Prognostic Impact of Plasma Glucose on Patients With Cardiogenic Shock With or Without Diabetes Mellitus from the SMART RESCUE Trial

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Although the presence of hyperglycemia has been shown to affect the clinical outcome of patients with cardiogenic shock, the extent of hyperglycemia and its association with prognosis have not been fully addressed in a large population. A total of 1,177 consecutive patients with cardiogenic shock were enrolled from January 2014 to December 2018 at 12 hospitals in South Korea. The primary outcome was in-hospital mortality. Patients were divided into 4 groups according to their initial plasma glucose level in patients with diabetes mellitus (DM) (n = 752) and patients without DM (n=425); group 1 (≤8 mmol/L or 144 mg/100 ml), group 2 (8 to 12 mmol/L or 144 to 216 mg/100 ml), group 3 (12 to 16 mmol/L or 216 to 288 mg/100 ml), and group 4 (≥16 mmol/L or 288 mg/100 ml). The groups with higher admission plasma glucose were associated with lower systolic blood pressure and higher lactic acid levels in patients with and without DM. In-hospital mortality increased in groups with higher admission plasma glucose level in patients without DM (group 1:24.2%, group 2: 28.6%, group 3: 38.1%, group 4: 49.0%, p <0.01), whereas in patients with DM, mortality and admission plasma glucose level showed no significant association (group 1: 45%, group 2: 35.4%, group 3: 33.3%, group 4: 43.1%, p = 0.26). Even after multivariate analysis, high plasma glucose was an independent predictor of in-hospital mortality in patients without DM. In patients with cardiogenic shock, plasma glucose obtained at admission was associated with in-hospital mortality in patients without DM. **(Am J Cardiol 2022;175:145−151)**

Introduction

Critically ill patients frequently present hyperglycemia regardless of having diabetes mellitus (DM). This hyperglycemic state is commonly referred to as "stress hyperglycemia."[1,2] The mechanism of this phenomenon is largely based on neuroendocrinologic alterations, which leads to hyperactivation of gluconeogenesis and insulin resistance hence causing hyperglycemia.[3,4] Hyperglycemia was associated with poor prognosis in patients with cardiogenic shock after ST-segment elevation myocardial infarction, acute coronary syndrome, and patients with acute decompensated heart failure.[5−11] However, the extent of hyperglycemia and its clinical implication on patients with cardiogenic shock is not yet fully understood, especially with large number data. Therefore, we sought to investigate the clinical relation between hyperglycemic status and in-hospital mortality in patients with cardiogenic shock enrolled in the RESCUE (Retrospective and

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prospective observational study to investigate the clinical outcomes and efficacy of left ventricular assist device for Korean patients with cardiogenic shock) registry.[9,12,13]

Methods

The RESCUE (NCT02985008 at *http://www.clinicaltrials.gov*) registry was an investigator-initiated, prospective, and retrospective multicenter trial conducted at 12 hospitals in South Korea. A total of 1,247 patients with cardiogenic shock were enrolled from January 2014 to December 2018. The inclusion criteria for our study were (1) systolic blood pressure <90 mm Hg for >30 minutes or catecholamine or vasopressor required to maintain pressure >90 mm Hg during systole, (2) clinical signs of pulmonary congestion and signs of impaired organ perfusion with at least 1 of the following criteria: altered mental status, cold, clammy skin, and extremities, oliguria with urine output <0.5 ml/kg/h for the first 6 hours of admission and serum lactate >2.0 mmol/L. Exclusion criteria were (1) out-of-hospital cardiac arrest and (2) septic or hypovolemic shock. Patients who were either using oral hypoglycemia agents or insulin were defined as having DM. The initial plasma glucose level taken at the emergency room was used to classify the patients. Enrolled patients were classified according to the review of glucose management in critically ill patients cut-off value.[14] Glycemic statuses were categorized as follows: group 1 (≤8 mmol/L or 144 mg/100 ml), group 2 (8 to 12 mmol/L or 144 to 216 mg/100 ml), group 3 (12 to 16 mmol/L or 216 to 288 mg/100 ml), and group 4 (≥16 mmol/L or 288 mg/100 ml).

