Association between body mass index and clinical outcomes in out-of-hospital cardiac arrest survivors treated with targeted temperature management

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Abstract

Background: To determine the impact of body mass index (BMI) on clinical outcomes in out-of-hospital cardiac arrest (OHCA) survivors treated with targeted temperature management (TTM).

Methods: We conducted a retrospective cohort study of 261 adult OHCA survivors who received complete TTM between January 2011 and December 2018 using data from the Research Patient Database Registry of Partners HealthCare system in Boston. Patients were categorized as underweight (BMI < 18.5 kg/m^2), normal weight (BMI = 18.5–24.9 kg/m^2), overweight (BMI = 25–29.9 kg/m^2), and obese (BMI ≥ 30 kg/m^2), according to the World Health Organization classification.

Results: The average BMI was 28.9 ± 7.1 kg/m^2. Patients with a higher BMI had higher rates of hypertension and diabetes mellitus, and were more likely to be witnessed on collapse. Patients with lower BMI levels had higher sequential organ failure assessment (SOFA) scores, blood urea nitrogen values, and mild thrombocytopenia rates (platelet count <150 K/μL) after the TTM treatment. The survival to discharge and favorable neurological outcome at discharge were reported in 117 (44.8%) and 76 (29.1%) patients, respectively. The survival at discharge, favorable neurologic outcomes at discharge, length of hospital admission, and the occurrence of acute kidney injury did not significantly differ between the BMI subgroups. In logistic regression model, BMI was not an independent predictor for survival at discharge (adjusted odds ratio 0.945, 95% CI 0.883–1.012, p = 0.108) nor for the favorable neurologic outcome at discharge (adjusted odds ratio 1.022, 95% CI 0.955–1.093, p = 0.528).

Conclusion: In OHCA patients treated with TTM, there was no significant difference across BMI subgroups for survival or favorable neurologic outcome at discharge.

Keywords: Body mass index; Cardiac arrest; Neurological outcome; Targeted temperature management; Therapeutic hypothermia; Survival

1. INTRODUCTION

Out-of-hospital cardiac arrest (OHCA) is a common public health concern that affects approximately 360 000 patients per year in the United States.[1] Despite several advances in resuscitation care, OHCA is still the main cause of death in numerous places worldwide.[2] Neurologic injury is the most common cause of death in OHCA patients and the subsequent anoxic brain injury still remains a major health burden for OHCA survivors with only 3% to 7% recovering to their precardiac arrest functional status.[3–5] The ensuing vegetative state or cognitive impairment then burdens the health system and patients' family members with considerable expenses related to temporary or permanent home care.[6]

Recently, the concept of postcardiac arrest care has been regarded as the fifth survival chain link, and this can potentially improve morbidity and mortality resulting from neurological injury.[7] Implementation of therapeutic hypothermia in selected OHCA survivors can improve the neurological outcome and survival.[7,8] Although moderate amounts of studies on targeted temperature management (TTM) exist, its neuroprotective mechanisms remain to be comprehensively understood and are thought to be multifactorial.[9] The growing evidence supports the assumption that the protective effect of TTM is influenced by patient-specific characteristics or circumstances concerning the cardiac arrest itself.[10]

Obesity has become increasingly common worldwide and is a major risk factor for diabetes, hypertension, dyslipidemia,

