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Clinical paper

Association between body mass index and clinical outcomes in patients with out-of-hospital cardiac arrest undergoing extracorporeal cardiopulmonary resuscitation: A multicenter observational study

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Abstract

Background: We examined the association between body mass index (BMI) and outcomes in patients with out-of-hospital cardiac arrest (OHCA) undergoing extracorporeal cardiopulmonary resuscitation (ECPR).

Methods: We retrospectively analyzed the database of an observational multicenter cohort in Japan. Adult patients with OHCA of cardiac etiology who received ECPR between 2013 and 2018 were categorized as follows: underweight, BMI < 18.5; normal weight, BMI = 18.5–24.9; overweight, BMI = 25–29.9; and obese, BMI $\geq$ 30 kg/m^2. The primary outcome was in-hospital mortality; secondary outcomes were unfavorable neurological outcomes at discharge (cerebral performance category $\geq$ 3) and ECPR-related complications. BMI's association with outcomes was assessed using a logistic regression model adjusted for age, sex, comorbidities, witness/bystander CPR, initial rhythm, prehospital return of spontaneous circulation, and low-flow time.

Results: In total, 1,044 patients were analyzed. Their median age was 61 (IQR, 49–69) years; the median BMI was 24.2 (21.5–26.9) kg/m^2. The overall rates of in-hospital mortality, unfavorable neurological outcome, and ECPR-related complications were 62.2%, 79.9%, and 31.7%, respectively. In multivariate analysis, the overweight and obese groups had higher in-hospital mortality odds than the normal BMI group (odds ratio [95%CI], 1.37 [1.02–1.85], $p = 0.035$; and 2.09 [1.31–3.39], $p < 0.001$, respectively). The odds ratio for unfavorable neurological outcomes increased more in the obese than in the normal BMI group (3.17 [1.69–6.49], $p < 0.001$). ECPR-related complications were not significantly different among groups.

Conclusions: In OHCA patients undergoing ECPR, a BMI $\geq$ 25 kg/m^2 was associated with increased in-hospital mortality, and a BMI $\geq$ 30 kg/m^2 was also associated with a worse neurological outcome.

Keywords: Cardiac arrest, Extracorporeal cardiopulmonary resuscitation, Neurological outcome, Obesity, Overweight

Introduction

Obesity has become increasingly prevalent in developed countries.[1] Increased body mass index (BMI) is known to increase the risk of various cardiovascular diseases, including coronary heart disease, heart failure, hypertension, stroke, and sudden cardiac death.[2,3] Previous studies consistently show that obesity increases cardiovascular morbidity and mortality.[4,5]

Resuscitation of patients with elevated BMI is challenging. In critically ill overweight patients, an increased risk of procedure-related complications of extracorporeal membrane oxygenation (ECMO)

Abbreviations: ECPR, Extracorporeal cardiopulmonary resuscitation, SAVE-J II, Study of Advanced life support for Ventricular fibrillation with Extracorporeal circulation in Japan, ECOG PS, Eastern Cooperative Oncology Group Performance Status, GAM, Generalized additive model, EDF, Estimated degrees of freedom

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has been reported.[6,7] With respect to survival to hospital discharge, the existing literature provides conflicting perspectives on patients with cardiac arrest (CA). Some large-scale studies have reported the association between increased BMI and the unfavorable outcomes of patients with CA.[4,5] Contrarily, others find no significant association or even suggest a survival benefit, a phenomenon referred to as the obesity paradox.[8,9] The association between higher BMI and increased mortality in patients with out-of-hospital cardiac arrest (OHCA) undergoing extracorporeal cardiopulmonary resuscitation (ECPR) has recently been reported[10]; however, large-scale studies on this topic are lacking and there is still room for research.

This study aimed to investigate the association between BMI and clinical outcomes in patients receiving ECPR following OHCA using data from a nationwide, multicenter ECPR registry in Japan.

Methods

Study design and setting

This retrospective cohort study utilized the data from the Study of Advanced life support for Ventricular fibrillation with Extracorporeal circulation in Japan (SAVE-J II).[11] The observation period was 6 years (January 2013–December 2018).

Patient selection

Adult patients with OHCA of presumed cardiac etiology who received ECPR from the SAVE-J II registry were included. The SAVE-J II study excludes patients with OHCA who were transferred to the participating institutions after being treated at another hospital, patients with in-hospital cardiac arrest, and patients who declined to participate through family or other means. For this study, we selected patients from SAVE-J II who met the inclusion criterion of initiation of venoarterial ECMO (VA-ECMO) before intensive care unit (ICU) admission. The exclusion criteria included non-cardiac conditions such as acute aortic dissection/ aortic aneurysm, hypothermia, primary cerebral disorder, and sepsis. The patients with missing values in BMI or discharge outcomes were also excluded.

Data collection

The following variables were included in the study analyses: patients' age, sex, weight, height, body temperature, Eastern Cooperative Oncology Group Performance Status (ECOG PS) before admission, comorbidities, the situation of CA (witnessed CA, initial CA rhythms, presence of prehospital return of spontaneous circulation [ROSC], low-flow time), the emergency procedure before arriving at the hospital (automated external defibrillator [AED] use, bystander CPR), and treatment after arriving at the hospital (coronary artery angiogram, percutaneous coronary intervention [PCI], intra-aortic balloon pumping [IABP]). Prehospital information was collected by paramedics based on the standardized Utstein format.[12] The ECOG PS was used to measure the overall condition of patients and indicate the extent of limitations in their daily activities.[13] A lower score indicates a higher level of daily activity performance: a score of 0 indicates that the patient is fully active and capable of engaging in all activities without any restrictions, while a score of 4 indicates complete disability, rendering the patient bedridden.