Data were collected using a web-based case record form. Additional information was obtained from medical records or by telephone contact, if necessary. The primary outcome was in-hospital mortality during follow-up period. The use of cardiac support devices such as intra-aortic balloon pump, extracorporeal membrane oxygenation (ECMO) along with mechanical ventilator, and continuous renal replacement therapy (CRRT) were also analyzed. The institutional review board of each hospital approved the study protocol and waived the requirement for written informed consent for patients enrolled in the retrospective registry. We obtained informed consent from the patients enrolled for prospective registry.

Continuous data were presented as mean ± SD. Categorical data were presented as percentage or absolute number. Analyses of continuous data were performed using analysis of variance test, and analyses of categorical data were performed using chi-square test to assess differences in the 4 groups. Cox proportional hazards regression analysis using the backward elimination method was performed to determine the association between hyperglycemic state and in-hospital mortality. Hazard ratios (HRs) were calculated as an estimate of the risk associated with a particular variable with 95% confidence intervals (CI), and the proportional hazards assumptions of the HR in the Cox proportional hazards models were graphically inspected in the "log minus log" plot and were also tested by Schoenfeld residuals. Omitted columns represent multivariate parameters that were not statistically significant. The Kaplan-Meier method was used to obtain an estimation of event-free survival. All analyses were performed using IBM SPSS Statistics for Windows, version 19.0 (Armonk, New York), and SAS version 9.3 (SAS Institute Inc., Cary, North Carolina). A $p < 0.05$ was considered statistically significant.

Results

A total of 1,177 consecutive patients with cardiogenic shock were enrolled from January 2014 to December 2018. Seventy patients were excluded because of the inability to obtain initial plasma glucose (Figure 1). A total of 752 patients without DM and 425 patients with DM were included for analysis. The median in-hospital period was 10 days (interquartile range: 4 to 21 days).

For patients with and without DM, the prevalence of conventional risk factors for coronary occlusive disease such as hypertension, dyslipidemia, and known co-morbidities attributing to poor prognoses such as chronic kidney disease, peripheral artery occlusive disease, previous myocardial infarction, and previous cerebrovascular accidents showed no difference in the 4 groups. The most common cause of cardiogenic shock was ischemic cardiomyopathy for all 4 groups in patients with and without DM. Lactic acid level and APACHE II score,[15] the severity index of critically ill patients, showed incremental tendency with respect to baseline serum glucose level in both patients with and without DM (Table 1).

The use of ECMO and organ support methods such as mechanical ventilation and CRRT were more frequent as serum glucose levels increased in patients without DM. However, in patients with DM, there was no correlation between serum glucose level and use of cardiac support devices or CRRT other than mechanical ventilation (Table 2).

In-hospital mortality in patients with and without DM were 40.9% and 32.4%, respectively. In-hospital mortality rate increased in accordance with increase of serum glucose level in patients without DM (group 1: 24.2%, group 2: 28.6%, group 3: 38.1%, group 4: 49%, $p < 0.01$). Although, in patients with DM, in-hospital mortality rate and serum glucose level showed no significant association (group 1: 45%, group 2: 35.4%, group 3: 33.3%, group 4: 43.1%, $p = 0.26$; Figure 2). When the in-hospital mortality rate of group 1 was referenced, in-hospital mortality rates were proportionally increased in group 2 (HR 1.2, 95% CI 0.9 to 1.7, $p = 0.19$), group 3 (HR 1.8, 95% CI 1.3 to 2.7, $p < 0.01$) and group 4 (HR 2.5, 95% CI 1.8 to 3.7, $p < 0.01$) only in patients without DM (Figure 3). The serum glucose level (HR 1.003, 95% CI 1.002 to 1.004, $p < 0.001$) was an independent predictor of in-hospital mortality only in patients without DM after multivariate cox proportional regression analysis (Supplementary Table 1).