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and coronary artery disease.[11] Previous studies have shown that an elevated body mass index (BMI) was linked to favorable short-term or long-term outcomes in cardiac arrest patients.[11,12] This phenomenon has been referred to as the "obesity paradox."[13] Moreover, obesity has been reported to be protective in patients who are elderly or hospitalized or who have cancer, end-stage renal disease, or acquired immune deficiency syndrome.[14–18] Possible causes of the reverse epidemiology of obesity include a more stable hemodynamic status, endotoxin-lipoprotein interaction, alterations in circulating cytokines, and unique neurohormonal constellations. However, obesity may influence cardiopulmonary resuscitation (CPR) quality, prolong TTM induction time, worsen postresuscitation shock, and increase therapeutic hypothermia failure.[11,19] Testori et al[12] analyzed the impact of BMI in cardiac arrest survivors, but not all patients received subsequent TTM. Recently, several studies have demonstrated neutral or poor results of survival or neurological outcomes in obese cardiac arrest patients.[19–21] Moreover, owing to varying backgrounds, a few OHCA and in-hospital cardiac arrest patients could not be compared.[12,19,20] Currently, limited data exist regarding the influence of BMI on the prognosis of OHCA patients after TTM.[11,20] Therefore, we aimed to examine the association between BMI and clinical outcomes among OHCA survivors who were treated with TTM.

2. METHODS

2.1. Study design and patient involvement

In this retrospective observational cohort study, we included data of OHCA survivors (ICD-10-CM Code I46.9) ≥18 years of age who received subsequent TTM between January 2011 and December 2018, from the Research Patient Database Registry of Partners HealthCare system in Boston. Patients were excluded if they expired during the treatment process, had missing data, did not complete TTM or reach the target temperature, or had a do-not-resuscitate order. The clinical, epidemiological, and resuscitation characteristics of cases were documented. This is a multicentered database comprising over 6.5 million patients who availed services at the Brigham and Women's Hospital, Massachusetts General Hospital, Faulkner Hospital, Spaulding Rehabilitation Hospital, Newton Wellesley Hospital, North Shore Medical Center or McLean hospital and over two billion medical records from patient encounters, laboratories results, and other medical care. This study was approved by Partners HealthCare Institutional Review Board (Protocol Number: 2019P000111).

TTM protocols may not be identically standardized among all hospitals in the Partners HealthCare system but are accepted by national academic societies. Eligible patients were actively cooled for a constant 24-hour period once they achieved a target temperature between 32 and 36°C. The decision to use TTM relied on the judgment of the attending physician. No absolute contraindications for TTM existed. Cooling was initiated to reach the desired target temperature as rapidly as possible. Sedation and/or neuromuscular blocking agents were administered to attain a Bedside Shivering Assessment Scale score of 0.[22] Patients were then maintained at the designated target temperature for 24 hours. Upon completion of the maintenance phase, patients were rewarmed slowly at a rate of 0.25°C/h, until the core temperature reached 37°C for 48 hours, which is the alleged normothermia stage. The goal of normothermia was to prevent a fever. Advanced critical care such as ventilation, oxygenation, glucose control, and hemodynamic optimization was executed according to the guidelines.

2.2. Data collection and outcomes

Data regarding cardiac arrest event variables and outcomes were documented according to the standardized Utstein-style definitions.[23] The enrolled patients were categorized according to the World Health Organization classification as underweight (BMI < 18.5 kg/m^2), normal weight (BMI = 18.5–24.9 kg/m^2), overweight (BMI = 25–29.9 kg/m^2), and obese (BMI ≥ 30 kg/m^2). The duration of return of spontaneous circulation (ROSC) was defined as the time from collapse or alarm call to spontaneous circulation reestablishment. The sequential organ failure assessment (SOFA) score within the first 24 hours after admission was used to evaluate the severity of multiple organ dysfunctions. Neurological outcomes and survival at hospital discharge were considered primary outcomes. Length of hospital admission and the occurrence of acute kidney injury (AKI) throughout the TTM treatment were considered secondary outcomes. The neurological outcome at discharge was assessed using the Cerebral Performance Categories scale, which is a 5-point scale with 1 representing good cerebral performance; 2, moderate disability; 3, severe disability; 4, vegetative state; and 5, death.[24] The neurological outcome at discharge was further dichotomized as favorable (1–2) or unfavorable (3–5). AKI was defined as oligoanuria (daily urine output < 0.5 mL/kg/h) and/or an increase in serum creatinine (≥0.3 mg/dL from admission value within 48 h or 1.5 times the baseline level).[25] We also documented TTM-associated electrolyte imbalance episodes. Hypernatremia was defined as sodium > 145 mmol/L; hyponatremia, sodium <136 mmol/L; hyperkalemia, potassium >5.0 mmol/L; and hypokalemia, potassium <3.4 mmol/L.