Definition and outcomes

The primary outcome was in-hospital mortality; secondary outcomes were unfavorable neurological outcomes at hospital discharge (cerebral performance category score $\geq$3 points) and ECPR-related complications. ECPR was defined as resuscitation from CA with VA-ECMO. ECMO-related complications were defined as cannulation site bleeding/hematoma, infections related to VA-ECMO, lower limb ischemia, retroperitoneal hematoma, internal bleeding, embolism, and other procedure-related complications (unsuccessful cannulation, cannula malposition, and machine failure) following previous studies.[11,14] Low-flow time was defined as the time from cardiac arrest to the establishment of ECMO if the location of cardiac arrest was an ambulance and the time from calling an ambulance to the establishment of ECMO if the location of cardiac arrest was other than the ambulance, as we have previously reported.[11]

Statistical analysis

Patients were classified into four groups based on their BMI according to the World Health Organization classification: underweight, BMI < 18.5; normal weight, BMI = 18.5–24.9; overweight, BMI = 25–29.9; and obese: BMI $\geq$ 30 kg/m^2. We examined differences in BMI groups using Fisher's exact test for nominal variables and the Kruskal-Wallis test for continuous variables. When there were significant differences among the four BMI groups, Dunn's test or post hoc Kruskal-Wallis analysis was used to identify the group with statistically significant differences compared with the normal BMI group. The associations between BMI and outcomes were assessed as follows. First, we examined the associations of BMI as a continuous variable with in-hospital mortality, unfavorable neurological outcome, and incidence of ECMO-related complications in the entire study cohort using a non-linear generalized additive model (GAM) to account for the possible non-linear relationship between BMI and the outcomes. Smoothed curves were plotted against the log odds of receiving an outcome, along with 95% confidence intervals, allowing BMI to predict categorical outcomes without insisting on a linear relationship. Adjustments were made for potential confounding variables, including age, sex, pre-existing comorbidities (diabetes, hypertension, dyslipidemia, chronic kidney disease, chronic heart disease, cerebrovascular disease, and dementia), witnessed CA, bystander CPR, initial rhythms, presence of prehospital ROSC, and low-flow time. These covariates were selected on the basis of previous publications and are considered clinically relevant.[7,11] Estimated degrees of freedom (EDF) and chi-square values were calculated for each plot, and a p-value of <0.05 was considered statistically significant.[15]

Second, logistic regression analyses were performed to assess the association between BMI categories and outcomes, adjusted for the same variables as the GAM. Subgroup analysis was conducted using logistic regression analysis based on the following subgroups: elderly (age $\geq$65 years) vs. non-elderly patients (age <65 years) and the presence or absence of PCI. Sensitivity analysis was performed using logistic regression analysis in the missing BMI-imputed dataset and the entire SAVE-J II study cohort including non-cardiac causes of CA. Missing values were imputed using patient characteristics (i.e., age, sex, pre-existing comorbidities), cardiac arrest event characteristics (i.e., witnessed cardiac arrest, bystander CPR, initial cardiac rhythms, AED use), and laboratory data (i.e., arterial blood gas) as variables using the random forest method via the missForest package (version 1.4) in the R software (version

3.6.1; R Foundation for Statistical Computing, Vienna, Austria). This imputation handles nonlinearities and interactions without specifying a parametric model, provides single-point estimates using normal distributions centered on conditional means, and reduces overfitting and merges estimates from different trees through bootstrapped regression trees.[16]

Analyses were conducted with R software, and figures were created using the ggplot2 package. The level of significance was set at p-value < 0.05.

Results

Patients' characteristics classified by BMI

A total of 1,044 patients with OHCA of presumed cardiac etiology were included in the study (Fig. 1). The distribution of BMI among the study population is presented in Supplemental Fig. 1. The background of the study population, divided into four groups based on BMI, is shown in Table 1. Briefly, the distribution of age and sex, as well as the proportion of patients with comorbidities, varied by BMI category. In particular, patients in the obese group (BMI $\geq$ 30 kg/m^2) were younger than those in the normal BMI group (BMI 18.5–24.9 kg/m^2). In addition, both the overweight (BMI 25–29.9 kg/m^2) and obese groups had a significantly higher incidence of hypertension and diabetes compared to the normal BMI group. Conversely, the underweight group (BMI < 18.5 kg/m^2) had a significantly lower prevalence of hypertension and dyslipidemia compared with the normal BMI group (Table 1).

Comparison of CA status and emergency procedure by the BMI group

CA rhythms, presence of witness and bystander CPR, and emergency procedures were summarized according to each BMI group (Table 2). There were no significant differences between the BMI groups in witness presence, bystander CPR rate, initial cardiac rhythms, AED use, or low-flow time. The rates of coronary angiography, PCI, and IABP placement were lower in the underweight group than in the normal BMI group (Table 2).

Comparison of outcomes and ECMO-related complications by the BMI group

The rates of in-hospital mortality, poor neurological outcome, and complications after ECMO were compared among the BMI groups. The rates of in-hospital mortality and neurological deterioration were found to increase proportionally with the BMI category (Table 2). No difference was observed in any of the complications between the BMI groups. Notably, the obese group (BMI $\geq$ 30 kg/m^2) had a significantly higher proportion of patients with in-hospital mortality and unfavorable neurological outcomes than the normal BMI group (Table 2).

