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Stress hyperglycemia ratio is associated with neurological outcome after cardiac arrest

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This study examined the association between glycemic parameters, including absolute glucose and stress hyperglycemia ratio (SHR), and neurological outcomes in out-of-hospital cardiac arrest (OHCA) survivors. We conducted a retrospective analysis using data from a prospective, multicenter registry comprising 743 adult comatose OHCA survivors. Glycemic measurements (glucose and SHR) were collected following return of spontaneous circulation (ROSC) and during the subsequent 24-hour period. The primary outcome was poor neurological outcome at 6 months. Subgroup analyses were stratified by glycemic status (HbA1c) and injury severity (the revised Post-Cardiac Arrest Syndrome for Therapeutic Hypothermia score). Both absolute glucose and SHR—measured after ROSC and as 24-hour means—were independently associated with poor neurological outcomes. Among these, SHR during the 24-hour post-ROSC period showed the most substantial predictive value (OR, 2.232; 95% CI, 1.316–3.785). Spline analysis revealed a linear relationship for SHR, contrasting with the U- or J-shaped curves observed for absolute glucose values. Prognostic significance was primarily observed in patients without pre-existing diabetes and those with moderate injury severity. The SHR measured after ROSC and during the first 24 h post-resuscitation is an independent predictor of poor neurological outcome in OHCA survivors. This association is most pronounced in non-diabetic and moderate-severity groups. Kew Words: Cardiac arrest; Hyperglycaemia; Stress Hyperglycaemia Ratio; Neurological outcome.

Keywords Cardiac arrest, Hyperglycaemia, Stress Hyperglycaemia Ratio, Neurological outcome

Hyperglycemia frequently occurs in critically ill patients and can exacerbate tissue injury, making glycemic control a key therapeutic target[1–5]. This condition arises from complex feedback mechanisms involving cytokines and stress hormones[6]. As a result, hyperglycemia serves as a prognostic marker that reflects illness severity[7,8]. However, recent studies suggest that in conditions such as myocardial infarction, heart failure, and stroke, relative hyperglycemia—rather than absolute glucose levels—offers a more accurate prediction of outcomes[3,4,9]. To quantify relative hyperglycemia, researchers developed the stress hyperglycemia ratio (SHR), which adjusts acute glucose levels against baseline glycemic control estimated by glycated hemoglobin (HbA1c)[10].

In patients resuscitated from cardiac arrest, hyperglycemia is common and consistently correlates with increased mortality and poor neurological outcomes[11,12]. Although one recent study identified SHR as a potential prognostic marker in this population[13], its registry-based design limited the ability to account for specific cardiac arrest characteristics. Therefore, the prognostic utility of SHR in a well-characterized cohort of cardiac arrest survivors remains unclear. Moreover, because a patient's diabetic status influences the prognostic value of absolute hyperglycemia[3], it is unknown whether SHR's predictive accuracy similarly depends on the presence or absence of diabetes in post-cardiac arrest survivors. Furthermore, SHR has traditionally been calculated as a static measure based on admission glucose, even though glycemic levels fluctuate significantly following resuscitation. The clinical relevance of dynamic changes in SHR over time also remains unexplored in this context.

The primary aim of this study was to investigate the association between SHR, calculated both immediately after return of spontaneous circulation (ROSC) and as a 24-hour mean, and neurological outcomes at 6 months.

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Secondary aims included assessing whether this association varied by baseline glycemic status (as determined by HbA1c) and by post-cardiac arrest syndrome severity, stratified using the revised Post-Cardiac Arrest Syndrome for Therapeutic Hypothermia (rCAST) score.

Results

Study population and characteristics

Of the 1,373 patients initially enrolled in the KORHN-PRO registry, we excluded 614 due to missing HbA1c data, 13 for hypoglycemia after ROSC, 2 for missing neurological outcome data, and 1 for missing glucose data after ROSC. The final analysis included 743 patients (Fig. 1). A sensitivity analysis was conducted to compare the characteristics of the included patients with those excluded due to missing HbA1c data (Supplementary Table 1).