2.3. Statistical analysis

Categorical variables are presented as n (%) and compared using the chi-squared or Fisher's exact test, as appropriate. Continuous variables are presented as mean ± SD or median (interquartile range [IQR]) and compared across the four groups with one-way analysis of variance or the Kruskal–Wallis test. Multivariable logistic regression was utilized to determine the independent predictors of survival and favorable neurological status at discharge. Predictors for the logistic regression were selected based on the significance in the univariate analysis (p < 0.05). All analyses were processed using the IBM SPSS Statistics software (version 20.0; IBM Corp., Armonk, NY). All tests were two-tailed, and a p value <0.05 was considered significant.

3. RESULTS

During the study period, 261 OHCA survivors who received complete TTM were enrolled (Fig. 1), with a mean age of 55.7 ± 17.9 years. There was a predominance of men (60.9%) and whites (70.1%). The average BMI was 28.9 ± 7.1 kg/m^2. The median Charlson comorbidity score was 3 (IQR 1–6); hypertension (47.5%), arrhythmia (37.2%), and coronary artery disease (31.8%) were the most prevalent comorbidities. A total of 113 patients (43.3%) had a shockable rhythm, 99 (37.9%) had a presumed cardiac etiology, 141 (54%) were witnessed on collapse, and 104 (39.8%) received bystander cardiopulmonary resuscitation. The median minutes to ROSC was 17 (IQR 10–27), and only three patients (1.1%) needed extracorporeal membrane oxygenation. Comparison of baseline demographics data and resuscitation variables among different BMI categories are shown in Table 1. Patients with a higher BMI had higher rates of hypertension and diabetes mellitus and were more likely to be witnessed on collapse.

Characteristics after ROSC, outcomes, and the associated complications of patients receiving TTM are listed in Table 2. After ROSC, patients had a median mean arterial pressure of 82

