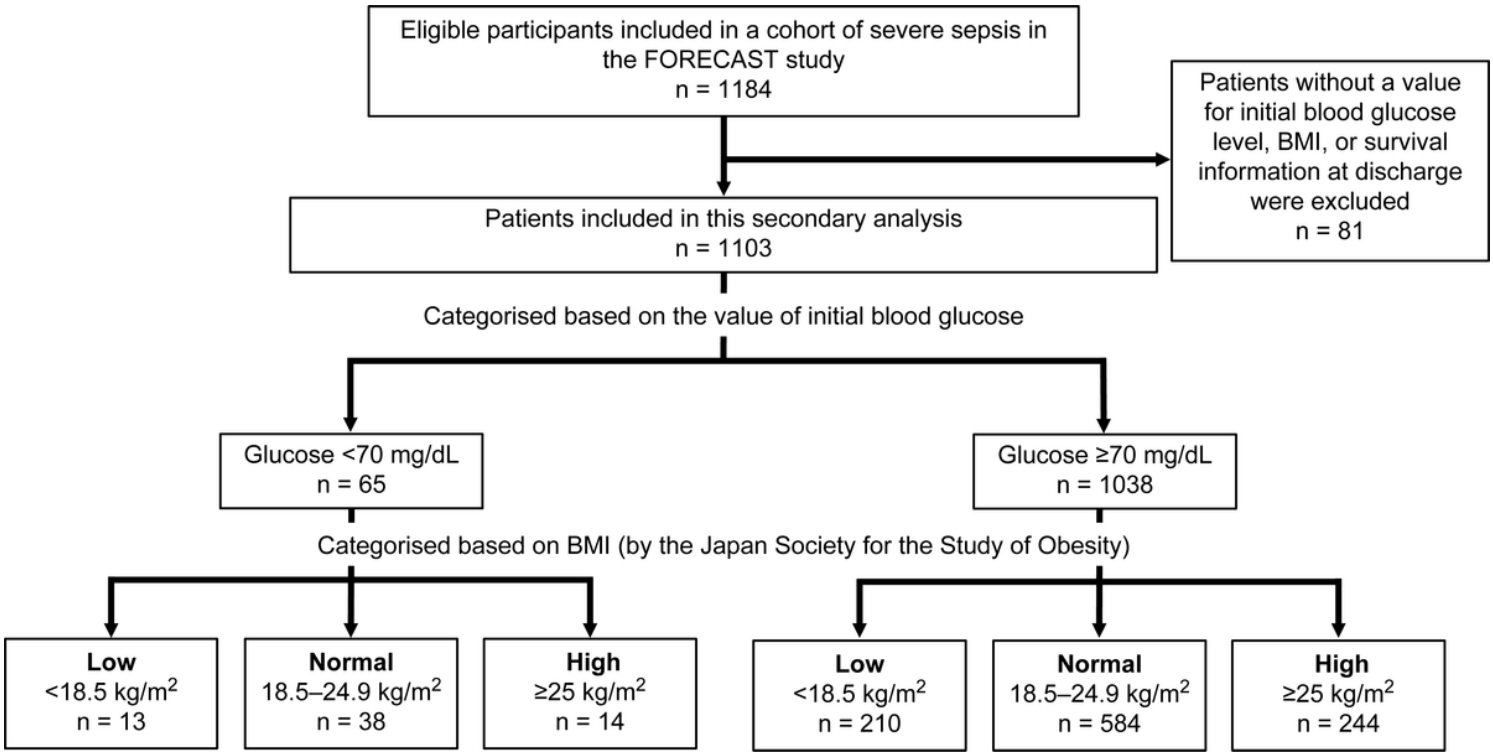

Figure 1

Flowchart of the patient selection process.

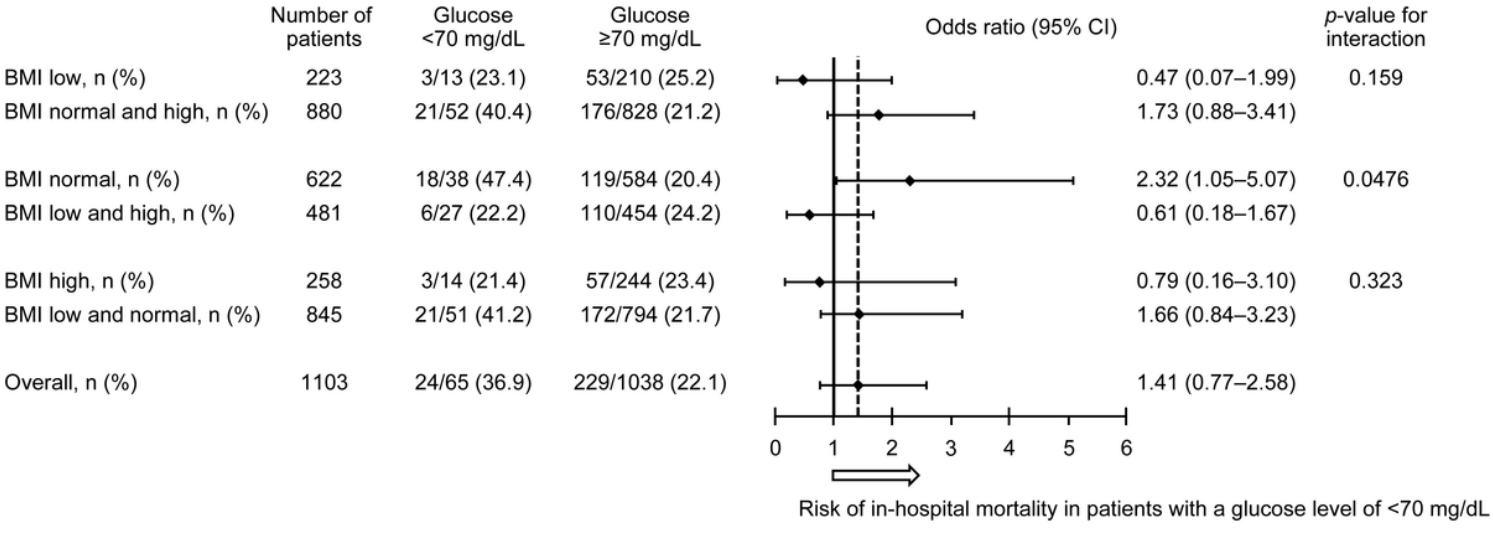

Figure 2

Interaction between body mass index category and hypoglycaemia for in-hospital morality. Odds ratios of hypoglycaemia for in-hospital mortality in each BMI category are shown. Odds ratios and 95% CIs were obtained using a multivariable logistic regression model. Squares indicate odds ratios. Horizontal bars indicate 95% confidence intervals. The dotted vertical line

indicates the odds ratio of hypoglycaemia for in-hospital mortality in all patients. Low BMI, <18.5 kg/m2; normal BMI, 18.5–24.9 kg/m2; high BMI, ≥25 kg/m2. BMI, body mass index; CI, confidence interval

Supplementary Files

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