Discussion

This study evaluated the prognostic value of glycemic status at admission in patients with and without DM who were in a cardiogenic shock condition. In-hospital mortality was significantly higher in patients with DM than in patients without DM. To assess the relation between baseline serum glucose level and its influence on in-hospital

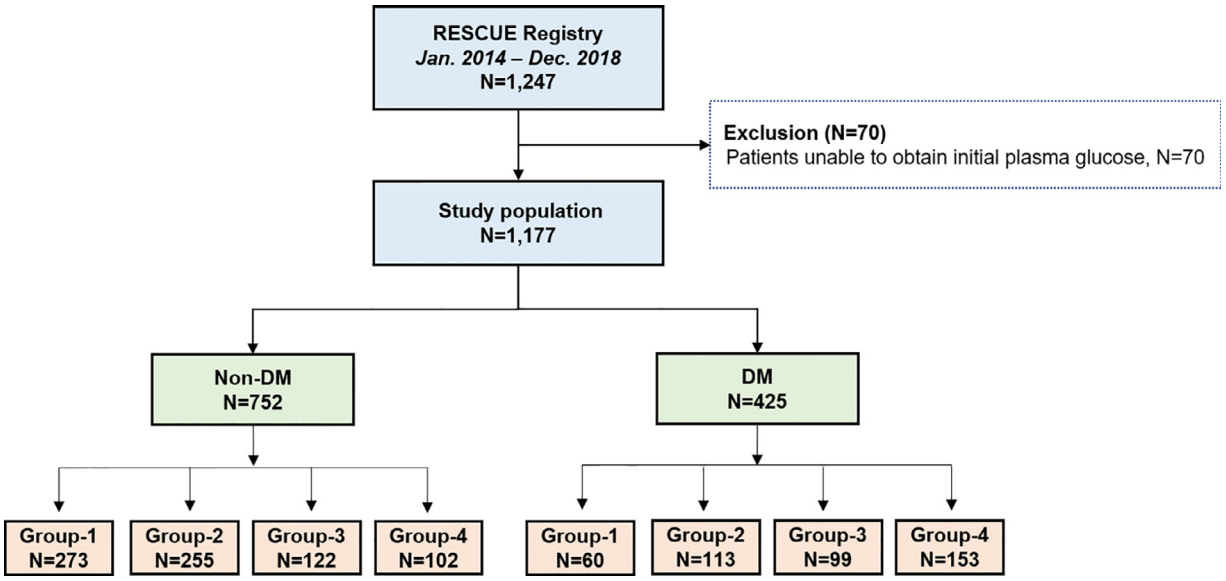

Figure 1. Flow chart of patient enrollment of RESCUE registry. Patients were divided into 4 groups according to admission glucose level, group 1: ≤8 mmol/L (144 mg/100 ml), group 2: 8 to 12 mmol/L (144 to 216 mg/100 ml), group 3: 12 to 16 mmol/L (216 to 288 mg/100 ml), and group 4: ≥16 mmol/L (288 mg/100 ml). Dec. = December; Jan. = January.

mortality, subcategorization was done based on their glucose status. In patients without DM, in-hospital mortality increased as admission glucose levels increased. However, for patients with DM, serum glucose level was not associated with in-hospital mortality. In patients without DM, mechanical organ support such as ECMO, mechanical ventilation, and CRRT showed incremental propensity in concordance with their serum glucose level.

Hyperglycemia in critically ill patients is a consequence of metabolic stress, which alters glucose metabolism, enhances peripheral glucose uptake, up-regulates glucose production, and decreases glycogen synthesis, which ultimately results in hyperglycemia.[1,2,4,5,16] Cardiogenic shock is a life-threatening condition with insufficient oxygenation to vital organs and tissue. This often leads to dysregulation of endocrinologic hormone distribution, and as a result, 'stress hyperglycemia' occurs.[17]