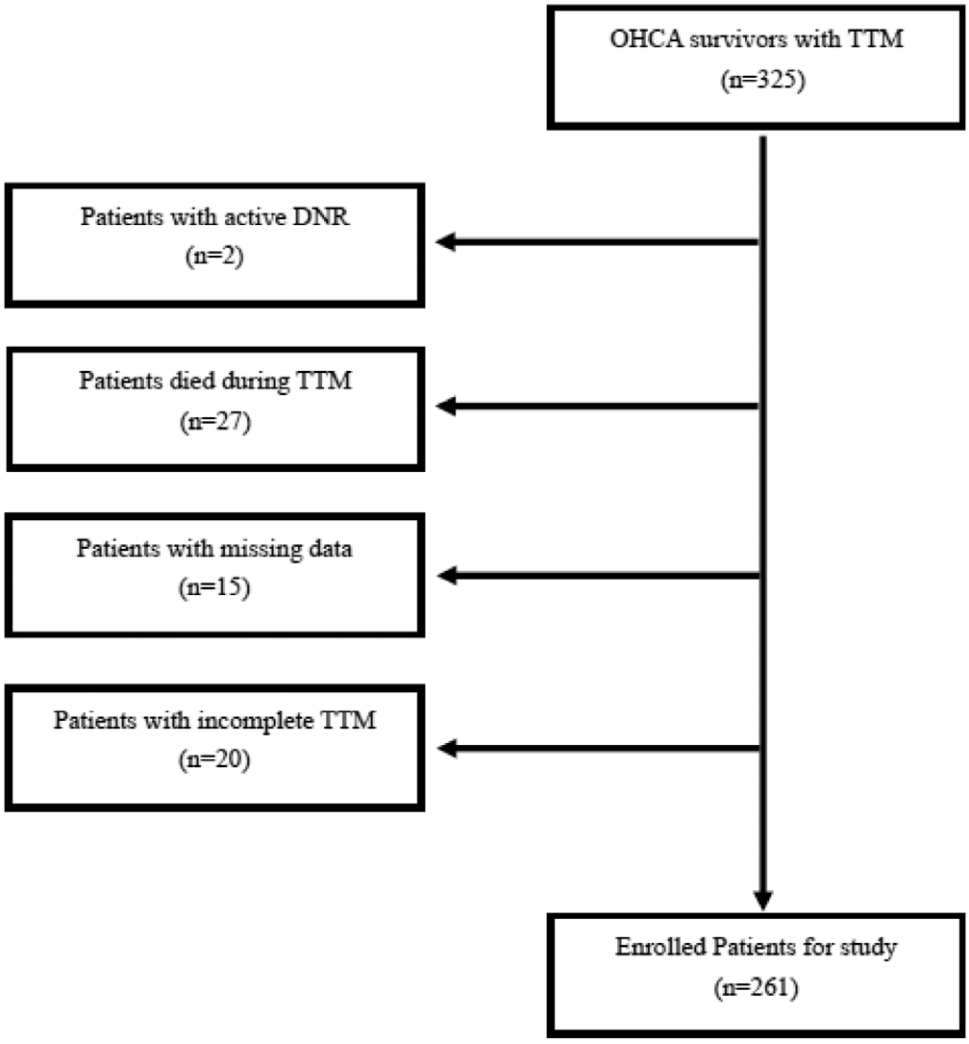

Fig. 1 Study flowchart.

(IQR 65–97) mmHg and a median SOFA score within 24 hours after a cardiac arrest event of 8.0 (IQR 7–10). The occurrence of AKI throughout the TTM treatment was noted in 36.4% of the cases. Patients had a median duration of hospital admission of 7 (IQR 4–16) days. The survival to discharge and favorable neurological outcome at discharge were reported in 117 and 76 patients, respectively. Patients with lower BMI levels had higher SOFA scores, blood urea nitrogen values, and mild thrombocytopenia rates (platelet count < 150 K/μL) after the TTM treatment. There was no significant discrepancy between the BMI subgroups regarding survival to hospital discharge, favorable neurologic outcome at discharge, length of hospital admission, and occurrence of AKI. There was a trend toward higher rates of survival at discharge in the normal weight group, but this did not reach statistical significance (p = 0.057). In logistic regression model, BMI was not an independent predictor for survival at discharge (adjusted odds ratio 0.945, 95% CI, 0.883–1.012, p = 0.108) nor for favorable neurologic outcome at discharge (adjusted odds ratio 1.022, 95% CI, 0.955–1.093, p=0.528) (Table 3).

4. DISCUSSION

In this study, we assessed the impact of BMI on clinical outcomes in OHCA survivors treated with TTM. We found that there was no significant difference across BMI subgroups for survival or favorable neurologic outcome at discharge, but a trend toward a better hospital survival in patients with normal BMI was shown. Obesity is an established risk factor for cardiovascular diseases and poor outcomes in the general population,[26,27] yet such an obesity paradox has been previously observed in other populations, such as the elderly and those with congestive heart failure.[28,29] Furthermore, a high BMI was also found to have a protective effect on mortality in patients with ST-segment elevation myocardial infarction, unstable angina, and non-ST-segment elevation myocardial infarction.[30]

Nevertheless, the existence of an obesity paradox among cardiac arrest patients is currently controversial. Obesity has been associated with an increased duration of time required to reach target temperature, although this does not necessarily correlate to a significant difference in survival or neurologic outcomes.[31] Besides, there may be logistical delays in morbidly obese patients owing to difficulties in the placement of defibrillator pads, establishment of vascular access, or initiation of a viable airway. Physical and biological factors related to a high or low BMI could affect the quality of chest compressions, efficacy of vasoactive drugs, or safety of defibrillator shocks because none of these measures are standardized per a patient's BMI or weight. In a previous study, a higher thoracic impedance was associated with decreased defibrillation