Among the final cohort, 518 patients (69.7%) experienced poor neurological outcomes at 6 months. Table 1 summarizes demographic and clinical characteristics by outcome group. Patients with poor outcomes were significantly older (63.0 years [52.0–74.0] vs. 55.0 years [45.0–63.0], $p < 0.001$) and had a lower proportion of males (69.7% vs. 77.8%, $p = 0.030$). The poor outcome group had higher rates of hypertension (42.5% vs. 32.0%), diabetes mellitus (32.2% vs. 16.4%), pulmonary disease (9.1% vs. 2.2%), and renal impairment (9.3% vs. 2.7%). Patients with poor neurological outcomes also had significantly lower rates of witnessed collapse (61.4% vs. 82.7%), bystander CPR (58.1% vs. 67.6%), shockable rhythm (17.4% vs. 72.9%), and cardiac etiology (52.9% vs. 89.8%). The time to ROSC was significantly longer (36.0 min [24.0–48.3] vs. 18.0 min [12.0–26.0]), and the total epinephrine dose was significantly higher (3 mg [1–5] vs. 0 mg [0–1]). After ROSC, patients with poor outcomes showed significantly higher levels of serum lactate (10.8 mg/dL [7.3–13.8] vs. 6.9 mg/dL [4.4–11.2]), $PaCO_2$ (54.0 mmHg [38.0–77.0] vs. 39.0 mmHg [32.0–48.0]), SOFA score (12 [10–14] vs. 9 [7–11]), glucose levels (275 mg/dL [206–357] vs. 224 mg/dL [183–303]), HbA1c (5.8% [5.4–6.4] vs. 5.6% [5.3–6.0]), and mean glucose over 24 h (171 mg/dL [138–226] vs. 148 mg/dL [126–175]). SHR values were also significantly higher in the poor outcome group both immediately after ROSC (2.20 [1.67–2.81] vs. 2.00 [1.55–2.49]) and over the first 24 h (1.39 [1.16–1.74] vs. 1.26 [1.10–1.51]).

Association between glycemic parameters and neurological outcomes

Table 2 presents multivariable logistic regression results. After adjusting for confounders, several glycemic parameters independently predicted a significant association with poor neurological outcomes: A higher glucose after ROSC (OR, 1.003; 95% CIs, 1.001–1.005); SHR after ROSC (OR, 1.438; 95% CIs, 1.081–1.912); mean glucose during the first 24 h after ROSC (OR, 1.007; 95% CIs, 1.003–1.011); and SHR during the first 24 h after ROSC (OR, 2.232; 95% CIs, 1.316–3.785).

Figure 2 presents restricted cubic spline regression analysis between glycemic parameters and their adjusted odds ratios for poor neurological outcomes. The glucose after ROSC exhibited a U-shaped relationship with risk, with a nadir at approximately 180 mg/dL (Fig. 2A). Mean glucose over 24 h after ROSC displayed a J-shaped relationship, with risk increasing above a threshold of roughly 140 mg/dL (Fig. 2B). In contrast, both the SHR

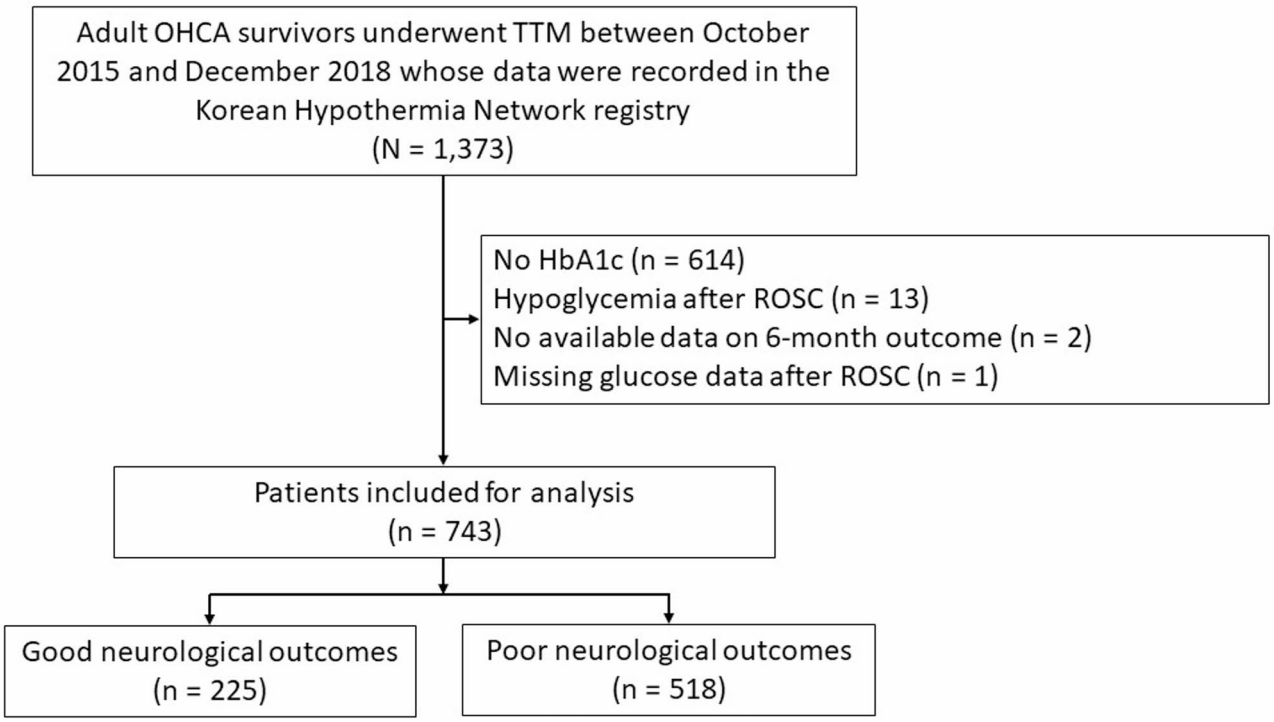

Fig. 1. Patients' inclusion flowchart. OHCA, out-of-hospital cardiac arrest; TTM, targeted temperature management; ROSC, return of spontaneous circulation.