Generalized additive model

Using a non-linear GAM that accounts for multiple covariates, the graphs showed an increasing trend toward increased incidence of in-hospital mortality and adverse neurological outcomes associated with elevated BMI (Fig. 2A, B). After adjustment for confounding variables, BMI as a continuous predictor was significantly associated with in-hospital mortality (chi-squared = 19.49, EDF = 2.999, $p < 0.001$) and unfavorable neurological outcomes (chi-squared = 14.07, EDF = 1.996, $p < 0.001$). In the context of in-hospital mortality, a BMI > 24.5 kg/m^2 was demonstrated to be a significant risk factor, as shown by the corresponding smoothed curve for odds consistently above the threshold of 1.0 (Fig. 2A). For adverse neurological outcomes, a BMI > 25.9 kg/m^2 was identified as a significant risk factor, as shown by both the smoothed curve and its 95% confidence interval for the adjusted odds of remaining consistently above 1.0 (Fig. 2B). In contrast, the model showed no significant association between BMI and ECMO-related complications (chi-squared = 2.648, EDF = 3.972, $p = 0.621$; Fig. 2C).

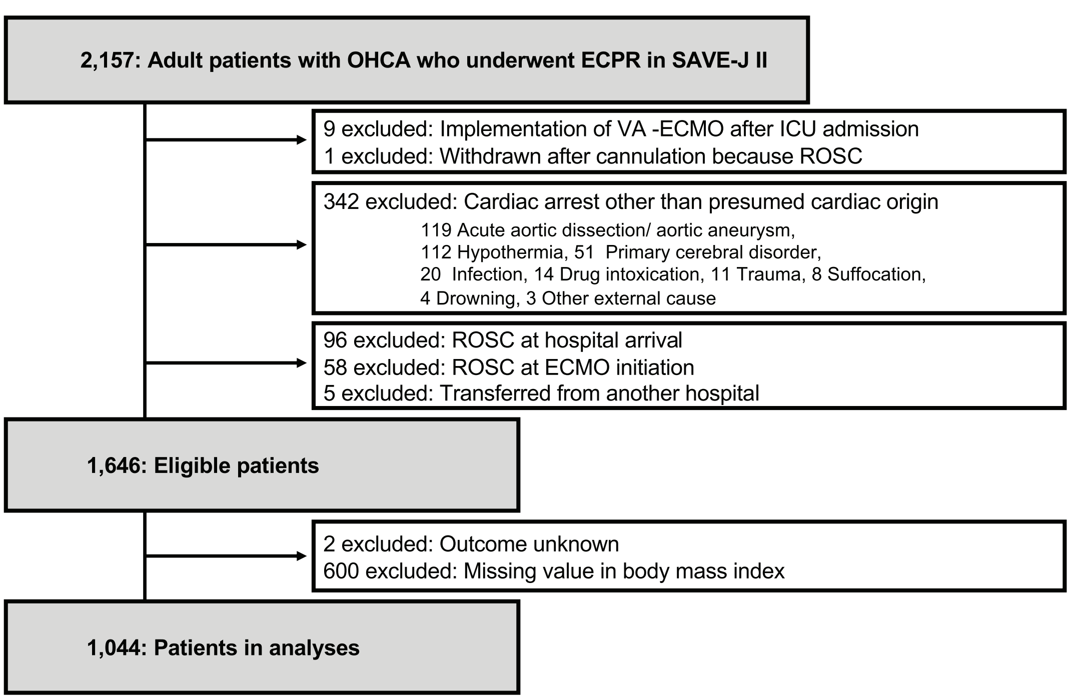

Fig. 1 – Flowchart showing the enrollment of study participants.

Table 1 – Baseline characteristics of patients according to BMI category.

Variables	Underweight (BMI < 18.5)	Normal (18.5–24.9)	Overweight (25–29.9)	Obese (≥30)	p-value
n	57	559	319	109	
Age, years	62.00 [45.00, 67.00]	63.00 [50.00, 70.00]	59.00 [50.00, 68.00]	52.00 [46.00, 63.00]*	<0.001
Male sex (%)	39 (68.4)	458 (81.9)	270 (84.6)	88 (80.7)	0.034
Weight, kg	46.70 [42.00, 50.00]*	61.70 [55.90, 68.00]	76.00 [70.00, 80.00]*	94.00 [87.50, 100.00]*	<0.001
Height, cm	165.00 [160.00, 169.00]	167.00 [161.00, 171.50]	168.00 [162.00, 173.00]	168.00 [161.00, 173.50]	0.014
BMI, kg/m^2	17.26 [16.32, 18.03]*	22.23 [20.77, 23.83]	26.83 [25.90, 28.07]*	32.39 [31.14, 33.91]*	<0.001
Body temperature, °C	34.70 [33.10, 35.60]	34.80 [33.95, 35.40]	35.00 [34.40, 35.70]	35.00 [34.60, 35.60]	0.004
Fully active (ECOG PS of 0)	49 (86.0)	494 (88.4)	293 (91.8)	98 (89.9)	0.343
Comorbidities					
Diabetes	10 (17.5)	104 (18.6)	79 (24.8)*	36 (33.0)*	0.004
Hypertension	12 (21.1)*	158 (28.3)	128 (40.1)*	38 (34.9)*	0.001
Dyslipidemia	3 (5.3)*	53 (9.5)	57 (17.9)*	12 (11.0)	0.001
Chronic kidney disease	4 (7.0)	35 (6.3)	14 (4.4)	7 (6.4)	0.655
Chronic heart disease	21 (36.8)	139 (24.9)	65 (20.4)	26 (23.9)	0.053
Cerebral vascular disease	0 (0.0)	25 (4.5)	30 (9.4)*	9 (8.3)	0.040
Dementia	1 (1.8)	4 (0.7)	3 (0.9)	0 (0.0)	0.633

BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group Performance Status.
* Indicates statistically significant difference vs. normal BMI group (18.5–24.9 kg/m^2).