Table 1

Baseline characteristics of patients

	Underweight (N = 6)	Normal (N = 79)	Overweight (N = 88)	Obese (N = 88)	*P*
Age, y, mean (SD)	55.5 ± 27.2	54.0 ± 16.6	59.3 ± 17.9	59.6 ± 15.2	0.158
Male sex, no. (%)	3 (50)	46 (58.2)	63 (71.6)	47 (53.4)	0.077
Smoking status, no. (%)					
Former smoker	1 (16.7)	19 (24.1)	18 (20.5)	19 (21.6)	0.936
Current smoker	2 (33.3)	18 (22.8)	19 (21.6)	31 (35.2)	0.159
Nonsomker	3 (50)	23 (29.1)	35 (39.8)	25 (28.4)	0.262
Unknown	0 (0)	19 (24.1)	16 (18.2)	13 (14.8)	0.283
Pre-existing medical history, no. (%)					
Hypertension	1 (16.7)	32 (40.5)	40 (45.5)	51 (58.0)	0.049*
Diabetes mellitus	0 (0)	17 (21.5)	13 (14.8)	38 (43.2)	<0.001*
Coronary artery disease	1 (16.7)	23 (29.1)	31 (35.2)	28 (31.8)	0.712
Heart failure	1 (16.7)	19 (24.1)	17 (19.3)	22 (25.0)	0.790
Arrhythmia	2 (33.3)	30 (38.0)	32 (36.4)	33 (37.5)	0.993
Cerebrovascular disease	0 (0)	8 (10.1)	9 (10.2)	7 (8.0)	0.810
Chronic obstructive pulmonary disease	0 (0)	14 (17.7)	16 (18.2)	22 (25.0)	0.345
Hepatic insufficiency	1 (16.7)	3 (3.8)	7 (8.0)	5 (5.7)	0.485
Renal insufficiency	1 (16.7)	16 (20.3)	15 (17.0)	22 (25.0)	0.620
Uremia under regular hemodialysis	1 (16.7)	9 (11.4)	12 (13.6)	13 (14.8)	0.924
Solid tumor	0 (0)	8 (10.1)	17 (19.3)	15 (17.0)	0.260
Leukemia/lymphoma	0 (0)	0 (0)	0 (0)	2 (2.3)	0.266
Charlson score, median (IQR)	3 (1–5)	3 (1–6)	4 (2–6)	0.100	
Resuscitation factors					
Bystander witnessed, no. (%)	2 (33.3)	36 (45.6)	43 (48.9)	60 (68.2)	0.010*
Bystander CPR, no. (%)	0 (0)	39 (49.4)	32 (36.4)	33 (37.5)	0.055
Presumed cardiac cause, no. (%)	1 (16.7)	28 (35.4)	39 (44.3)	31 (35.2)	0.368
PCI, no. (%)	2 (33.3)	27 (34.2)	41 (46.6)	26 (29.5)	0.117
Initial rhythm, no. (%)	0.188				
Shockable	0 (0)	34 (43.0)	40 (45.5)	39 (44.3)	
Nonshockable	6 (100)	45 (57.0)	48 (54.5)	49 (55.7)	
Minutes to ROSC, median (IQR)	19 (15–32)	16 (10–29)	16 (10–25)	18 (10–30)	0.615
Total adrenalin dose, median (IQR)	3 (2–6)	2 (1–4)	3 (0–4)	2 (1–4)	0.732
ECMO use, no. (%)	0 (0)	1 (1.3)	1 (1.1)	1 (1.1)	0.994

CPR = cardiopulmonary resuscitation; ECMO = extracorporeal membrane oxygenation; IHCA = in-hospital cardiac arrest; IQR = interquartile range; PCI = percutaneous coronary intervention; ROSC = return of spontaneous circulation.