Variables	Total ($n=743$)	Good ($n=225$)	Poor ($n=518$)	p
Age, years	60.0 (49.0–71.0)	55.0 (45.0–63.0)	63.0 (52.0–74.0)	< 0.001
Male	536 (72.1)	175 (77.8)	361 (69.7)	0.030
Body mass index, kg/m^2	23.4 (21.3–25.8)	23.6 (21.6–25.8)	23.4 (21.0–25.8)	0.326
Pre-existing illness				
Coronary artery disease	104 (14.0)	35 (15.6)	69 (13.3)	0.489
Heart failure	27 (3.6)	7 (3.1)	20 (3.9)	0.773
Hypertension	292 (39.3)	72 (32.0)	220 (42.5)	0.009
Diabetes mellitus	204 (27.5)	37 (16.4)	167 (32.2)	< 0.001
Stroke or TIA	41 (5.5)	11 (4.9)	30 (5.8)	0.749
Pulmonary disease	52 (7.0)	5 (2.2)	47 (9.1)	0.001
Renal impairment	54 (7.3)	6 (2.7)	48 (9.3)	0.002
Liver cirrhosis	12 (1.6)	1 (0.4)	11 (2.1)	0.176
Cardiac arrest characteristics				
Witnessed	504 (67.8)	186 (82.7)	318 (61.4)	< 0.001
Bystander CPR	453 (61.0)	152 (67.6)	301 (58.1)	0.019
Shockable rhythm	254 (34.2)	164 (72.9)	90 (17.4)	< 0.001
Cardiac etiology	476 (64.1)	202 (89.8)	274 (52.9)	< 0.001
Time to ROSC, min	30.0 (18.0–44.0)	18.0 (12.0–26.0)	36.0 (24.0–48.3)	< 0.001
Epinephrine dose, mg	2 (0–4)	0 (0–1)	3 (1–5)	< 0.001
After ROSC				
Serum lactate, mg/dL	9.6 (6.1–13.2)	6.9 (4.4–11.2)	10.8 (7.3–13.8)	< 0.001
PaO_2, mmHg	117.0 (77.0–218.7)	118.0 (76.8–228.8)	116.2 (77.0–209.8)	0.969
$PaCO_2$, mmHg	48.0 (35.2–69.0)	39.0 (32.0–48.0)	54.0 (38.0–77.0)	< 0.001
$PaCO_2$				< 0.001
Hypocarbia	180 (24.7)	82 (37.6)	98 (19.2)	
Normocarbia	150 (20.6)	68 (31.2)	82 (16.0)	
Hypercarbia	399 (54.7)	68 (31.2)	331 (64.8)	
SOFA	11 (9–13)	9 (7–11)	12 (10–14)	< 0.001
HgA1c, %	5.7 (5.3–6.3)	5.6 (5.3–6.0)	5.8 (5.4–6.4)	0.019
Glucose after ROSC, mg/dL	262 (199–337)	224 (183–303)	275 (206–357)	< 0.001
SHR after ROSC	2.15 (1.61–2.70)	2.00 (1.55–2.49)	2.20 (1.67–2.81)	0.001
Mean glucose 24 h after ROSC, mg/dL	162 (133–205), 709*	148 (126–175), 215*	171 (138–226), 494*	< 0.001
SHR during 24 h after ROSC	1.34 (1.13–1.67), 709*	1.26 (1.10–1.51), 215*	1.39 (1.16–1.74), 494*	< 0.001

Table 1. Baseline characteristics stratified by neurological outcomes. TIA, transient ischemic attack; CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation; SOFA, sequential organ failure assessment; SHR, stress hyperglycemia ratio. *, included number of patients

Parameter	Adjusted odds ratio (95% Confidence intervals)	p
HbA1c, %	1.074 (0.929–1.240)	0.335
Glucose after ROSC, mg/dL	1.003 (1.001–1.005)	0.006
SHR after ROSC	1.438 (1.081–1.912)	0.013
Mean glucose 24 h after ROSC, mg/dL	1.007 (1.003–1.011)	< 0.001
SHR during 24 h after ROSC	2.232 (1.316–3.785)	0.003

Table 2. Association between glycemic parameters and poor neurological outcomes. Adjusted with age, witnessed, shockable rhythm, cardiac etiology, and time to ROSC. ROSC, return of spontaneous circulation; SHR, stress hyperglycemia ratio.

after ROSC and the SHR during the 24 h after ROSC demonstrated a linear, positive association with the risk of poor outcome (Fig. 2C and D). HbA1c was not associated with the neurological outcome (Fig. 2E).