The association between hyperglycemia and mortality in patients with cardiovascular disease has been widely reported in the past.[3,10,11,18] However, the results regarding prognosis and hyperglycemia do not share coherence in these studies. Some studies report that prognostic relation was valid in all patients regardless of having DM.[3,5,17] Others suggest that validity was confirmed only in patients without DM.[18] In this study, the association of hyperglycemia and all-cause mortality differed between patients with and without DM. Multivariate cox regression analysis also showed that baseline serum glucose level in patients with DM had no prognostic effect, whereas in patients without DM, in-hospital mortality rate proportionately increased as baseline serum glucose level increased. Indeed, previous studies have shown that admission glucose levels only influenced critically ill patients without DM admitted to the cardiac intensive care unit.[8] Furthermore, numerous studies have been conducted recently to elaborate on the prognostic impact of hyperglycemia in a variety of clinical settings. Hyperglycemia in ST-segment elevation myocardial infarction was a risk factor of stent restenosis in patients without DM even after adjusting for other risk factors (HR 1.026, 95% CI 1.008 to 1.045, p = 0.005).[19] The prognostic role of hyperglycemia in patients with ischemic stroke was another intriguing subject because ischemic stroke bares similar pathophysiology to patients with cardiovascular disease. Several studies were able to demonstrate that patients without DM with ischemic stroke suffered from a worse neurologic deficit and cerebrovascular complications because of hyperglycemia.[20,21]

The pathophysiologic evidence to support this finding is still unclear. Nevertheless, there have been several hypotheses conjected to explain this phenomenon. Firstly, "stress hyperglycemia" in patients without DM is a clinical manifestation driven by up-regulation of glucose transporters, causing excessive production of free radicals, which results in tissue damage.[2,4,22] For patients with DM, chronic exposure to hyperglycemia downregulates glucose transportation capacity and protects cells from glucose toxicity.[6,14,23,24] This defense mechanism would lead to an elevated threshold of plasma glucose level in relation to a poor prognosis. Secondly, patients with DM are more likely to be treated with either insulin or oral hypoglycemic agents before their admission, and these medications could mitigate the increase in glycoxidative stress.[5] Furthermore, the use of insulin and oral hypoglycemic agents diminishes the significance of admission plasma glucose levels because their plasma glucose level is already affected by their previous treatment.

Numerous previously mentioned studies have investigated the clinical relation between hyperglycemic status and mortality in patients with cardiovascular disease. They have successfully demonstrated the prognostic effect of hyperglycemia in a variety of patients with cardiovascular disease. However, data regarding patients with cardiogenic shock with diverse disease entities is relatively sparse. Our study was able to reappraise a previously reported notion

