


Proportion of time spent in blood glucose range 70 to 140 mg/dL is associated with increased survival in patients admitted to ICU after cardiac arrest

A multicenter observational study

Dawei Zhou, MD, Zhimin Li, MD, Guangzhi Shi, PhD, MD^{*} , Jianxin Zhou, PhD, MD^{*}

Abstract

The benefit of any specific target range of blood glucose (BG) for post-cardiac arrest (PCA) care remains unknown.

We conducted a multicenter retrospective study of prospectively collected data of all cardiac arrest patients admitted to the ICUs between 2014 and 2015. The main exposure was BG metrics during the first 24 hours, including time-weighted mean (TWM) BG, mean BG, admission BG and proportion of time spent in 4 BG ranges (≤ 70 mg/dL, 70–140 mg/dL, 140–180 mg/dL and > 180 mg/dL). The primary outcome was hospital mortality. Multivariable logistic regression, Cox proportion hazard models and generalized estimating equation (GEE) models were built to evaluate the association between the different kinds of BG and hospital mortality.

2,028 PCA patients from 144 ICUs were included. 14,118 BG measurements during the first 24 hours were extracted. According to TWM-BG, 9 (0%) were classified into the ≤ 70 mg/dL range, 693 (34%) into the 70 to 140 mg/dL range, 603 (30%) into the 140 to 180 mg/dL range, and 723 (36%) into the > 180 mg/dL range. Compared with BG 70 to 140 mg/dL range, BG 140 to 180 mg/dL range and > 180 mg/dL range were associated with higher hospital mortality probability. Proportion of time spent in the 70 to 140 mg/dL range was associated with good outcome (odds ratio 0.984, CI [0.970, 0.998], $P = .022$, for per 5% increase in time), and > 180 mg/dL range with poor outcome (odds ratio 1.019, CI [1.009, 1.028], $P < .001$, for per 5% increase in time). Results of the 3 kinds of statistical models were consistent.

The proportion of time spent in BG range 70 to 140 mg/dL is strongly associated with increased hospital survival in PCA patients. Hyperglycemia (> 180 mg/dL) is common in PCA patients and is associated with increased hospital mortality.

Abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation, AUC = area under the curve, BG = blood glucose, CA = cardiac arrest, CPR = cardiopulmonary resuscitation, CRRT = continuous renal replacement therapy, CV = coefficient of variation, GEE = generalized estimating equation, GV = glycemic variability, IQR = interquartile range, IRB = institutional review board, NIH = National Institutes of Health, PCA = post-cardiac arrest, ROSC = return of spontaneous circulation, SD = standard deviation, SOFA = sequential organ failure assessment, TWM = time-weighted mean, VIF = variance inflation factor.

Keywords: blood glucose, cardiac arrest, hyperglycemia, hypoglycemia, prognosis

Editor: Yoshifumi Saisho.

GS and JZ are co-corresponding authors.

This work was supported by grants from "Beijing Municipal Science and Technology Commission-Capital clinical application research" (Z181100001718068).

The data were available on the eICU website at <https://eicu-crd.mit.edu>.

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

The datasets generated during and/or analyzed during the current study are publicly available.

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How to cite this article: Zhou D, Li Z, Shi G, Zhou J. Proportion of time spent in blood glucose range 70 to 140 mg/dL is associated with increased survival in patients admitted to ICU after cardiac arrest: a multicenter observational study. *Medicine* 2020;99:33(e21728).

Received: 28 March 2020 / Received in final form: 17 June 2020 / Accepted: 13 July 2020

<http://dx.doi.org/10.1097/MD.00000000000021728>

1. Introduction

Cardiac arrest (CA) is one of the major health problems, with a yearly incidence of about 50 to 110 per 100,000 people worldwide.^[1–3] Despite initially successful cardiopulmonary resuscitation (CPR), a high proportion of patients who survive cardiac arrest die prior to hospital discharge or have severe neurologic injury.^[4,5] After the return of spontaneous circulation (ROSC), the initial hours and days are defined as the post-cardiac arrest (PCA) syndrome, which often represents the extreme of critical illness and has a high risk of morbidity and mortality.^[6] PCA care requires vigilant monitoring and intervention and must be tailored to the particular disease and dysfunction that affect each patient.^[7,8]

Metabolic derangements following cardiac arrest, such as hyperglycemia and higher glycemic variability, may contribute to secondary brain injury and poor neurologic outcome.^[9–12] Resuscitated patients usually require intensive care of blood glucose (BG).^[13] However, the optimum BG concentration and interventional strategy to manage blood glucose in the PCA period are unknown.^[8] There may be a U-shaped relationship between BG and mortality outcomes in PCA patients.^[10,14,15] Time in BG range 70 to 140 mg/dL is strongly associated with reduced mortality in critically ill patients.^[16,17] The approach to glucose management chosen for other critically ill patients may not be suitable for cardiac arrest patients.^[18,19] The benefit of BG range 70 to 140 mg/dL is uncertain in adult PCA patients.

The main aim of the present study was to investigate the associations between different BG ranges and clinical outcomes in PCA patients. Our hypothesis was BG range 70 to 140 mg/dL could be associated with good hospital mortality outcomes in PCA patients.