Glucose variables depending on the long-term glycemic status

We stratified patients by baseline HbA1c into non-diabetic ($n=344$, 46.3%), pre-diabetic ($n=236$, 31.8%), and diabetic ($n=163$, 21.9%) groups (Table 3). HbA1c levels differed significantly across the three groups. Glucose

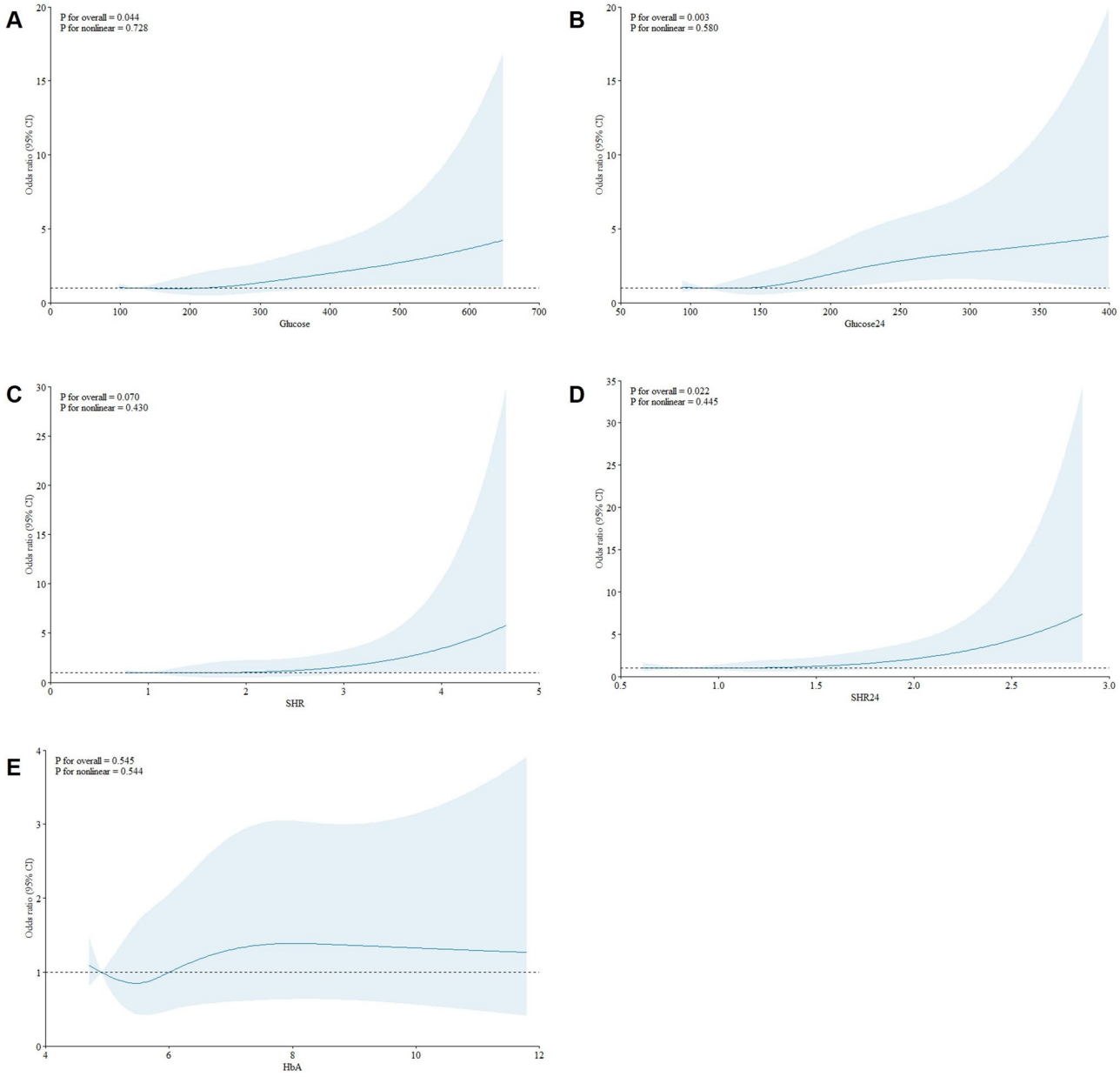

Fig. 2. Restricted cubic spline analysis of the relationship between glycemic parameters and poor neurological outcomes. (**A**) The restricted cubic spline (RCS) curve shows a U-shaped relationship between glucose after return of spontaneous circulation (ROSC) and the adjusted odds ratio (OR) for poor neurological outcome. The risk was lowest at a glucose level of approximately 180 mg/dL. (**B**) The RCS curve shows a J-shaped relationship between mean glucose during the first 24 h after ROSC and the adjusted OR for poor neurological outcomes. The risk increases steeply above a threshold of approximately 140 mg/dL. (**C**) The RCS curve shows a positive, linear-like relationship between the stress hyperglycemia ratio (SHR) after ROSC and the adjusted OR for poor neurological outcome. A higher SHR is associated with a progressively increased risk. (**D**) The RCS curve shows a strong, positive, and linear-like relationship between the SHR during the first 24 h after ROSC and the adjusted OR for poor neurological outcomes. The risk increases steeply with higher 24-hour mean SHR values. (**E**) The RCS curve shows no significant association between baseline HbA1c and the adjusted OR for poor neurological outcome.

after ROSC and mean glucose during the first 24 h after ROSC were highest in the diabetic groups. SHR and SHR during the first 24 h after ROSC were progressively lower across the groups from non-diabetic to diabetic.