Table 1
Baseline characteristics of non-DM and DM patients

Variables	Non DM					DM				
	Group-1 (273)	Group-2 (255)	Group-3 (122)	Group-4 (102)	p-Value	Group-1 (60)	Group-2 (113)	Group-3 (99)	Group-4 (153)	p-Value
Age (years)	62.36 ± 15.90	65.19 ± 14.84	66.69 ± 12.75	60.84 ± 12.86	< 0.01	71.30 ± 10.40	68.83 ± 10.52	69.22 ± 11.62	67.75 ± 12.21	0.23
Body mass index (kg/m^2)	23.50 ± 3.78	22.95 ± 3.35	23.36 ± 4.19	23.54 ± 3.21	0.31	23.14 ± 4.00	23.93 ± 3.24	23.76 ± 3.64	23.26 ± 3.37	0.32
Gender, women	88 (32.2%)	81 (33.9%)	32 (26.2%)	29 (28.4%)	0.61	24 (40%)	31 (27.4%)	21 (21.2%)	54 (35.3%)	0.03
Hypertension	111 (40.7%)	103 (40.4%)	52 (42.6%)	42 (41.2%)	0.98	41 (68.3%)	87 (77.0%)	75 (75.8%)	16 (69.3%)	0.39
Dyslipidemia	53 (19.4%)	50 (19.6%)	37 (30.3%)	21 (20.6%)	0.07	17 (28.3%)	38 (33.6%)	45 (45.5%)	58 (37.9%)	0.14
Smoking					0.02					0.24
Non-smoker	137 (50.2%)	135 (52.9%)	53 (43.4%)	37 (36.3%)		37 (61.7%)	58 (51.3%)	47 (47.5%)	92 (60.1%)	
Ex-smoker	53 (19.4%)	47 (18.4%)	24 (19.7%)	16 (15.7%)		14 (23.3%)	27 (23.9%)	30 (30.3%)	28 (18.3%)	
Current smoker	83 (30.4%)	73 (28.6%)	45 (36.9%)	49 (48.0%)		9 (15%)	28 (24.8%)	22 (22.2%)	33 (21.6%)	
Chronic kidney disease	16 (5.9%)	8 (3.1%)	11 (9.0%)	5 (4.9%)	0.11	13 (21.7%)	24 (21.2%)	19 (19.2%)	24 (15.7%)	0.63
Peripheral artery occlusive disease	9 (3.3%)	5 (2%)	5 (4.1%)	1 (1%)	0.39	3 (5.0%)	7 (6.2%)	10 (10.1%)	10 (6.5%)	0.57
Previous myocardial infarction	28 (10.3%)	27 (10.6%)	15 (12.3%)	5 (4.9%)	0.29	9 (15.0%)	17 (15.0%)	31 (22.8%)	15 (10.8%)	0.06
Previous cerebrovascular accident	26 (9.8%)	17 (6.7%)	10 (8.2%)	2 (2%)	0.08	7 (11.7%)	15 (13.3%)	17 (17.2%)	17 (11.1%)	0.56
Cardiomyopathy					0.04					< 0.01
Ischemic	194 (71.1%)	199 (78%)	102 (83.6%)	78 (76.5%)		42 (70.0%)	86 (76.1%)	85 (85.9%)	133 (86.9%)	
Non ischemic	79 (28.9%)	56 (22%)	20 (16.4%)	24 (23.5%)		18 (30.0%)	27 (23.9%)	14 (14.1%)	20 (13.1%)	
Acute physiology and chronic health evaluation II score	4.77 ± 3.32	5.03 ± 3.04	5.52 ± 3.09	5.97 ± 3.15	< 0.01	5.42 ± 3.67	5.30 ± 3.38	5.59 ± 3.35	6.07 ± 3.18	0.27
N-terminal pro b-type natriuretic peptide (pg.mL)	7292.40 ± 10612.55	8580.02 ± 11193.74	8150.57 ± 16823.01	4675.72 ± 9413.77	0.33	12214.78 ± 14889.89	8748.17 ± 12281.67	9523.66 ± 11921.01	11137.53 ± 12972.18	0.51
Lactic acid (mmol/L or mg/dL)	5.51 ± 4.51 or 49.6 3± 40.63	5.76 ± 3.75 or 51.89 ± 33.78	7.93 ± 4.56 or 71.44 ± 41.08	10.28 ± 4.28 or 92.61 ± 38.56	< 0.01	5.71 ± 4.21 or 51.44 ± 37.92	5.52 ± 3.79 or 49.72 ± 34.14	5.79 ± 3.81 or 52.16 ± 34.32	7.73 ± 5.04 or 69.63 ± 45.40	< 0.01
Aspartate transaminase (U/L)	410.51 ± 1697.769	253.63 ± 980.73	151.75 ± 239.10	262.84 ± 424.5	0.19	160.17 ± 465.44	160.56 ± 394.57	171.65 ± 537.66	178.02 ± 467.11	0.99
Alanine transaminase (U/L)	194.99 ± 665.63	151.24 ± 543.99	109.46 ± 213.95	161.14 ± 264.20	0.49	112.65 ± 292.60	90.60 ± 298.17	84.92 ± 254.84	104.60 ± 296.58	0.92
Left ventricular ejection fraction (%)	38.99 ± 16.82	38.54 ± 16.19	39.32 ± 16.22	35.03 ± 18.11	0.27	36.62 ± 16.24	37.78 ± 14.67	37.57 ± 15.13	31.28 ± 14.65	< 0.01

Data are presented as mean ± standard deviation or number (%).