2. Methods

2.1. Setting

This study used data stored in the high-resolution database, the eICU (eicu-cr.d.mit.edu), which comprises patients admitted between 2014 and 2015 at 208 hospitals located throughout the US. The elaborate description of eICU is available elsewhere.^[20] The eICU was exempt from institutional review board (IRB) approval due to the retrospective design, lack of direct patient intervention, and the security schema, for which the re-identification risk was certified as meeting safe harbor standards by Privacert (Cambridge, MA) (Health Insurance Portability and Accountability Act Certification no. 1031219–2). Due to the HIPAA compliant de-identification in this database, our institutional IRB requirement was waived. After completing a National Institutes of Health (NIH) web-based training course (Protecting Human Research Participants), the author (certification number: 28795067) was approved to access to the database for research aims.

2.2. Study population

All patients in the eICU database were eligible for inclusion in the present investigation. If a patient had more than 1 ICU admission, only the first ICU stay was taken into consideration. We selected all adult patients whose admission diagnosis was cardiac arrest. Patients were excluded for the following reasons:

- (1) Incomplete hospital mortality data
- (2) ICU stay less than 24 hours

- (3) Numbers of blood glucose measurements less than 2 during the first 24 hours after admission to ICU.

2.3. Clinical variables

Data on the following information were extracted: demographics, comorbidities, hospital admit source, sequential organ failure assessment (SOFA) score, Acute Physiology and Chronic Health Evaluation (APACHE) IV score, physiological parameters that provided the highest APACHE IV score during the first 24 hours, use of vasopressors, insulin, glucocorticoid, mechanical ventilation, use of continuous renal replacement therapy (CRRT) and use of hypothermia.

All of the blood glucose (BG) tests, that is BG from laboratory and bedside, during the first 24 hours in the ICU were extracted. For every patient, we calculated maximum BG, minimum BG, mean BG, first BG after admitted to ICU (admission BG), time-weighted mean BG (TWM-BG), proportion of time spent in 4 BG ranges (≤ 70 mg/dL, 70–140 mg/dL, 140–180 mg/dL, and > 180 mg/dL) and coefficient of variation (CV), defined as the ratio of the standard deviation (SD) to the mean of BG during the first 24 hours (see supplemental material; <http://links.lww.com/MD/E716>, <http://links.lww.com/MD/E717>, <http://links.lww.com/MD/E718>, <http://links.lww.com/MD/E719>, <http://links.lww.com/MD/E720>, <http://links.lww.com/MD/E721>). TWM-BG was obtained as an area under the curve (AUC) by integrating BG over time divided by the whole time (24 hours). Patients were classified into 4 ranges: ≤ 70 mg/dL, 70 to 140 mg/dL, 140 to 180 mg/dL, and > 180 mg/dL. Mild hypoglycemia was defined as BG ≤ 70 mg/dL, while severe hypoglycemia was defined as BG ≤ 40 mg/dL.

The first measured BG value represented the time from admission to the first measurement. BG remained constant at the levels observed in the previous measurement until the time point of the next measurement. We calculated time intervals between BG measurements and the proportion of time spent in different BG categories during the first 24 hours. Thus, during the first 24 hours, for each patient, time spent in each of the predefined BG categories ranged from 0% to 100%.

2.4. Outcomes

The primary outcome measure was hospital mortality. Secondary outcomes were ICU length of stay in overall and survival patients, ICU mortality, hospital length of stay in overall and survival patients, locations at hospital discharge.

2.5. Statistical analysis

Data were initially assessed for normality. Continuous variables are shown as mean and standard deviation (SD) or median and interquartile range (IQR). Categorical variables were reported as numbers and percentages. Group comparisons were made using χ^2 tests for equal proportion, analysis of variance for normally distributed variables, and Kruskal–Wallis tests otherwise. For missing values, the missing rate of variables was evaluated. Multiple imputations with “MICE” package of R software was performed for missing values.^[21]

Given the retrospective nature of this study, multivariable logistic regression models were constructed using all available baseline information that related to patient demographics (sex and chronic comorbidities), hospital admit source, disease

severity (APACHE IV score) and treatments (use of vasopressors, insulin, glucocorticoid, mechanical ventilation, CRRT, and hypothermia) along with separate BG metrics. The models were constructed using backward stepwise selection, with variables that were significant ($P < .1$) included. Besides, the covariates were also determined by subject-matter knowledge, for example, past history of diabetes mellitus was not statistically significant, but was selected in the final models. Potential multicollinearity between different covariates was quantified by calculation of the variance inflation factor (VIF), which provided an index of how much the variance of an estimated regression coefficient is increased due to collinearity and VIF less than 5 was considered acceptable. The Hosmer–Lemeshow goodness-of-fit test was used to assess the calibration of the models. Sensitivity analysis was performed in patients with and without diabetes.

Generalized estimating equations (GEE) were used to account for potential correlation in outcomes among patients sampled within hospital clusters. Independence pattern (no association) were examined for within-hospital correlation. Covariates were selected similarly as those in the multivariable logistic regression models.

Hospital mortality was considered as a time-to-event variable. The event was death within hospital. Patients were censored when hospital discharged alive. The analysis truncated at 30 days. Duration of survivals in hospital were presented as Kaplan–Meier curves with log-rank test comparing different BG ranges. Cox regression model was fitted to test for an association between different BG metrics (TWM-BG ranges and proportion of time spent in different BG ranges) and hospital mortality after adjusting for potential confounders.

Data extraction was performed using PostgreSQL (version 10, www.postgresql.org). R software (version 3.5.1, www.r-project.org) was used for statistical analysis. A 2-sided P value of $< .05$ was considered statistically significant.