*$p < 0.05$.

success,[32] and BMI has previously been shown to correlate to thoracic impedance.[33] Bunch et al[34] described a lower long-term survival in patients with normal or low weight after witnessed OHCA due to ventricular fibrillation. However, Bunch's study only comprised patients who had experienced OHCA due to ventricular fibrillation or nonperfusion ventricular tachycardia. Two previous studies proclaimed that obesity was independently associated with mortality in cardiac arrest patients who underwent a posttherapeutic hypothermia protocol.[11,21] However, the obese patients in both studies were older and more frequently men, which might inevitably cause a detrimental impact on the outcome. In addition, both studies did not further evaluate the neurological outcome among their study population. Leary et al[19] stated that there was no significant difference across BMI groups with respect to survival or good neurologic outcome among patients following post-arrest TTM. However, Leary's study included in-hospital cardiac arrest patients as well; this population possesses quite different features when compared with those of OHCA patients and may hold an unevaluable influence upon the results. Another Asian study concluded that an overweight BMI than a normal BMI was associated with a lower 6-month mortality and poor neurologic outcome at discharge in cardiac arrest survivors treated with TTM.[20] However, this was a single-center study and it adopted a different BMI classification as it consisted solely the Asian population.

Conversely, a prospective observational study in Greece found that survival to intensive care unit (ICU) admission and ICU discharge was higher in the elevated BMI group among OHCA patients.[35] In addition, Testori et al[12] conducted a cohort study, which elucidated that cardiac arrest survivors with moderately elevated BMI may have a better neurological prognosis. However, only a small number of patients (26.6%) in this study were treated with TTM; hence, it may not holistically evaluate the effect of TTM on obese patients.

Our study involves a large cohort of diverse patients who experienced OHCA and were shifted to multiple centers, making our findings fairly generalizable. Nevertheless, this study must be viewed in the context of certain limitations. First, BMI may not be an optimal surrogate of visceral obesity when compared with waist circumference, which better reflects intra-abdominal (truncal) fat. Although BMI has been accepted as one of the most reliable anthropometric indices for obesity and has been used widely in research and for guidelines on obesity, BMI has a limited ability to differentiate adiposity from muscle mass. Second, this study did not evaluate long-term survival, and patients with poor neurologic outcome at discharge may have a higher risk of long-term mortality. Third, there were some variations in the methods followed by ICUs and different institutions while providing TTM and while selecting patients. The decision to use TTM for some of the patients may have affected