Table 2
Prevalence of organ support according to hyperglycemic status in non-DM and DM patients

Modality of organ support	Group-1	Group-2	Group-3	Group-4	P value
Non DM					
Mechanical ventilator	124 (45.4%)	125 (49%)	82 (67.2%)	84 (82.4%)	< 0.01
Continuous Renal Replacement therapy	47 (17.2%)	43 (16.9%)	31 (25.4%)	33 (32.4%)	< 0.01
Extra corporeal membrane oxygenation	92 (33.7%)	96 (37.6%)	49 (40.2%)	60 (58.8%)	< 0.01
Intra-aortic balloon pump	55 (20.1%)	59 (23.1%)	48 (39.3%)	26 (25.5%)	< 0.01
Vasoactive inotropic score	62.66 ± 118.61	65.21 ± 108.92	99.86 ± 212.13	135.60 ± 145.14	< 0.01
DM					
Mechanical ventilator	29 (48.3%)	60 (53.1%)	64 (64.6%)	108 (70.6%)	< 0.01
Continuous renal replacement therapy	14 (23.3%)	30 (26.5%)	28 (28.3%)	43 (28.1%)	0.89
Extra corporeal membrane oxygenation	24 (40.0%)	38 (33.6%)	33 (33.3%)	73 (47.7%)	0.06
Intra-aortic balloon pump	16 (26.7%)	31 (27.4%)	26 (26.3%)	44 (28.8%)	0.98
Vasoactive inotropic score	60.03 ± 113.84	62.13 ± 109.84	77.86 ± 214.69	67.05 ± 87.98	0.82

Data are presented as mean ± standard deviation or number (%).

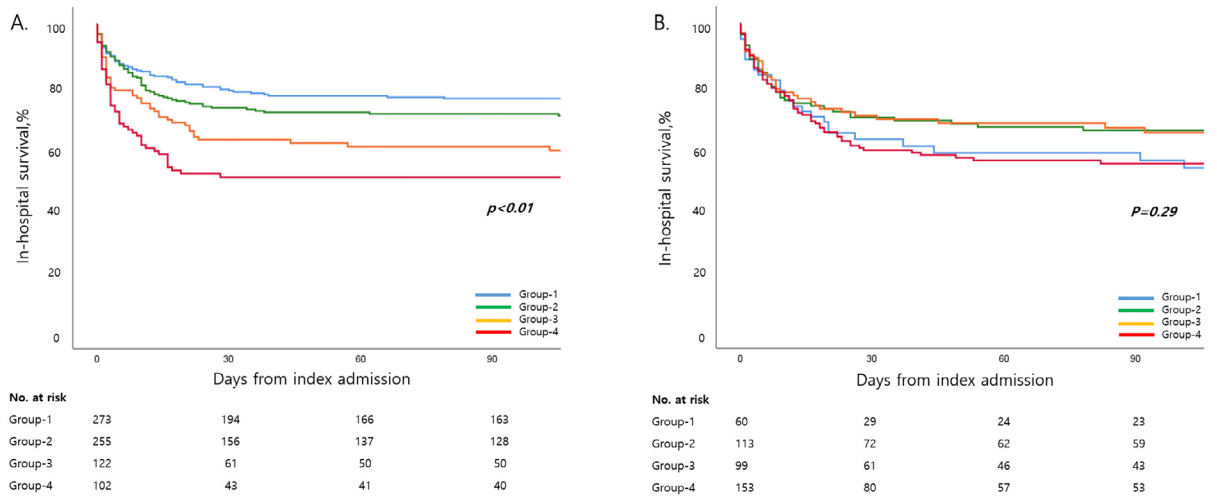

Figure 2. In-hospital mortality based on serum glucose in patients with and without DM *(A)* patients without DM, *(B)* patients with DM. Patients were divided into 4 groups according to admission glucose level, group 1: ≤8 mmol/L (144 mg/100 ml), group 2: 8 to 12 mmol/L (144 to 216 mg/100 ml), group 3: 12 to 16 mmol/L (216 to 288 mg/100 ml), and group 4: ≥16 mmol/L (288 mg/100 ml).