3. Results

The eICU database contained 200,839 patient admissions. After exclusion, a total of 2028 patients from 144 hospitals were analyzed in our study (Supplemental Figure 1, <http://links.lww.com/MD/E716>), including 964 non-survivors and 1064 survivors, giving hospital mortality of 47.5%. ICU mortality was 37%. Non-survivors were slightly older, lower proportion of men and higher proportion of admitting from emergency department. Detailed information regarding the rate of missing values were displayed in Supplemental Figure 2, <http://links.lww.com/MD/E717>. Baseline characteristics and treatments of study patients between survivors and non-survivors were presented in Supplemental Table 1, <http://links.lww.com/MD/E718>.

A total of 14,118 measurements of blood glucose were extracted from 2028 PCA patients, 7 times per patient on average. Of the 14,118 measurements, 279 (2%) were equal or less than 70 mg/dL and 42 (0.3%) were equal or less than 40 mg/dL. TWM-BG for overall patients was 159 mg/dL, non-survivors had higher TWM-BG than survivors (170 vs 149, $P < .001$). The proportion of time spent in 70 to 140 mg/dL range was higher in survivors than non-survivors (38.4 vs 28.7, $P < .001$). Figure 1 shown the density distribution of the proportion of time spent in different BG ranges.

According to TWM-BG, 9 (0%) were classified into the ≤ 70 mg/dL range group, 693 (34%) into the 70 to 140 mg/dL

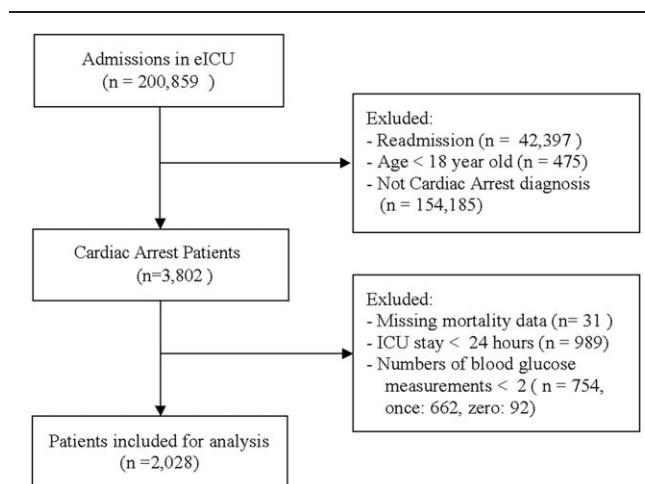


Figure 1. Flow chart of patient selection.

range group, 603 (30%) into the 140 to 180 mg/dL range group and 723 (36%) into the > 180 mg/dL range group. TWM-BG range > 180 mg/dL group was oldest, had the highest body mass index (BMI), the highest percentage of diabetes mellitus, the highest APACHE IV score, and the highest percentage of using insulin. TWM-BG range > 180 mg/dL group also had the lowest percentage of hypoglycemia (moderate or severe). Comparisons of baseline characteristics and treatments of different TWM-BG categories were displayed in Table 1. TWM-BG range 70 to 140 mg/dL group had the lowest ICU and hospital mortality and the highest proportion of discharging home. TWM-BG range 70 to 140 mg/dL group also had minimum hospital length of stay. Patient-centered outcomes were displayed in Table 2.

After adjusting for sex, ICU admit source, past history (diabetes mellitus, cancer), APACHE IV score, use of insulin, vasopressors, CRRT and hypothermia, patients with TWM-BG range in 140 to 180 mg/dL and > 180 mg/dL groups had higher odds ratio for hospital mortality in multivariable logistic regression and higher hazard ratio for hospital mortality in Cox proportional hazard model than 70 to 140 mg/dL group. Proportion of time spent in 70 to 140 mg/dL range was associated with lower odd ratio (OR 0.984, CI [0.970, 0.998], $P = .022$) and hazard ratio (HR 0.986, CI [0.977, 0.996], $P = .005$) for hospital mortality. The proportion of time spent in > 180 mg/dL range was associated with higher odds ratio and hazard ratio for hospital mortality (Table 3). With GEE model accounting for potential correlation in outcomes among patients sampled within hospital clusters, similar results were found (Fig. 2 and Supplemental Table 2–6, <http://links.lww.com/MD/E719>). Sensitivity analysis showed time in BG 70 to 140 mg/dL was associated with low risk of death in patients without diabetes ($P = .002$) but not with mortality in patients with diabetes ($P = .294$), whereas time in BG range 140 to 180 mg/dL was associated with lower mortality in patients with diabetes ($P = .013$) but not with mortality in patient without diabetes ($P = .931$) (Supplemental Table 7, <http://links.lww.com/MD/E720>). Figure 3 displayed the Kaplan–Meier survival curves by TWM-BG categories, which showed that 70 to 140 mg/dL group was associated with the highest probability of survival (log-rank $P < .001$).

Table 1
Comparison of baseline characteristics and treatment of different TWM-BG (mg/dL) ranges during the first 24 hours.