Table 4 presents the association between glycemic parameters and poor neurological outcome in the subgroup of long-term glycemic status. In the non-diabetic group, the glucose after ROSC (OR, 1.005; 95% CIs, 1.001–1.009); SHR after ROSC (OR, 1.704; 95% CIs, 1.153–2.518); mean glucose during the first 24 h after ROSC (OR, 1.010; 95% CIs, 1.002–1.017); and SHR during the first 24 h after ROSC (OR, 2.676; 95% CI, 1.205–5.943) were associated with poor outcome. In the pre-diabetic group, only SHR during the first 24 h after ROSC was

Variables	Non-diabetic ($n=344$)	Pre-diabetic ($n=236$)	Diabetic ($n=163$)	p
Diabetes mellitus	30 (8.7)	52 (22.0)	122 (74.8)	< 0.001
HbA1c, %	5.3 (5.1–5.5)[a]	5.9 (5.8–6.1)[b]	7.6 (6.9–8.5)[c]	< 0.001
Glucose after ROSC, mg/dL	243 (184–307)[a]	259 (195–324)[a]	331 (254–443)[b]	< 0.001
SHR	2.32 (1.75–2.89)[a]	2.08 (1.60–2.65)[b]	1.90 (1.43–2.36)[c]	< 0.001
Mean glucose during 24 h after ROSC, mg/dL	146 (127–186), 330[*a]	162 (140–195), 220[*b]	229 (167–282), 159[*c]	< 0.001
SHR during 24 h after ROSC	1.39 (1.21–1.75), 330[*a]	1.31 (1.12–1.58), 220[*b]	1.26 (0.94–1.59), 159[*b]	< 0.001

Table 3. Diabetes and glycemic parameters according to long-term glycemic status. Different superscript letters (a, b, c) indicate statistically significant differences between groups, as determined by the Mann-Whitney U test with Bonferroni correction for post-hoc analysis ($p < 0.016$). ROSC, return of spontaneous circulation; SHR, stress hyperglycemia ratio. [*], included number of patients.

	Adjusted odds ratio (95% Confidence intervals)		
Parameters	Non-diabetic ($n=344$)	Pre-diabetic ($n=236$)	Diabetic ($n=163$)
HbA1c, %	1.170 (0.328–4.171)	0.536 (0.072–4.001)	0.858 (0.681–1.083)
Glucose after ROSC, mg/dL	1.005 (1.001–1.009)	1.000 (0.995–1.005)	1.002 (0.998–1.005)
SHR after ROSC	1.704 (1.153–2.518)	1.071 (0.572–2.005)	2.040 (0.962–4.326)
Mean glucose 24 h after ROSC, mg/dL	1.010 (1.002–1.017)	1.010 (1.000–1.020)	1.004 (0.997–1.010)
SHR during 24 h after ROSC	2.676 (1.205–5.943)	3.918 (1.118–13.725)	2.664 (0.934–7.601)

Table 4. Multivariable logistic regression analysis of glycemic parameters for poor neurological outcome according to long-term glycemic status. Adjusted with age, witnessed, shockable rhythm, cardiac etiology, and time to ROSC. ROSC, return of spontaneous circulation; SHR, stress hyperglycemia ratio.

	Adjusted odds ratio (95% Confidence intervals)		
Parameter	Low ($n=110$)	Moderate ($n=365$)	High ($n=268$)
HbA1c, %	1.128 (0.640–1.989)	1.135 (0.958–1.344)	0.816 (0.598–1.115)
Glucose after ROSC, mg/dL	1.003 (0.996–1.010)	1.003 (1.001–1.006)	1.000 (0.996–1.004)
SHR after ROSC	1.527 (0.587–3.972)	1.326 (0.913–1.924)	1.255 (0.696–2.260)
Mean glucose 24 h after ROSC, mg/dL	1.005 (0.995–1.014)	1.010 (1.004–1.016)	0.999 (0.991–1.006)
SHR during 24 h after ROSC	2.069 (0.612–6.988)	2.348 (1.153–4.782)	1.314 (0.416–4.151)

Table 5. Multivariable logistic regression analysis of glycemic parameters for poor neurological outcome according to rCAST severity groups. Adjusted with age, witnessed, shockable rhythm, cardiac etiology, and time to ROSC. rCAST, revised Post-Cardiac Arrest Syndrome for Therapeutic Hypothermia; ROSC, return of spontaneous circulation; SHR, stress hyperglycemia ratio. Supplementary Table 1. Baseline characteristics between include and excluded patients.

associated with poor outcome (OR, 3.918; 95% CIs, 1.118–13.725). No glycemic parameters were predictive in the diabetic group.