Logistic regression analysis

We performed multivariate analysis using logistic regression to investigate the factors associated with the incidence of in-hospital mortality, unfavorable neurological outcomes, and ECMO-related complications. Compared to a normal BMI, overweight and obesity were independent risk factors for in-hospital mortality in ECPR cases (odds ratio [95%CI], 1.37 [1.02–1.85], p = 0.035; and 2.09 [1.31–3.39], p < 0.001, respectively). The obese group with a BMI ≥ 30 kg/m^2 showed higher odds of unfavorable neurological outcomes compared to the normal BMI group (3.17 [1.69–6.49], p < 0.001). In addition to BMI, age, shockable cardiac rhythms, and prehospital ROSC were associated with the odds of in-hospital mortality. Increasing age was also associated with poor neurological outcomes, whereas the odds of poor neurological outcomes were significantly lower with bystander CPR, ROSC before hospital arrival, and ventricular tachycardia (Table 3). There was no significant association between the BMI categories and the incidence of ECMO-related complications (Table 3).

Subgroup analysis

As there were differences in factors, such as age and PCI rate among BMI groups (Table 1), we conducted a subgroup analysis to examine their effects on the outcomes. Regardless of the presence of PCI, there was an increased odds of in-hospital mortality and poor neurological outcomes in the obese group with a BMI ≥ 30 kg/m^2, consistent with the overall analysis (Table 4). The association between BMI and outcome was no longer observed in patients aged ≥65 years (Table 4). There was no correlation between BMI and the incidence of procedure-related complications in any subgroup (Table 4).

Sensitivity analysis

Among 2,157 of the entire SAVE-J II cohort including both cardiac and non-cardiac etiology, increased odds of both in-hospital mortality and the unfavorable neurological outcome remained in the overweight (odds ratio [95%CI], in-hospital mortality: 1.73 [1.37–2.18], p < 0.001; and unfavorable neurological outcome: 1.64 [1.24–2.19], p = 0.002, respectively) and obese (1.67 [1.29–3.33], p = 0.022, and 2.54 [1.40–5.01], p < 0.001, respectively) groups. Similar results were also observed in the missing BMI-imputed cohort (n = 1,644); overweight group (in-hospital mortality: 1.67 [1.11–2.27], p < 0.001; and unfavorable neurological outcome: 1.64 [1.19–2.22], p = 0.041, respectively) and obese group (1.88 [1.61–2.54], p = 0.020, and 3.27 [1.61–7.51], p = 0.019, respectively).

Discussion

In this study, we examined the association between BMI and outcomes in patients undergoing ECPR. Interestingly, among patients with OHCA who received ECPR, those with a BMI ≥ 25 kg/m^2 had a higher in-hospital mortality rate compared with the patients with normal BMI. Second, in addition to mortality, the rate of adverse neurological outcomes after ECPR in patients with a BMI ≥ 30 kg/m^2 was significantly higher. There was no association between BMI and ECMO-related complications.

Obesity is generally considered a high-risk factor for poor outcomes, even in patients without OHCA.[1,17,18] Our findings showed that obesity is a poor prognostic factor for OHCA, consistent with those of previous studies.[4,5,19] Despite no difference in initial CA rhythms or whether the event was witnessed between BMI groups, obesity remained associated with poor prognosis compared to the normal BMI group probably because obesity is often associated with underlying diseases, such as cardiovascular disease and diabetes mellitus, which increases the risk of complications in the ICU.[9,18,20] In this study, patients with obesity tended to have reduced arterial blood gas oxygen concentrations upon admission to the emergency

Table 2 – Characteristics of cardiac arrest events, laboratory tests, emergency procedures and outcomes according to the BMI category.