Variables	≤70 (n =9)	70-140 (n =693)	140-180 (n =603)	> 180 (n =723)	P value
Age, yr (median, [IQR])	59 (50, 72)	62 (50, 73)	63 (53, 74)	66 (56, 75)	<.001
Sex: male (n (%))	5 (56)	425 (61)	366 (61)	412 (57)	.333
BMI (median, [IQR])	25.9 (24.1, 27)	28.1 (23.6, 32.8)	28.6 (24.1, 33.5)	30.2 (25.8, 35.9)	<.001
ICU admit source, n (%)					.813
Emergency Department	5 (56)	338 (49)	300 (50)	339 (47)	
Floor	1 (11)	108 (16)	74 (12)	98 (14)	
Direct Admit	0 (0)	67 (10)	60 (10)	73 (10)	
Operating Room	0 (0)	7 (1)	9 (1)	14 (2)	
Others	3 (33)	173 (25)	160 (27)	199 (28)	
Comorbidities (n (%))					
Hypertension	6 (67)	333 (48)	291 (48)	405 (56)	.005
Diabetes mellitus	3 (33)	165 (24)	193 (32)	367 (51)	<.001
Respiratory disease	2 (22)	117 (17)	106 (18)	137 (19)	.724
Heart failure	0 (0)	150 (22)	110 (18)	132 (18)	.167
Cirrhosis	2 (22)	10 (1)	9 (1)	8 (1)	.019
Chronic renal failure	3 (33)	142 (20)	98 (16)	122 (17)	.088
Cancer	3 (33)	79 (11)	56 (9)	86 (12)	.071
Admission vital sign (median, [IQR])					
Temperature, °C	34.5 (33.2, 35.4)	35.6 (32.8, 36.4)	34.4 (32.5, 36.4)	33.8 (32.5, 36.3)	<.001
Respiratory rate	31 (15, 36)	27 (9, 35)	29 (9, 37)	29 (10, 37)	.117
HR, beats/min	109 (92, 130)	104 (55, 120)	105 (57, 124)	109 (60.5, 126)	.006
MBP, mmHg	141 (109, 152)	67 (51, 139)	68 (50, 144)	64 (48, 142)	.31
BG analyses (median, IQR)					
Admission BG, mg/dL	68 (57, 101)	129 (110, 159)	185 (148, 223)	276 (218, 364)	<.001
Maximum BG, mg/dL	86 (73, 101)	145 (125, 171)	206 (182, 245)	320 (259, 398)	<.001
Minimum BG, mg/dL	37 (21, 53)	95 (81, 109)	120 (103, 135)	154 (122, 190)	<.001
Mean BG, mg/dL	57 (55, 70)	121 (107, 131)	160 (150, 170)	227 (199, 279)	<.001
TWM BG, mg/dL	57 (53, 68)	120 (106, 130)	159 (149, 168)	224 (197, 277)	<.001
CV (%)	50 (26, 60)	18 (11, 29)	24 (15, 36)	29 (17, 44)	<.001
BG ≤70 (% of patients)	9 (100)	95 (14)	29 (5)	2 (4)	<.001
BG ≤40 (% of patients)	6 (67)	18 (3)	4 (1)	2 (0)	<.001
Severity of illness					
APACHE IV score, (median, [IQR])	106 (83, 159)	103 (72, 117)	106 (87, 126)	113 (97, 136)	<.001
SOFA (median, [IQR])	10 (7, 15)	9 (6, 11)	9 (7, 12)	10 (8, 12)	<.001
Treatments during 24 hours (n (%))					
Mechanical ventilation	8 (89)	538 (78)	524 (87)	625 (87)	<.001
CRRT	3 (33)	65 (9)	36 (6)	47 (7)	.005
Hypothermia	0 (0)	165 (24)	175 (29)	202 (28)	.034
Vasopressors	7 (78)	246 (35)	265 (44)	389 (54)	<.001
Insulin	0 (0)	78 (11)	88 (15)	157 (22)	<.001
Glucocorticoid	0 (0)	11 (2)	6 (1)	10 (1)	.695

APACHE=Acute Physiology and Chronic Health Evaluation, BG=blood glucose, BMI=body mass index, CRRT=continuous renal replacement therapy, CV=coefficient of variation, HR=heart rate, ICU=intensive care unit, IQR=interquartile range, MBP=mean blood pressure, MV=mechanical ventilation, SOFA=sequential organ failure assessment.

4. Discussion

This multicenter retrospective analysis of a large, heterogeneous cohort of PCA patients admitted in ICU supports the finding that the proportion of time spent in BG range 70 to 140 mg/dL is strongly associated with increased hospital survival. Hyperglycemia (> 180 mg/dL) is common to PCA patients and is associated with higher odd ratio and hazard ratio for hospital mortality. Hypoglycemia is not statistically significant associated with hospital mortality probably due to low incidence.

Glycemic control and targets are contentious for PCA patients.^[8,22] Due to the scarcity of studies on the PCA period, resuscitation guidelines acknowledged that the optimum BG concentration and interventional strategy to manage BG in the PCA period are unknown.^[8] One RCT of 90 subjects showed no difference in day 30 mortality between strict (72–108 mg/dL) and moderate (108–144 mg/dL) BG management.^[23] However, in this RCT study, standard treatment protocol for OHCA patients

had been targeted below 144 mg/dL, which cannot answer the question whether strict BG control is better than BG exceeding 144 mg/dL. One before-and-after observational study of 119 subjects showed reduced in-hospital mortality after implementation of a bundle of care that included defined BG range 5 to 8 mmol/L. However, the effect of BG management cannot be separated from the effects of other parts of the bundle.^[24] Both hyperglycemia and hypoglycemia were associated with poor neurologic outcome,^[11] suggesting a U-shaped relationship between BG and poor outcome in PCA patients. The nadir or optimal range are still not clear. Two retrospective studies demonstrated that BG concentrations of 116 to 143 mg/dL or 104.5 to 122.5 mg/dL were associated with increased survival and a favorable neurological outcome.^[14,25] In critically ill patients, time in BG range 70 to 140 mg/dL is strongly associated with increased survival.^[16,17] Our study supports the benefit of BG range 70 to 140 mg/dL in PCA patients.