Association between glucose variables and neurological outcomes according to severity

We stratified patients by the rCAST score into low ($n=110$, 14.8%), moderate ($n=365$, 49.1%), and high severity ($n=268$, 36.1%) groups. In the moderate severity group, the glucose after ROSC (OR, 1.003; 95% CIs, 1.001–1.006); mean glucose during the first 24 h after ROSC (OR, 1.010; 95% CI, 1.004–1.016); and SHR during the first 24 h after ROSC (OR, 2.348; 95% CI, 1.153–4.782) were significantly associated with poor outcomes (Table 5). In contrast, no significant associations were observed between any of the glycemic parameters and neurological outcome in either low or high severity subgroups.

Discussion

In this multicenter registry-based study, we identified that several glycemic parameters independently predicted poor neurological outcomes following cardiac arrest. Among these, markers of sustained hyperglycemia, specifically mean glucose and the SHR during the first 24 h after ROSC, demonstrated more substantial prognostic value than single-point measurements taken immediately after ROSC. The nature of these associations differed: glucose levels exhibited U-shaped or J-shaped relationships with outcome risk, whereas the SHR showed a more consistent, linear relationship. Notably, the prognostic impact of these glycemic markers was most pronounced in specific subgroups, patients without diabetes and those with moderate severity of post-cardiac arrest syndrome.

Although absolute hyperglycemia is a well-established predictor of poor outcomes after cardiac arrest[7,8,11,12], its clinical utility is limited by its inability to distinguish acute stress responses from chronic hyperglycemia. SHR addresses this limitation by quantifying relative hyperglycemia and has been validated as a superior prognostic marker in other critical illnesses[3,4,9,13,14]. To our knowledge, this is the first study to evaluate SHR specifically in a post–cardiac arrest population. We found that SHR, particularly the SHR during the first 24 h after ROSC, demonstrated a strong and linear association with poor neurological outcomes. This contrasts sharply with the more complex U-shaped or J-shaped curves observed for absolute glucose, suggesting that SHR may more accurately reflect the severity of stress-induced metabolic disruption contributing to secondary injury. Although a previous study in a general intensive care unit population reported a U-shaped association for SHR[15], this differs from our findings. This discrepancy likely reflects differences in cohort characteristics; in that study, nearly half of the patients had SHR values below 1.0, with a risk nadir between 0.75 and 0.99[15]. Such a distribution was not observed in our cardiac arrest cohort, which may explain the different shape of the risk curves. Another key finding is that glycemic parameters sustained over the first 24 h were more robust prognosticators of outcome than immediate single-point post-ROSC measurements. This was most evident in the multivariable analysis, where the OR for SHR during the first 24 h was substantially higher than that of the SHR after ROSC (2.232 vs. 1.438). These results suggest that the duration of hyperglycemia stress, rather than its initial intensity, plays a more critical role in the pathophysiology of secondary brain injury. Our findings reinforce the importance of the initial 24 h after resuscitation as a key therapeutic window and align with previous studies linking sustained hyperglycemia to adverse outcomes[16,17].

In critically ill patients and cardiac arrest survivors, previous studies have reported that the association between absolute hyperglycemia and mortality is attenuated in those with pre-existing diabetes compared to those without[8,18,19]. Similarly, in studies of acute myocardial infarction, the relationship between the SHR and mortality has also been shown to be weaker in diabetic patients[20,21]. Absolute glucose levels, both immediately after ROSC and the 24-hour mean, were significantly lower in the non-diabetic group than in the diabetic group. However, an inverse relationship was observed for relative hyperglycemia, with both the initial and 24-hour SHR being significantly higher in non-diabetic patients in the present study. Furthermore, consistent with prior findings, significant associations between all glycemic parameters and neurological outcomes were evident only in the non-diabetic subgroup. The observation that non-diabetic patients exhibited significantly higher SHR than diabetic patients, despite lower absolute glucose, suggests a heightened sensitivity to ischemic-reperfusion injury. This may reflect a more pronounced physiological stress response in individuals without chronic hyperglycemia, whereas patients with diabetes may be partially adapted or desensitized to elevated glucose levels[19,20]. This heightened reaction may contribute to the stronger prognostic power of SHR in the non-diabetic patients. Taken together, this background and our findings highlight that the chronic glycemic status significantly modifies the predictive power of the SHR.