Variables	Underweight (BMI < 18.5)	Normal (18.5–24.9)	Overweight (25–29.9)	Obese (≥30)	p-value
n	57	559	319	109	
Witnessed cardiac arrest (%)	45 (78.9)	435 (77.8)	256 (80.3)	97 (89.0)	0.068
Bystander CPR	39 (68.4)	336 (60.1)	198 (62.1)	70 (64.2)	0.574
Initial cardiac rhythm at the scene					0.277
Asystole	6 (10.5)	42 (7.5)	15 (4.7)	4 (3.7)	
Pulseless electrical activity	6 (10.5)	83 (14.8)	61 (19.1)	24 (22.0)	
Ventricular tachycardia	17 (29.8)	165 (29.5)	94 (29.5)	32 (29.4)	
Ventricular fibrillation	28 (49.1)	269 (48.1)	149 (46.7)	49 (45.0)	
AED use	35 (61.4)	348 (62.3)	193 (60.5)	67 (61.5)	0.966
ROSC before ED arrival	9 (15.8)	82 (14.7)	38 (11.9)	11 (10.1)	0.442
VT/VF at ED arrival	28 (49.1)	269 (48.1)	149 (46.7)	49 (45.0)	0.944
Arterial blood gas in ED					
pH at ED arrival	6.93 [6.84, 7.07]	6.96 [6.83, 7.08]	6.94 [6.82, 7.06]	6.91 [6.81, 7.04]	0.148
pO_2, mmHg	116.00 [49.80, 359.00]	92.30 [39.20, 300.95]	81.90 [38.50, 283.90]	71.80 [25.20, 258.00]	0.098
pCO_2, mmHg	60.40 [31.70, 84.50]	63.10 [44.03, 83.90]	65.10 [47.55, 85.10]	68.20 [44.70, 92.50]	0.225
Base excess	−18.80 [–23.52, −14.07]	−18.55 [–23.52, −13.90]	−18.25 [-24.52, −12.97]	−19.40 [–23.75, −14.38]	0.704
Low-flow time, min	60.00 [45.00, 77.00]	56.00 [45.00, 73.00]	55.00 [44.00, 66.00]	56.00 [47.00, 66.00]	0.401
Emergency coronary angiography	38 (66.7) *	461 (82.5)	264 (82.8)	92 (84.4)	0.022
Percutaneous coronary intervention	16 (28.1) *	274 (49.0)	166 (52.0)	59 (54.1)	0.007
Intra-aortic balloon pumping	29 (50.9) *	387 (69.2)	231 (72.4)	80 (73.4)	0.010
Outcomes					
In-hospital mortality	29 (50.9)	332 (59.4)	209 (65.5)	79 (72.5) *	0.010
Unfavorable neurological outcome	42 (73.7)	432 (77.3)	262 (82.1)	98 (89.9) *	0.009
ECMO-related complications	18 (31.6)	176 (31.5)	102 (32.0)	35 (32.1)	0.966
Cannulation site bleeding	9 (16.1)	111 (19.9)	54 (16.9)	24 (22.0)	0.549
Infections related to ECMO	3 (5.4)	36 (6.7)	30 (9.7)	5 (4.7)	0.229
Limb ischemia	6 (10.5)	50 (8.9)	38 (11.9)	9 (8.3)	0.497
Retroperitoneal hematoma	3 (5.3)	14 (2.5)	11 (3.4)	1 (0.9)	0.338
Gastrointestinal bleeding	3 (5.3)	52 (9.3)	27 (8.5)	9 (8.3)	0.769
Intracranial hemorrhage	0 (0.0)	1 (0.2)	3 (0.9)	1 (0.9)	0.362
Surgical cannulation	3 (5.3)	14 (2.5)	7 (2.2)	4 (3.7)	0.528

BMI, body mass index; CPR, cardiopulmonary resuscitation; AED, automated external defibrillator; ROSC, return of spontaneous circulation; ED, emergency department; VT, ventricular tachycardia; VF, ventricular fibrillation; ECMO, extracorporeal membrane oxygenation,

* Indicates statistically significant difference vs. normal BMI group (18.5–24.9 kg/m^2).

department. Although the mean low-flow time did not differ significantly among the four BMI categories, patients with obesity may have already been hypoxic upon arrival at the emergency department. Additionally, chest compressions during cardiac resuscitation may be less effective in patients with obesity.[21,22] Collectively, we hypothesize that CPR efficacy may be reduced in patients with obesity who may experience hypoxia during transport and neurological damage upon arrival at the hospital. Additionally, mortality from delayed complications related to comorbidities, such as diabetes, may occur in patients with obesity after ICU admission.

Patients with low BMI have been reported to be associated with poor prognosis following resuscitation, which may indicate their malnutrition status.[23] Additionally, patients with extremely low BMI who experienced CA may also include those with inherently compromised conditions, such as congenital heart disease, advanced stages of malignancy, or neurogenic anorexia nervosa. Complications, such as chest trauma, pulmonary hemorrhage, and intra-abdominal organ injury, may be more likely with chest compressions in the low BMI group.[24–27] However, in this study, no significant differences in outcomes were observed between patients with normal BMI and those in the underweight group. This may be attributable to the BMI cut-off for the underweight group being set at <18.5 kg/m^2. Indeed, the median BMI for the underweight group was approximately 17 kg/m^2, with very few cases having a BMI below 16 kg/m^2, which may explain the deviation from findings in other studies.

We postulated that obesity would prolong the duration of the ECMO insertion procedure and that obese patients would have a longer low-flow time. However, contrary to our hypothesis, the time from hospital arrival to the completion of ECMO insertion was not significantly different between the BMI groups. Previous studies have reported that patients with a higher BMI require more time for ECMO establishment and have an increased incidence of procedure-related complications.[28] Alvarez et al. postulated that thick subcutaneous tissue in patients who are severely obese may lead to confounding anatomical landmarks.[6] This can increase periprocedural morbidity and cannulation difficulty relative to patients with a normal BMI.[6,29,30] Here, obesity was defined as a BMI ≥ 30 kg/m^2. In the patients included in this study, only 14.6% of those with obesity had class II obesity (BMI ≥ 35 kg/m^2). In contrast, a study of ECMO-related complications in the US found that 47.2% of the patients had a BMI ≥ 30 kg/m^2, with more than 50% of those classified as obese