Table 2
Comparison of outcomes in patients with different time-weighted mean blood glucose (mg/dL) ranges.

Variables	<= 70 (n=9)	70-140 (n=693)	140-180 (n=603)	> 180 (n=723)	P value
Status at hospital discharge, n (%)					<.001
Death	4 (44)	247 (36)	307 (51)	406 (56)	
Discharged home	1 (11)	223 (32)	142 (24)	128 (18)	
Discharged to nursing home	1 (11)	11 (2)	10 (2)	5 (1)	
Discharged to skilled nursing facility	2 (22)	67 (10)	46 (8)	79 (11)	
Discharged to rehabilitation	0 (0)	22 (3)	29 (5)	21 (3)	
Discharged to other places	1 (11)	123 (18)	69 (11)	84 (12)	
Status at ICU discharge, n (%)					<.001
Death	4 (44)	184 (27)	244 (40)	325 (45)	
Duration of stay, median (IQR)					
Hospital LOS, d	5 (2, 13)	6 (3, 12)	6 (3, 11)	6 (3, 11)	.037
Hospital LOS, survivors, d	13 (5, 21)	8 (4, 15)	9 (5, 16)	10 (6, 17)	.017
Hospital LOS, deaths, d	2 (2, 3)	4 (2, 7)	3 (2, 6)	3 (2, 6)	.179
ICU LOS, d	4 (3, 6)	4 (3, 7)	4 (3, 7)	4 (3, 7)	.511
ICU LOS, survivors, d	3 (2, 4)	4 (3, 6)	4 (3, 6)	4 (2, 6)	.239
ICU LOS, deaths, d	3 (2, 4)	4 (2, 6)	4 (3, 5)	3 (2, 5)	.293

ICU=intensive care unit, IQR=interquartile range, LOS=length of stay.

Hyperglycemia is common in the early phase of PCA syndrome.^[26] Global ischemia-reperfusion condition after OHCA, metabolic derangements, chronic prearrest comorbid conditions, exogenous epinephrine, hypothermia treatment might be associated with hyperglycemia after ROSC.^[27,28] The association between hyperglycemia after ROSC and worse clinical outcome in cardiac arrest patients is clear.^[11,29-31] Furthermore, a high glycemic variability (GV) is associated with increased mortality and poor neurologic outcome.^[9,11] GV might by itself have a true deleterious biological effect and less GV may be potentially a surrogate for the quality of medical and nursing

care. In the present study, 723 (36%) PCA patients had TWM-BG >180mg/dL. The high percentage of hyperglycemia may reflect the principle of ‘first, do no harm’, which may be not benefit for our patients.

Tight glycemic control in critically ill including PCA patients is still controversial. The main harm of tight glucose control may be hypoglycemia,^[18] which is associated with increased mortality, morbidity and length of hospital stay.^[32,33] Overall, 159 (8%) patients in the present study had at least 1 episode of moderate hypoglycemia and 30 (1%) had severe hypoglycemia, which were lower than what had been observed in many of the other intensive

Table 3
Adjusted hospital mortality (logistic regression and Cox proportional hazards analysis) in patients with different BG variables.

BG variables	Logistic Regression Analysis		Cox Proportional Hazard Models	
	OR [95% CI]	P value	HR [95% CI]	P value
TWM -BG				
70-140 mg/dL	1.00 [Reference]		1.00 [Reference]	
<=70 mg/dL	1.00 [0.20, 4.67]	.995	1.40 [0.52, 3.78]	.509
140-180 mg/dL	1.53 [1.20, 1.96]	.001	1.36 [1.15, 1.61]	<.001
> 180 mg/dL	1.47 [1.15, 1.88]	.002	1.34 [1.13, 1.58]	.001
Admission - BG				
70-140 mg/dL	1.00 [Reference]		1.00 [Reference]	
<=70 mg/dL	0.63 [0.30, 1.31]	.224	0.75 [0.44, 1.28]	.294
140-180 mg/dL	1.17 [0.87, 1.58]	.307	1.06 [0.86, 1.32]	.566
> 180 mg/dL	1.45 [1.14, 1.85]	.003	1.31 [1.11, 1.54]	.002
Mean - BG				
70-140 mg/dL	1.00 [Reference]		1.00 [Reference]	
<=70 mg/dL	0.63 [0.12, 2.70]	.556	0.85 [0.27, 2.67]	.777
140-180 mg/dL	1.62 [1.26, 2.08]	<.001	1.42 [1.20, 1.69]	<.001
> 180 mg/dL	1.80 [1.40, 2.30]	<.001	1.52 [1.29, 1.80]	<.001
Proportion of time (%) spent in BG range (every 5%)				
<=70 mg/dL	0.941 [0.879, 1.004]	.073	0.969 [0.927, 1.014]	.179
70-140 mg/dL	0.984 [0.970, 0.998]	.022	0.986 [0.977, 0.996]	.005
140-180 mg/dL	0.989 [0.971, 1.008]	.250	0.992 [0.980, 1.005]	.245
> 180 mg/dL	1.019 [1.009, 1.028]	<.001	1.019 [1.009, 1.028]	<.001

BG=blood glucose, TWM-BG=time-weighted mean blood glucose.

Logistic regression models and Cox proportional hazards models were constructed using sex, ICU admit source, past history (diabetes mellitus, cancer), APACHE IV score, use of insulin, vasopressors, CRRT and hypothermia along with separate BG metrics. As for proportion of time (%) spent in BG ranges, <=70, 70 to 140, 140 to 180 and > 180 were considered separate variables in different logistic regression models and Cox proportional hazards models, that is, 4 models were created using the same covariates respectively.