Table 2

Characteristics after ROSC and outcomes of patients receiving TTM

	Underweight (N = 6)	Normal (N = 79)	Overweight (N = 88)	Obese (N = 88)	*p*
Mean arterial pressure, median (IQR)	79 (55–101)	87 (73–99.5)	79 (65–95)	80 (65–96)	0.277
SOFA within 24 h after event					
Median (IQR)	11 (9–12)	8 (6–9)	8 (7–10)	8 (7–10)	0.034*
Glucose (mg/dL), median (IQR)	148 (121–211)	214 (160–286)	206 (148–286)	248 (160–316)	0.064
BUN (mg/dL), median (IQR)	50 (25–61)	20 (14–27)	17 (13–24)	22 (15–35)	0.004*
Creatinine (mg/dL), median (IQR)	2.2 (1.1–4.0)	1.3 (1.0–1.7)	1.2 (1.0–1.6)	1.4 (1.0–1.9)	0.180
Lactate (mmol/L) after ROSC, median (IQR)	8.0 (4.4–15.5)	5.9 (3.0–9.1)	5.7 (3.3–8.1)	5.9 (2.8–9.5)	0.668
Lactate (mmol/L) after TTM, median (IQR)	3.2 (1.5–7.6)	1.5 (1.1–2.8)	1.4 (1.1–2.4)	1.5 (1.1–2.8)	0.379
Coagulopathy after TTM, no. (%)					
Thrombocytopenia < 150 K/μL	4 (100)	26 (38.8)	38 (49.4)	29 (36.7)	0.039*
Thrombocytopenia < 50 K/μL	0 (0)	2 (3.0)	0 (0)	3 (3.8)	0.400
Prolonged PT > 14.4 s	4 (100)	45 (64.3)	48 (62.3)	55 (67.1)	0.463
Prolonged aPTT > 36.6 s	2 (66.7)	23 (35.9)	30 (39.5)	28 (36.4)	0.725
Electrolyte imbalance after TTM, no. (%)					
Hypernatremia	0 (0)	4 (6.0)	6 (7.8)	6 (7.5)	0.916
Hyponatremia	1 (25.0)	19 (28.4)	20 (26.0)	21 (26.2)	0.988
Hyperkalemia	1 (25.0)	5 (7.5)	5 (6.5)	9 (11.4)	0.453
Hypokalemia	0 (0)	2 (3.0)	6 (7.8)	2 (2.5)	0.353
Outcome					
Acute renal injury, no. (%)	4 (66.7)	23 (35.4)	26 (32.9)	31 (38.3)	0.401
Length of hospital stay, median (IQR)	6 (2–12)	7 (4–18)	8 (4–14)	7 (4–13)	0.549
Survival at discharge, no. (%)	1 (16.7)	43 (54.4)	41 (46.6)	32 (36.4)	0.057
Favorable CPC scale at discharge, no. (%)	0 (0)	19 (24.1)	30 (34.1)	27 (30.7)	0.2

aPTT = activated partial thromboplastin time; BUN = blood urea nitrogen; CPC scale = cerebral performance category scale; IQR = interquartile range; PT = prothrombin time; ROSC = return of spontaneous circulation; SOFA = sequential organ failure assessment; TTM = targeted temperature management.
*$p < 0.05$.

Table 3

Logistic regression model of survival to hospital discharge and favorable neurologic outcome at discharge

	Survival at discharge			
	Crude OR (95% CI)	*p*	Adjusted OR[a] (95% CI)	*p*
BMI	0.926 (0.938–0.996)	0.030*	0.945 (0.883–1.012)	0.108
	Favorable neurologic outcome			
	Crude OR (95% CI)	*p*	Adjusted OR[b] (95% CI)	*p*
BMI	1.006 (0.969–1.044)	0.758	1.022 (0.955–1.093)	0.528

BMI = body mass index; CPR = cardiopulmonary resuscitation; OR = odds ratio; ROSC = return of spontaneous circulation; SOFA = sequential organ failure assessment; TTM = targeted temperature management..
*$p < 0.05$.
[a]Variables included in the model: BMI, age, male, initial shockable rhythm, minutes to ROSC, witnessed cardiac arrest, total adrenal indose, bystander CPR, presumed cardiac cause, SOFA, BUN after ROSC, lactate after ROSC, lactate after TTM, glucose after ROSC, and CAD history.
[b]Variables included in the model: BMI, age, initial shockable rhythm, minutes to ROSC, witnessed cardiac arrest, total adrenal indose, bystander CPR, presumed cardiac cause, SOFA, BUN after ROSC, lactate after ROSC, lactate after TTM, glucose after ROSC.

the results. Part of the differences reported might be related to a before-after effect or observation bias. Therefore, we can only report an association and cannot conclude about the causality. Fourth, the observational period in our study was relatively long, and general intensive care treatment strategies may have changed over the past 8 years.

In conclusion, BMI was not an independent factor for survival to hospital discharge, favorable neurologic outcomes at discharge, length of hospital admission, and the occurrence of AKI in OHCA survivors receiving TTM. We did not observe that the "obesity paradox" existed in clinical outcomes of OHCA patients who treated with TTM.

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