The prognostic significance of glycemic parameters was confined to the subgroup with moderate severity of the rCAST score in the present study. Post-cardiac arrest survivors represent a heterogeneous population, and the performance of prognostic markers or the efficacy of therapeutic interventions can differ according to the initial severity of injury[22–24]. The benefit of targeting a lower temperature (33–34℃ vs. 35–36℃) on good neurological outcome and survival was only observed in the moderate-severity group, suggesting this cohort is most amenable to therapeutic intervention[23]. Similarly, our finding that glycemic parameters were only predictive in the moderate-severity subgroup likely reflects these underlying characteristics. The moderate-severity group represents a population with an indeterminate prognosis, where secondary injuries, such as those mediated by sustained hyperglycemic stress, can be the critical factor that determines the final neurological outcome. This highlights the potential value of precise glycemic control, particularly in patients with moderate injury severity, where secondary insults may critically determine the outcome.

This study had several limitations. First, the primary limitation is its retrospective design based on a prospectively collected registry. Although the registry design ensures a certain quality of data, this observational nature precludes the establishment of a causal relationship between glycemic parameters and neurological outcomes; we can only infer associations. Inherent selection biases may exist, and despite multivariable adjustment, the influence of unmeasured confounders cannot be excluded entirely. Despite this limitation, it is based on an extensive, multicenter, prospectively collected registry, which enhances the external validity of our results compared to single-center studies. The registry provided comprehensive data on cardiac arrest characteristics and severity scores, allowing for robust subgroup analyses that have, to our knowledge, not been previously explored. This allowed us to be the first to specifically evaluate the dynamic changes of SHR over 24 h and its prognostic value according to both baseline glycemic status and injury severity in a dedicated post-cardiac arrest cohort. Second, a significant number of patients (n = 614) were excluded from the initial cohort due to missing HbA1c data, which could introduce selection bias. To assess the potential impact of this bias, we performed a sensitivity analysis comparing the baseline characteristics between included and excluded groups (Supplementary Table 1). This analysis revealed the included patients were slightly older and had higher rates of hypertension and diabetes, as well as higher initial post-ROSC glucose levels. However, most key prognostic factors, including the rates of witnessed arrest, bystander CPR, and shockable rhythm, were not significantly different between the two groups. Crucially, the proportion of patients with a poor neurological outcome at 6 months was identical in both cohorts (68.9%). While this finding suggests that the exclusion of these patients may not have substantially skewed our main conclusions regarding the prognostic value of SHR, the possibility of bias from other unmeasured confounders cannot be entirely dismissed. Third, although data were collected from 22 academic hospitals, glycemic management protocols were not standardized across institutions. Variations in glucose monitoring practices, insulin therapy thresholds, and treatment intensity introduced considerable heterogeneity[11]. This variability represents a key confounding factor influenced both the 24-hour mean glucose levels and the neurological outcomes. This heterogeneity in practice could have specifically impacted our

primary exposure of interest, the 24-hour mean SHR, potentially introducing measurement variability into our analysis. Fourth, the frequency of glucose measurement during the initial 24-hour was not standardized across the participating hospitals. The calculation of the 24-hour mean glucose was based on intermittent blood sampling, which may not accurately capture the true mean glycemic level or the extent of glycemic variability. More frequent or continuous glucose monitoring would have provided a more precise measurement.

In conclusion, sustained hyperglycemia over 24 h, particularly SHR in post-cardiac arrest survivors, is a strong independent predictor of poor 6-month neurological outcomes. Unlike absolute glucose, SHR demonstrated a consistent, linear relationship with risk. The prognostic value of these glycemic markers was most significant in specific subgroups: patients without pre-existing diabetes and those with moderate illness severity. This suggests that relative hyperglycemic stress may play an important role in secondary brain injury, highlighting the potential importance of precise glycemic control, especially for patients with an indeterminate prognosis.

Methods

Study design and population

This study retrospectively analyzed data from the Korean Hypothermia Network Prospective Registry (KORHN-PRO), a multicenter prospective registry that enrolled adult (≥ 18 years) comatose survivors of out-of-hospital cardiac arrest (OHCA) who received targeted temperature management (TTM) at 22 academic hospitals in South Korea between October 2015 and December 2018 (NCT02827422)[25]. The ethics committees and institutional review boards of all participating hospitals approved the registry. Legal representatives of all patients provided written informed consent in accordance with the Declaration of Helsinki[26]. The registry excluded patients with any of the following: (1) acute ischemic or hemorrhagic stroke; (2) terminal illness (life expectancy < 6 months); (3) pre-documented "Do Not Resuscitate" orders; (4) Cerebral Performance Category (CPC) 3 or 4 before cardiac arrest; (5) body temperature < 30 ℃ on admission. An independent researcher assessed neurological outcomes at 6 months post-arrest using the CPC scale, conducted via structured phone interviews following a standardized protocol[27].

For this study, we included adult OHCA survivors from the KORHN-PRO registry who had available data for both post-ROSC blood glucose and admission HbA1c. We excluded patients for the following reasons: (1) missing glucose data after ROSC; (2) missing admission HbA1c; (3) hypoglycemia (glucose < 70 mg/dL after ROSC); (4) missing 6-month neurological outcome data.