APACHE=Acute Physiology and Chronic Health Evaluation, CRRT=continuous renal replacement therapy, ICU=intensive care unit.

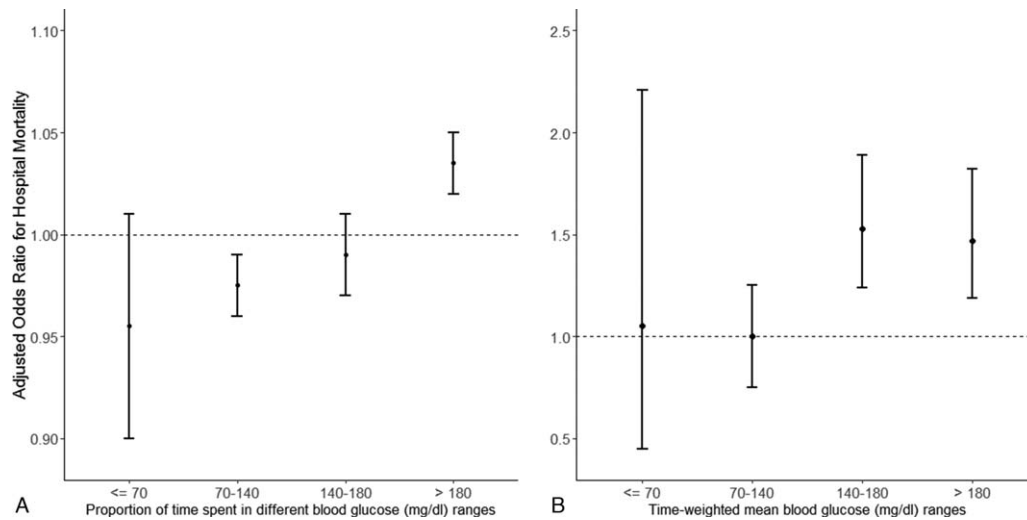


Figure 2. (A) Adjusted odds ratio for hospital mortality with generalized estimating equation (GEE) model according to proportion of time (per 5% increase) spent in different time-weighted mean blood glucose ranges after multivariable adjustment. (B) Adjusted odds ratio for hospital mortality with GEE model according to time-weighted mean blood glucose ranges (the 70-140 mg/dL category as reference) after multivariable adjustment. The odds ratio and 95% confidence intervals (error bars) for each variable were calculated after multivariable adjustment for sex, ICU admit source, past history (diabetes mellitus, cancer), APACHE IV score, use of insulin, vasopressors, CRRT and hypothermia (Supplemental Tables 2–6, <http://links.lww.com/MD/E719>).

insulin therapy studies with critically ill patients.^[33–35] Strict glucose control (72–108 mg/dL) leads to the higher incidence of hypoglycemia in OHCA survivors and moderate glucose control (below 180 mg/dL) was acceptable owing to the potentially detrimental effect of hypoglycemia arising from strict glucose control.^[23,36] In the present study, sensitivity analyses suggested time in BG range ≤ 70 mg/dL was not associated with mortality both in PCA patients with and without diabetes. The results may be attributed to the inadequately statistical power and the skew

distribution of time in BG range ≤ 70 mg/dL (Supplemental Figure 2, <http://links.lww.com/MD/E717>).

However, better glycemic control without a higher risk of hypoglycemia can be achieved. Closed-loop glucose control (Artificial Pancreas) consists of a continuous glucose monitor and an insulin pump, coupled with a control algorithm that directs insulin delivery on the basis of real-time sensor glucose measurements,^[37] which reduced the rate of hypoglycemia and may avoid the events of severe hypoglycemia.^[38,39] Andrew et al.

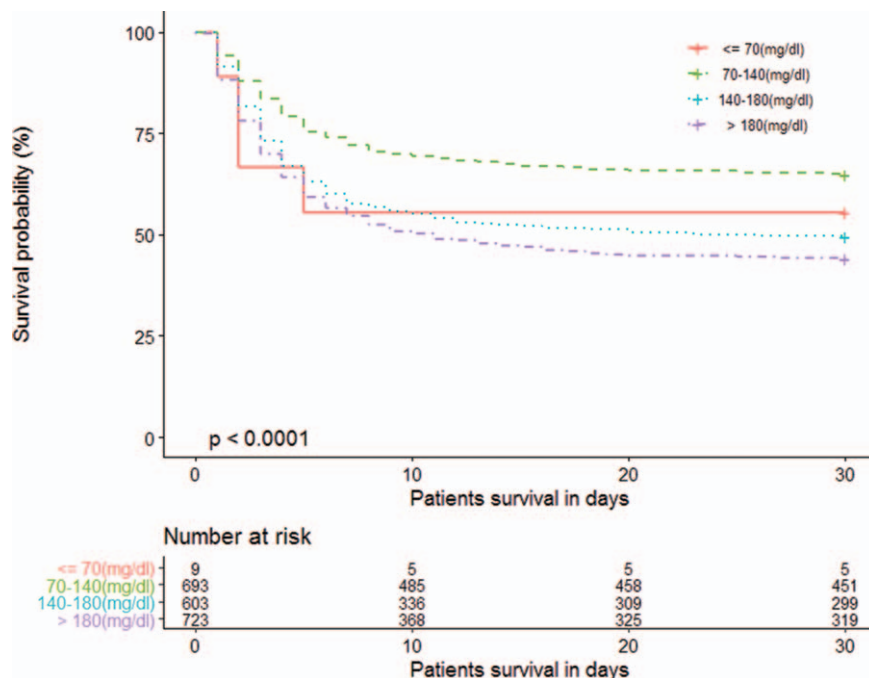


Figure 3. Kaplan-Meier survival curves by time-weighted mean blood glucose ranges (log-rank $P < .001$).