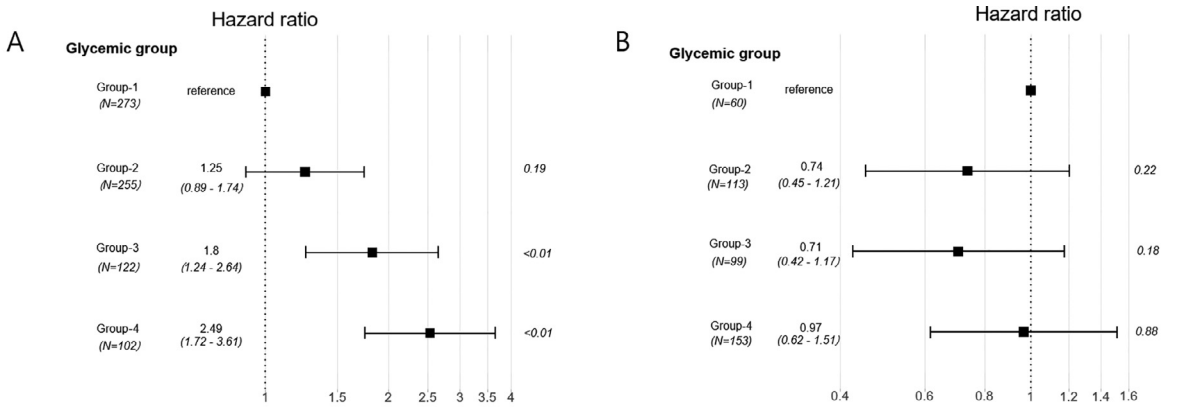

Figure 3. Cox regression analysis of in-hospital mortality. *(A)* patients without DM; *(B)* patients with DM; Patients were divided into 4 groups according to admission glucose level, group 1: ≤8 mmol/L (144 mg/100 ml), group 2: 8 to 12 mmol/L (144 to 216 mg/100 ml), group 3: 12 to 16 mmol/L (216 to 288 mg/100 ml), and group 4: ≥16 mmol/L (288 mg/100 ml).

that patients without DM with hyperglycemia were at a higher risk of mortality proportionate to their hyperglycemic state and also show that patients without DM under cardiogenic shock were much more vulnerable when exposed to hyperglycemia. Recently published studies not only comprising cardiovascular patients but also ischemic stroke patients showed similar results that hyperglycemia, especially in patients without DM, is a clear risk factor for poor prognosis, which reinforces the results of our study.[19–21]

Our study has several limitations. Firstly, patients with hypoglycemia were not excluded and were considered as group 1. Hypoglycemia is a condition that renders critical consequences in patients with or without DM. This inclusion could have influenced the mortality rate in group 1 in both patients with and without DM. Because hypoglycemia is mostly observed in patients with DM, the mortality of group 1 patients without DM could have been spared by this inclusion, but for group 1 patients with DM, the mortality shown in our study could have been exaggerated. Secondly, our study could not deliver new insight into therapeutic strategies regarding glucose management. Many studies have extensively emphasized the importance of glucose control in critically ill patients, and the Diabetes Control and Complication Trial stated that well-tolerated glycemic control reduces the risks of cardiovascular complications in patients with type 2 DM.[25,26] However, there is no concrete, evidence-based randomized study postulating the clinical implication of glucose control in patients without DM with hyperglycemia, and our study design did not encompass the glucose management aspect. Thirdly, this was a retrospective, observational study comprising only Korean patients. Therefore, further prospective multinational studies designed to assess the diverse aspect of hyperglycemia and its prognostic influence, including glycemic management strategy, are warranted.

In conclusion, admission serum glucose level proportionately increased in-hospital mortality in patients without DM with cardiogenic shock. Multivariate cox regression analysis showed that severe hyperglycemia was a poor prognostic factor in patients without DM.

Disclosures

The authors have no conflicts of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2022.04.008.

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