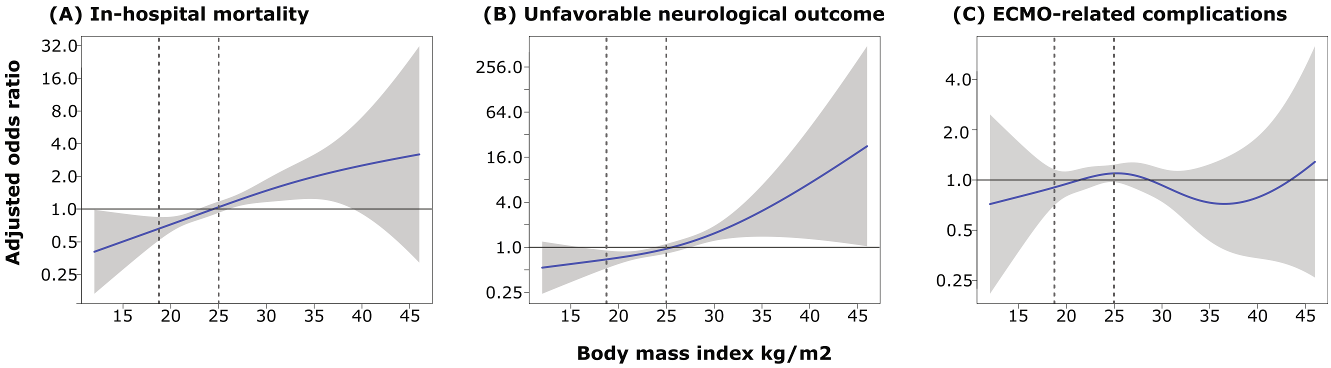

Fig. 2 – Generalized additive model evaluating the association between body mass index and outcomes. Association between body mass index (BMI) and in-hospital mortality (A), unfavorable neurological outcome (B), and ECMO-related complications (C). Outcomes were analyzed using the non-linear generalized additive model adjusted for age, sex, witnessed cardiac arrest, bystander CPR, initial rhythms, presence of the prehospital return of spontaneous circulation, low-flow time, and presence of percutaneous coronary intervention. The vertical dotted line represents a BMI range of 18.5–24.9 kg/m^2, indicating normal weight. The shaded area represents the 95% confidence intervals for the estimated points.

Table 3 – Multivariate analysis of factors associated with clinical outcomes.

	In-hospital mortality			Unfavorable neurologicaloutcome			ECMO-related complication		
Variables	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
BMI category									
Underweight	0.79	0.44–1.41	0.419	0.99	0.52–1.97	0.992	1.13	0.40–3.06	0.738
Normal	1.00	Reference	–	1.00	Reference	–	1.00	Reference	–
Overweight	1.37	1.02–1.85	0.035	1.39	0.98–2.00	0.071	1.01	0.59–1.97	0.770
Obese	2.09	1.31–3.39	<0.001	3.17	1.69–6.49	<0.001	1.05	0.66–1.64	0.801
Age	1.01	1.01–1.02	<0.001	1.02	1.01–1.03	<0.001	0.99	0.98–1.00	0.927
Male, sex	1.28	0.91–1.81	0.181	1.27	0.83–1.91	0.246	1.22	0.86–1.80	0.240
Pre-existing comorbidities[#]	1.17	0.87–1.53	0.284	0.94	0.66–1.34	0.770	1.05	0.66–1.70	0.801
Witnessed cardiac arrest	0.80	0.56–1.13	0.221	0.75	0.47–1.15	0.204	1.12	0.79–1.60	0.520
Bystander CPR	1.14	0.86–1.51	0.359	0.68	0.48–0.96	0.034	0.79	0.59–1.05	0.113
Initial rhythm									
Asystole	1.00	Reference	–	1.00	Reference	–	1.00	Reference	–
Pulseless electrical activity	1.08	0.58–1.94	0.807	0.68	0.29–1.47	0.360	1.02	0.59–1.80	0.936
Ventricular fibrillation	0.56	0.31–0.95	0.039	0.44	0.19–0.89	0.032	0.79	0.47–1.35	0.388
Ventricular tachycardia	0.45	0.15–1.22	0.115	0.29	0.08–0.99	0.044	1.06	0.37–2.87	0.906
ROSC before arrival	0.44	0.29–0.65	<0.001	0.49	0.31–078	0.002	1.09	0.72–1.63	0.673
Low-flow time	1.01	1.00–1.02	<0.001	1.00	0.99–1.00	0.465	0.99	0.99–1.00	0.373
Percutaneous coronary intervention	1.08	0.82–1.43	0.568	1.01	0.71–1.41	0.974	1.29	0.98–1.71	0.066

ECMO, extracorporeal membrane oxygenation; BMI, body mass index; CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation; OR, odds ratio; CI, confidence interval.

[#] Pre-existing comorbidities include diabetes, hypertension, dyslipidemia, chronic kidney disease, chronic heart disease, cerebrovascular disease, and dementia.

having a BMI $\geq$ 35 kg/m^2, indicating class II obesity or greater.[6] This discrepancy in BMI distribution may account for the observed differences between our findings and those of other studies. The severity of the cohort, with a mortality rate of nearly 70%, may also explain the lack of significant differences in the incidence of ECMO-related complications in this study. This mortality bias may have prevented many cases from developing complications before death.[30] A cohort with a lower mortality rate, such as patients with postoperative cardiogenic shock supported by ECMO, may be more appropriate to study ECMO-related complications.[31]

Strengths and limitations of the study

A major strength of this study is the collection of cases from multiple advanced medical institutions nationwide, and to our knowledge, this study is the largest cohort of patients with OHCA who have received ECPR to date.[1] However, this study presents several limitations. First, this was a retrospective study with different inclusion and exclusion criteria at each participating institution; therefore, we have reported the inclusion and exclusion criteria at all 36 SAVE-J II hospitals in another paper.[32] As shown in Fig. 1, 36.4% of patients had missing height or weight records, and their BMI could not be calculated. Therefore, as a sensitivity analysis, we repeated the main

Table 4 – Subgroup analysis of in-hospital mortality and unfavorable neurological outcomes.