demonstrated that in a population of medical and surgical cardiac patients treated with a validated insulin administration algorithm (e-protocol), a BG target of 80 to 110 mg/dL can be achieved with low rates of severe hypoglycemia and was associated with lower 30-day mortality compared with a 90 to 140 mg/dL BG target.^[40] Maybe it is time to rethink BG targets in critically ill patients including PCA patients in the setting of continuous BG monitor.^[41]

This study had several strengths. First, the data was extracted from multiple ICUs, making its findings highly generalizable. Second, there were 14,118 arterial BG measurements for 2028 patients during the first 24 h, which may reduce errors. Third, this study used different kinds of BG, including TWM-BG, mean BG, admission BG, and proportion of time spent in different BG ranges, which made the results robust. As a metric, proportion of time spent in different BG ranges captures both level and variability of BG. Fourth, we used multivariable logistic regression models, Cox proportional hazard models and GEE models. The findings were consistent, indicating that conclusions were not dependent on the chosen statistical approach.

There were several obvious limitations to this study. First, the study was retrospective in nature and was subject to the inherent limitations of the design. For instance, the time and numbers of BG for every patient were not same. Many potential confounding factors might not be included in the analysis, leading to biased results. Also, the study design only allowed us to show statistical associations and not causality between BG and hospital mortality. The results could be considered hypothesis generating only, rather than proof of causality. Second, initial rhythm, quality, and duration of cardiopulmonary resuscitation, which was an important prognostic factor, could not be assessed by the database. Third, we used the BG range 70 to 140 based on previously published studies,^[16,17] thus the exact BG levels associated with good outcomes are unknown. Fourth, we extracted BG measurements from laboratory and bedside, sampling was intermittent and included measurements made on point-of-care glucose meters, which may overestimate blood glucose concentration. It may explain the low incidence of hypoglycemia. Finally, we excluded the patients with only 1 BG measurement, and the reasons for few BG measurement were unknown. Among potential factors, few BG measurement could have been due to premature death or rapidly regained consciousness. In our study, few BG measurement may be inclined to rapid recovery (Supplemental Table 8, <http://links.lww.com/MD/E721>).

5. Conclusions

In summary, proportion of time spent in BG range 70 to 140 mg/dL is strongly associated with increased hospital survival in PCA patients. Hyperglycemia (> 180 mg/dL) is common in PCA patients and is associated with higher odd ratio and hazard ratio for hospital mortality. These results merit further investigation and prospective validation.

Author contributions

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References

- [1] Berdowski J, Berg RA, Tijssen JG, et al. Global incidences of out-of-hospital cardiac arrest and survival rates: systematic review of 67 prospective studies. *Resuscitation* 2010;81:1479–87.
- [2] Andersen LW, Holmberg MJ, Berg KM, et al. In-hospital cardiac arrest: a Review. *Jama* 2019;321:1200–10.
- [3] Wissenberg M, Lippert FK, Folke F, et al. Association of bystander initiatives to improve cardiac arrest management with rates of bystander intervention and patient survival after out-of-hospital cardiac arrest. *Jama* 2013;310:1377–84.
- [4] Cronberg T, Lilja G, Horn J, et al. Neurologic function and health-related quality of life in Patients following targeted temperature management at 33 degrees C vs 36 degrees C after out-of-hospital cardiac arrest: a randomized clinical trial. *JAMA neurology* 2015; 72:634–41.
- [5] Sandroni C, D'Arrigo S, Callaway CW, et al. The rate of brain death and organ donation in patients resuscitated from cardiac arrest: a systematic review and meta-analysis. *Intensive Care Med* 2016;42:1661–71.
- [6] Walker AC, Johnson NJ. Critical care of the post-cardiac arrest patient. *Cardiology clinics* 2018;36:419–28.
- [7] Stub D, Bernard S, Duffy SJ, et al. Post cardiac arrest syndrome: a review of therapeutic strategies. *Circulation* 2011;123:1428–35.
- [8] Callaway CW, Donnino MW, Fink EL, et al. Part 8: post-cardiac arrest care: 2015 American heart association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2015;132(Suppl 2):S465–82.
- [9] Cueni-Villoz N, Devigili A, Delodder F, et al. Increased blood glucose variability during therapeutic hypothermia and outcome after cardiac arrest. *Crit Care Med* 2011;39:2225–31.
- [10] Beiser DG, Carr GE, Edelson DP, et al. Derangements in blood glucose following initial resuscitation from in-hospital cardiac arrest: a report from the national registry of cardiopulmonary resuscitation. *Resuscitation* 2009;80:624–30.
- [11] Borgquist O, Wise MP, Nielsen N, et al. Dysglycemia, glycemic variability, and outcome after cardiac arrest and temperature management at 33 degrees C and 36 degrees C. *Crit Care Med* 2017;45:1337–43.
- [12] Daviaud F, Dumas F, Demars N, et al. Blood glucose level and outcome after cardiac arrest: insights from a large registry in the hypothermia era. *Intensive Care Med* 2014;40:855–62.
- [13] Girotra S, Chan PS, Bradley SM. Post-resuscitation care following out-of-hospital and in-hospital cardiac arrest. *Heart (British Cardiac Society)* 2015;101:1943–9.
- [14] Losert H, Sterz F, Roine RO, et al. Strict normoglycaemic blood glucose levels in the therapeutic management of patients within 12 h after cardiac arrest might not be necessary. *Resuscitation* 2008;76:214–20.
- [15] Padkin A. Glucose control after cardiac arrest. *Resuscitation* 2009;80:611–2.
- [16] Krinsley JS, Preiser JC. Time in blood glucose range 70 to 140 mg/dL > 80% is strongly associated with increased survival in non-diabetic critically ill adults. *Crit Care* 2015;19:179.
- [17] Lanspa MJ, Krinsley JS, Hersh AM, et al. Percentage of time in range 70 to 139 mg/dL is associated with reduced mortality among critically ill patients receiving IV insulin infusion. *Chest* 2019;156:878–86.
- [18] Wiener RS, Wiener DC, Larson RJ. Benefits and risks of tight glucose control in critically ill adults: a meta-analysis. *Jama* 2008;300:933–44.
- [19] Marik PE, Preiser JC. Toward understanding tight glycemic control in the ICU: a systematic review and meta-analysis. *Chest* 2010;137:544–51.
- [20] Pollard TJ, Johnson AEW, Raffa JD, et al. The eICU collaborative research database, a freely available multi-center database for critical care research. *Sci Data* 2018;5:180178.
- [21] Zhang Z. Decision tree modeling using R. *Ann Transl Med* 2016;4: 275–375.
- [22] Callaway CW, Soar J, Aibiki M, et al. Part 4: advanced life support: 2015 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment Recommendations. *Circulation* 2015;132(Suppl 1):S84–145.
- [23] Oksanen T, Skrifvars MB, Varpula T, et al. Strict versus moderate glucose control after resuscitation from ventricular fibrillation. *Intensive Care Med* 2007;33:2093–100.