Patient management and glucose control

All patients received standardized post-cardiac arrest care in accordance with the advanced cardiac life support guidelines in effect at the time[28]. TTM was applied for 24 h using automated feedback devices to maintain a temperature between 33 °C and 36 °C, followed by controlled rewarming at a rate of 0.25–0.5 °C/hr. Clinicians routinely administered sedation and analgesia, while neuromuscular blockade was used at the discretion of the attending physician. Throughout post-arrest care, medical teams closely monitored blood glucose levels to prevent dysglycemia and managed hyperglycemia according to each hospital's institutional insulin protocol.

Data collection

We extracted data from the KORHN-PRO registry, including demographic variables (age, sex, body mass index), pre-existing medical conditions, and detailed cardiac arrest characteristics (witnessed collapse, bystander CPR, initial monitored rhythm, etiology, time to ROSC, and total epinephrine dose). Post-ROSC clinical data included initial serum lactate, arterial blood gas values (pH, PaO_2, $PaCO_2$), Glasgow Coma Scale motor score, Sequential Organ Failure Assessment (SOFA) score within the first 24 hours[29], glucose after ROSC, admission HbA1c, glucose levels during the first 24 h post-ROSC, and six-month CPC scores.

We categorized patients based on several clinical variables. $PaCO_2$ levels were classified as hypocarbia (< 35 mmHg), normocarbia (35 mmHg ≤ $PaCO_2$ < 45 mmHg), or hypercarbia (≥ 45 mmHg). Glycemic status was stratified using HbA1c: non-diabetic (HbA1c < 5.7%), pre-diabetic (5.7% ≤ HbA1c < 6.5%), and diabetic (HbA1c ≥ 6.5%). Injury severity was categorized using the rCAST score as mild (≤ 5.5), moderate (6–14), and high (≥ 14.5)[30]. We calculated the SHR using the formula: SHR = Glucose/[(28.7 × HbA1c) − 46.7]. Two SHR values were derived: an initial SHR using the glucose measured after ROSC, and a 24-hour mean SHR using the mean glucose over the first 24 h.

The primary outcome was poor neurological outcome at 6 months after cardiac arrest, defined as CPC scores of 3–5.

Statistical analysis

We presented categorical variables as frequencies and percentages, and compared them between groups using χ^2 tests with continuity correction in 2 × 2 tables or Fisher's exact test, as appropriate. Continuous variables, which were non-normally distributed, were presented as medians with interquartile ranges. We used the Mann-Whitney *U* test for two-group comparisons and the Kruskal-Wallis test for comparison across three groups, followed by the pair-wise Mann-Whitney U tests with Bonferroni correction for post-hoc analysis to adjust the alpha-error.

To assess the association between glycemic parameters (glucose after ROSC, HbA1c, SHR after ROSC, mean glucose during the first 24 h, and SHR during the first 24 h) and neurological outcomes, we performed multivariable logistic regression. Variables with $p < 0.20$ in univariable analyses were then included in a logistic regression analysis to build the final model. Covariates in the final model included age, witnessed arrest, shockable rhythm, cardiac etiology, and time to ROSC. We reported results as odds ratios (OR) with 95% confidence intervals (CIs). A non-linear relationship between glycemic parameters and neurological outcomes was visualized using restricted cubic spline curves. Subgroup analyses were conducted based on baseline

glycemic status (HbA1c) and injury severity (rCAST score). Sensitivity analysis was performed to address overall differences in baseline characteristics between included and excluded groups to evaluate robustness of our results. All statistical analyses were performed using IBM SPSS Statistics 27.0 for Windows (IBM Corp., Armonk, NY) and R software (version 4.5.1). A two-sided p-value < 0.05 was considered statistically significant.

Data availability

Anonymized data not published in this article can be made available upon reasonable request from any qualified investigator, subject to approval from Korean Hypothermia Network and Chonnam National University Hospital Institutional Review Board. The data supporting the findings of this study can be requested from the corresponding author, Byung Kook Lee, bbukkuk@hanmail.net.

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Author contributions

Dong Hun Lee: Data curation, Formal analysis, and Writing-original draft; Seok Jin Ryu: Data curation, Formal analysis, and Writing-original draft; Byung Kook Lee: Funding acquisition, Investigation, Conceptualization, Project administration, Writing-original draft, review& editing; Yong Hun Jung: Formal analysis, Investigation, and Writing-review & editing; Hyoung Youn Lee: Formal analysis, Methodology, and Writing-review & editing; Soo Hyun Kim: Investigation, Data curation, and Writing-review & editing; Chun Song Youn: Investigation and Writing-review & editing; Youn-Jung Kim: Data curation and Writing-review & editing; Won Young Kim: Investigation and Writing-review & editing; Kyung Woon Jeung: Data curation and Writing – review & editing.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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