		In-hospital mortality			Unfavorable neurological outcome			ECMO-related complication		
Variables	N	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Age										
		<65 years			*<65 years*			*<65 years*		
Underweight	33	0.84	0.39–1.82	0.672	1.66	0.69–4.48	0.276	1.08	0.46–2.35	0.842
Normal weight	300	1.00	Reference	–	1.00	Reference	–	1.00	Reference	–
Overweight	209	1.42	0.97–2.08	0.070	1.38	0.89–2.17	0.149	1.07	0.71–1.58	0.747
Obese	84	2.34	1.36–4.15	<0.001	2.88	1.45–6.28	<0.001	1.03	0.59–1.75	0.912
		≥65 years			*≥65 years*			*≥65 years*		
Underweight	24	0.74	0.30–1.85	0.513	0.47	0.18–1.32	0.138	1.25	0.47–3.07	0.626
Normal weight	259	1.00	Reference	–	1.00	Reference	–	1.00	Reference	–
Overweight	110	1.25	0.77–2.08	0.364	1.26	0.66–2.51	0.436	1.07	0.66–1.72	0.775
Obese	25	1.43	0.58–3.85	0.451	4.94	0.97–90.32	0.125	1.38	0.56–3.24	0.459
PCI										
		PCI			*PCI*			*PCI*		
Underweight	16	1.34	0.44–4.36	0.607	0.96	0.29–3.91	0.960	1.60	0.54–4.55	0.372
Normal weight	274	1.00	Reference	–	1.00	Reference	–	1.00	Reference	–
Overweight	166	1.28	0.83–1.98	0.253	1.28	0.76–2.17	0.344	0.79	0.51–1.20	0.278
Obese	59	2.15	1.11–4.32	0.002	5.93	2.18–20.96	0.001	1.22	0.65–2.23	0.502
		No PCI			*No PCI*			*No PCI*		
Underweight	41	0.69	0.35–1.37	0.299	1.00	0.47–2.24	0.988	0.99	0.45–2.06	0.995
Normal weight	285	1.00	Reference	–	1.00	Reference	–	1.00	Reference	–
Overweight	153	1.62	1.06–2.49	0.025	1.78	1.06–3.08	0.003	1.32	0.86–2.03	0.206
Obese	50	2.32	1.18–4.79	0.017	2.15	0.98–5.44	0.077	9.21	0.44–18.07	0.817

ECMO, extracorporeal membrane oxygenation; PCI, percutaneous coronary intervention; OR, odds ratio; CI, confidence interval.

analysis with cases in which BMI was imputed and found that an increase in BMI was still associated with poor outcomes. This was a retrospective exploratory study, and we did not calculate the required sample size. There were relatively few underweight patients and patients with obesity, with the majority having a BMI of 18.5–25 kg/m^2. High mortality in OHCA cases may have led to survival bias, influencing the occurrence of complications. The inclusion criteria for estimating CA etiology may have resulted in a heterogeneous population. A subgroup analysis of cases undergoing emergency PCI yielded results similar to the overall analysis. The study only used data from Japan, potentially affecting the generalizability to other countries. Finally, the exclusion of cases due to missing height and weight data, along with the self-reported nature of complication occurrence, may have led to facility bias.

Conclusions

Among patients with OHCA who underwent ECPR, those with a BMI of ≥25 kg/m^2 had higher in-hospital mortality rates than those with a normal BMI. In patients with obesity who had a BMI $\geq$ 30 kg/m^2, significantly worse neurological outcomes were observed after resuscitation. There is considerable interest in incorporating BMI into ECPR prognostication, which should be explored in future prospective studies.

Ethics approval

All studies with the SAVE-J II registry were conducted according to the principles expressed in the Declaration of Helsinki. This study was approved by the institutional review board of Kagawa University (approval number: 2018-110) and of each participating institution.

Consent for publication

In all the participating institutions, the requirement for patient consent was waived owing to the retrospective nature of this study.

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Availability of data and materials

Please contact the author for data requests.

CRediT authorship contribution statement

Mitsuaki Kojima: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft. **Yuzuru Mochida:** Formal analysis, Investigation, Writing – review & editing. **Tomohisa Shoko:** Writing – review & editing, Supervision, Project administration. **Akihiko Inoue:** Conceptualization, Methodology, Data curation, Writing – review & editing, Project administration, Funding acquisition. **Toru Hifumi:** Conceptualization, Methodology, Data curation, Writing – review & editing, Project administration, Funding acquisition. **Tetsuya Sakamoto:** Conceptualization, Writing – review & editing, Supervision. **Yasuhiro Kuroda:** Conceptualization, Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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REFERENCES