- [24] Sunde K, Pytte M, Jacobsen D, et al. Implementation of a standardised treatment protocol for post resuscitation care after out-of-hospital cardiac arrest. *Resuscitation* 2007;73:29–39.
- [25] Skrifvars MB, Pettila V, Rosenberg PH, et al. A multiple logistic regression analysis of in-hospital factors related to survival at 6 months in patients resuscitated from out-of-hospital ventricular fibrillation. *Resuscitation* 2003;59:319–28.
- [26] Kim SH, Park KN, Choi SP, et al. Time to reach target glucose level and outcome after cardiac arrest patients treated with therapeutic hypothermia. *J Crit Care* 2015;30:1204–9.
- [27] Vihonen H, Kuisma M, Salo A, et al. Mechanisms of early glucose regulation disturbance after out-of-hospital cardiopulmonary resuscitation: an explorative prospective study. *PLoS One* 2019;14:e0214209.
- [28] Dungan KM, Braithwaite SS, Preiser JC. Stress hyperglycaemia. *Lancet* (London, England) 2009;373:1798–807.
- [29] Nurmi J, Boyd J, Anttalainen N, et al. Early increase in blood glucose in patients resuscitated from out-of-hospital ventricular fibrillation predicts poor outcome. *Diabetes care* 2012;35:510–2.
- [30] Kim SH, Choi SP, Park KN, et al. Association of blood glucose at admission with outcomes in patients treated with therapeutic hypothermia after cardiac arrest. *Am J Emerg Med* 2014;32:900–4.
- [31] Mullner M, Sterz F, Binder M, et al. Blood glucose concentration after cardiopulmonary resuscitation influences functional neurological recovery in human cardiac arrest survivors. *J Cereb Blood Flow Metab* 1997;17:430–6.
- [32] Nirantharakumar K, Marshall T, Kennedy A, et al. Hypoglycaemia is associated with increased length of stay and mortality in people with diabetes who are hospitalized. *Diabet Med* 2012;29:e445–8.
- [33] Finfer S, Liu B, Chittock DR, et al. Hypoglycemia and risk of death in critically ill patients. *N Engl J Med* 2012;367:1108–18.
- [34] Griesdale DE, de Souza RJ, van Dam RM, et al. Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. *CMAJ* 2009;180:821–7.
- [35] Yatabe T, Inoue S, Sakaguchi M, et al. The optimal target for acute glycemic control in critically ill patients: a network meta-analysis. *Intensive Care Med* 2017;43:16–28.
- [36] Nolan JP, Soar J, Cariou A, et al. European resuscitation council and European society of intensive care medicine guidelines for post-resuscitation care 2015. *Resuscitation* 2015;95:202–22.
- [37] Bally L, Thabit H, Hovorka R. Closed-loop for type 1 diabetes - an introduction and appraisal for the generalist. *BMC medicine* 2017;15:14.
- [38] Bally L, Thabit H, Hartnell S, et al. Closed-loop insulin delivery for glycemic control in noncritical care. *N Engl J Med* 2018;379:547–56.
- [39] Okabayashi T, Shima Y, Sumiyoshi T, et al. Intensive versus intermediate glucose control in surgical intensive care unit patients. *Diabetes care* 2014;37:1516–24.
- [40] Hersh AM, Hirshberg EL, Wilson EL, et al. Lower glucose target is associated with improved 30-day mortality in cardiac and cardiothoracic patients. *Chest* 2018;154:1044–51.
- [41] Krinsley JS. Is it time to rethink blood glucose targets in critically ill patients. *Chest* 2018;154:1004–5.