1. Afshin A, Forouzanfar MH, Reitsma MB, et al. Health effects of overweight and obesity in 195 countries over 25 years. N Engl J Med 2017;377:13–27.
2. Poirier P, Giles TD, Bray GA, et al. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. Circulation 2006;113:898–918.
3. Schetz M, De Jong A, Deane AM, et al. Obesity in the critically ill: a narrative review. Intensive Care Med 2019;45:757–69.
4. Sung CW, Huang CH, Chen WJ, et al. Obese cardiogenic arrest survivors with significant coronary artery disease had worse in-hospital mortality and neurological outcomes. Sci Rep 2020;10:18638.
5. Geri G, Savary G, Legriel S, et al. Influence of body mass index on the prognosis of patients successfully resuscitated from out-of-hospital cardiac arrest treated by therapeutic hypothermia. Resuscitation 2016;109:49–55.
6. Alvarez NH, O'Malley TJ, Abai B, Salvatore DM, DiMuzio PJ, Hirose H. Complications of peripheral cannulation site in obese patients on adult extracorporeal membrane oxygenation. ASAIO J 2021;67:1294–300.
7. Gil E, Na SJ, Ryu JA, et al. Association of body mass index with clinical outcomes for in-hospital cardiac arrest adult patients following extracorporeal cardiopulmonary resuscitation. PLoS One 2017;12:e0176143.
8. Kakavas S, Georgiopoulos G, Oikonomou D, et al. The impact of body mass index on post resuscitation survival after cardiac arrest: a meta-analysis. Clin Nutr ESPEN 2018;24:47–53.
9. Matinrazm S, Ladejobi A, Pasupula DK, et al. Effect of body mass index on survival after sudden cardiac arrest. Clin Cardiol 2018;41:46–50.
10. Kosmopoulos M, Kalra R, Alexy T, et al. The impact of BMI on arrest characteristics and survival of patients with out-of-hospital cardiac arrest treated with extracorporeal cardiopulmonary resuscitation. Resuscitation 2023;188:109842.
11. Inoue A, Hifumi T, Sakamoto T, et al. Extracorporeal cardiopulmonary resuscitation in adult patients with out-of-hospital cardiac arrest: a retrospective large cohort multicenter study in Japan. Crit Care 2022;26:129.
12. Perkins GD, Jacobs IG, Nadkarni VM, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update of the utstein resuscitation registry templates for out-of-hospital cardiac arrest: a statement for healthcare professionals from a task force of the international liaison committee on resuscitation (American Heart Association, European Resuscitation Council, Australian and New Zealand Council on Resuscitation, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa, Resuscitation Council of Asia); and the American

Heart Association Emergency Cardiovascular Care Committee and the Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation. Resuscitation 2015;96:328–40.
13. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649–55.
14. Kim K, Leem AY, Kim SY, et al. Complications related to extracorporeal membrane oxygenation support as a bridge to lung transplantation and their clinical significance. Heart Lung 2022;56:148–53.
15. Kim RY, Glick C, Furmanek S, et al. Association between body mass index and mortality in hospitalised patients with community-acquired pneumonia. ERJ Open Res 2021;7:00736–2020.
16. Kudo D, Goto T, Uchimido R, et al. Coagulation phenotypes in sepsis and effects of recombinant human thrombomodulin: an analysis of three multicentre observational studies. Crit Care 2021;25:114.
17. Kenchaiah S, Evans JC, Levy D, et al. Obesity and the risk of heart failure. N Engl J Med 2002;347:305–13.
18. Aune D, Schlesinger S, Norat T, Riboli E. Body mass index, abdominal fatness, and the risk of sudden cardiac death: a systematic review and dose-response meta-analysis of prospective studies. Eur J Epidemiol 2018;33:711–22.
19. Bang HJ, Park KN, Youn CS, et al. The relationship between body mass index and neurologic outcomes in survivors of out-of-hospital cardiac arrest treated with targeted temperature management. PLoS One 2022;17:e0265656.
20. Powell-Wiley TM, Poirier P, Burke LE, et al. Obesity and cardiovascular disease: a scientific statement from the American Heart Association. Circulation 2021;143:e984–e.
21. Secombe P, Sutherland R, Johnson R. Body mass index and thoracic subcutaneous adipose tissue depth: possible implications for adequacy of chest compressions. BMC Res Notes 2017;10:575.
22. Lee H, Oh J, Lee J, et al. Retrospective study using computed tomography to compare sufficient chest compression depth for cardiopulmonary resuscitation in obese patients. J Am Heart Assoc 2019;8:e013948.
23. Rozen G, Elbaz-Greener G, Marai I, et al. The relationship between the body mass index and in-hospital mortality in patients admitted for sudden cardiac death in the United States. Clin Cardiol 2021;44:1673–82.
24. Testerman GM. Adverse outcomes in younger rib fracture patients. South Med J 2006;99:335–9.
25. Liebsch C, Hübner S, Palanca M, Cristofolini L, Wilke HJ. Experimental study exploring the factors that promote rib fragility in the elderly. Sci Rep 2021;11:9307.
26. Karadayi S, Nadir A, Sahin E, Celik B, Arslan S, Kaptanoglu M. An analysis of 214 cases of rib fractures. Clinics (Sao Paulo) 2011;66:449–51.
27. Elkbuli A, Boserup B, Liu A, Rowe S, McKenney M. The association of body mass index and outcomes in adult patients with chest wall injuries. J Surg Res 2021;267:544–55.
28. Lee SN, Moon D, Jo MS, Yoo KD. Associations between body mass index and clinical outcomes in acute myocardial infarction supported with extracorporeal membrane oxygenation. Acta Cardiol Sin 2020;36:448–55.
29. Swol J, Buchwald D, Strauch JT, Schildhauer TA, Ull C. Effect of body mass index on the outcome of surgical patients receiving extracorporeal devices (VV ECMO, pECLA) for respiratory failure. Int J Artif Organs 2017;40:102–8.
30. Lamhaut L, Hutin A, Puymirat E, et al. A pre-hospital Extracorporeal Cardio Pulmonary Resuscitation (ECPR) strategy for treatment of refractory out hospital cardiac arrest: an observational study and propensity analysis. Resuscitation 2017;117:109–17.
31. Fux T, Holm M, Corbascio M, et al. Venoarterial extracorporeal membrane oxygenation for postcardiotomy shock: risk factors for mortality. J Thorac Cardiovasc Surg 2018;156:1894–902.
32. Hifumi T, Inoue A, Takiguchi T, et al. Variability of extracorporeal cardiopulmonary resuscitation practice in patients with out-of-hospital cardiac arrest from the emergency department to intensive care unit in Japan. Acute Med Surg 2021;8:e647.