RESUSCITATION PLUS 19 (2024) 100705

Available online at www.sciencedirect.com

Resuscitation Plus

journal homepage: www.elsevier.com/locate/resuscitation-plus

Clinical paper

Extracorporeal cardiopulmonary resuscitation in hypothermic cardiac arrest: A secondary analysis of multicenter extracorporeal cardiopulmonary resuscitation registry data in Japan

Shu Tanizawa[a,b], *Mitsuaki Kojima*[a,b,*], *Tomohisa Shoko*[a], *Akihiko Inoue*[c], *Toru Hifumi*[d], *Tetsuya Sakamoto*[e], *Yasuhiro Kuroda*[f], *on behalf of the SAVE-J study group*

Abstract

Aim: Extracorporeal cardiopulmonary resuscitation (ECPR) is used to resuscitate patients with cardiac arrest; however, its effect in treating hypothermic cardiac arrest has not been well studied. Therefore, in this study, we aimed to examine the characteristics and outcomes of patients with hypothermic cardiac arrest who underwent ECPR, using a multicenter out-of-hospital cardiac arrest (OHCA) registry in Japan.

Methods: Baseline characteristics of patients with hypothermic OHCA and body temperature below 32 °C were assessed. Logistic regression analysis was performed to identify factors associated with in-hospital mortality and neurological outcomes in these patients. Outcomes of hypothermic and cardiogenic OHCA cases were compared using propensity-score matching to investigate differences among subgroups.

Results: We included 2,157 patients, with 102 and 1,646 in the hypothermic and cardiogenic groups, respectively. Higher age and longer low-flow time were independent risk factors for mortality, and higher age was an independent risk factor for unfavorable neurological outcomes in the hypothermic OHCA group.

Eighty matched pairs were selected during propensity-score matching, and the mortality rate was lower in the hypothermic group than in the cardiogenic group (46.2% vs. 77.5%; $p < 0.01$). Unfavorable neurological outcome rate was lower in the hypothermic group than in the cardiogenic group (62.5% vs. 87.5%; $p < 0.01$).

Conclusions: Increased age and prolonged low-flow time were identified as negative prognostic factors in patients with hypothermic OHCA who underwent ECPR. These patients showed lower mortality and unfavorable neurological outcome rates than patients with cardiogenic OHCA, suggesting that ECPR is a promising strategy for treating hypothermic OHCA.

Keywords: Cardiopulmonary resuscitation, Extracorporeal Circulation, Out-of-hospital cardiac arrest, Hypothermia, Outcome, Survival rate

Introduction

Accidental hypothermia (AH) is a medical emergency and potentially life-threatening condition.[1] Severe AH can trigger fatal arrhythmias, such as ventricular fibrillation (VF), which can lead to cardiac arrest. Therefore, prompt and appropriate intervention is critical to improve a patient's chances of survival. Accordingly, in addition to immediate cardiopulmonary resuscitation (CPR), rewarming should be initiated in patients with AH. Various external rewarming techniques,

Abbreviations: AH, accidental hypothermia, VF, ventricular fibrillation, CPR, cardiopulmonary resuscitation, ECMO, extracorporeal membrane oxygenation, ECPR, extracorporeal cardiopulmonary resuscitation, OHCA, out-of-hospital cardiac arrest, SAVE-J II registry, Advanced Life Support for VF with Extracorporeal Circulation in Japan registry, ROSC, return of spontaneous circulation, CPC score, cerebral performance category score, IQR, interquartile range, ECLS, extracorporeal life support

* Corresponding author at: Emergency and Critical Care Center, Tokyo Women's Medical University Adachi Medical Center, 4-33-1, Kohoku, Adachi, Tokyo, Japan.

E-mail address: kojiaccm@tmd.ac.jp (M. Kojima).

https://doi.org/10.1016/j.resplu.2024.100705

Received 22 March 2024; Received in revised form 13 June 2024; Accepted 20 June 2024

including passive and active methods, and invasive measures, such as warmed intravenous fluids or catheter-based heat exchange systems, have been used to achieve successful resuscitation.[2]

Simultaneously, extracorporeal membrane oxygenation (ECMO) can provide circulatory support and rewarm patients using a heat exchanger. The European Resuscitation Council guidelines recommend the use of ECMO in patients with AH-related cardiac arrest or circulatory instability.[3] Therefore, extracorporeal cardiopulmonary resuscitation (ECPR) combined with ECMO may be a promising therapeutic strategy for patients with cardiac arrest and severe hypothermia.[4] However, evidence regarding the effect of rewarming with ECMO in patients with severe AH is limited, primarily owing to limited eligible patients.[3] In this study, we conducted descriptive statistics on hypothermic cardiac arrest solely in cases of ECPR and identified factors related to prognosis.

A recent multicenter observational study suggested that ECPR improved survival and neurological outcomes in patients with AH and cardiac arrest.[4] However, in this study, only 13 patients underwent ECMO for out-of-hospital cardiac arrest (OHCA), which accounts for approximately 5% of all cases. Therefore, we aimed to study the outcome of ECPR in a larger population of patients with hypothermia-related OHCA by using data from a large ECPR registry of patients with AH-related cardiac arrest. Additionally, because few studies have compared the outcomes of ECPR cases by the cause of cardiac arrest, we aimed to investigate the impact of etiology of cardiac arrest, particularly comparing outcomes between cardiogenic and hypothermic cardiac arrests.

Methods

Study setting and design

We conducted a secondary analysis of the Advanced Life Support for VF with Extracorporeal Circulation in Japan (SAVE-J II) registry, which includes data on initial cardiac rhythm, age, time (low-flow or no-flow), and outcomes of patients with OHCA who underwent ECPR at 36 hospitals in Japan between January 1, 2013, and December 31, 2018.[5]

Ethics approval and consent to participate

All studies using the SAVE-J Ⅱ registry were conducted in accordance with the principles outlined in the Declaration of Helsinki. This study was approved by the institutional review board of Kagawa University (approval number: 2018–110) and each participating institution. The requirement for patient consent was waived at all participating institutions because of the retrospective nature of this study.

Patient and public involvement

This study did not include patient and public involvement.

Study population

We selected patients with OHCA from the SAVE-J II registry who met the inclusion criteria for hypothermic and cardiogenic cardiac arrest. Hypothermic cardiac arrest was defined by a body temperature (BT) $\leq$ 32 °C on admission to the emergency department. Patients without cardiac or hypothermic conditions were excluded. Additionally, patients who achieved a return of spontaneous circulation (ROSC) upon hospital arrival and ECMO initiation were excluded, along with those missing data on BT.

Data collection

The following patient variables were collected from the SAVE-J II registry: age, sex, patient vital signs at hospital arrival (blood pressure, pulse rate, BT, Glasgow Coma Scale score, and pupil diameter), comorbidities, BT upon hospital arrival, cerebral performance category (CPC) score, the incidence of witnessed cardiac arrest, bystander CPR, an initial cardiac rhythm at the scene, cardiac arrest location, use of defibrillation, prehospital airway management, cardiac rhythm before ECMO initiation, time course, cause of cardiac arrest, ROSC after hospital arrival, and ECMO information. Furthermore, the initial shockable rhythm was defined as VF, pulseless ventricular tachycardia, or rhythm for defibrillation in an automated external defibrillator used by emergency medical staff.[5] Evaluated comorbidities comprised heart disease, cerebrovascular disease, and chronic kidney disease. ROSC was defined as at least 1 min of continuing confirmation of pulsation. The estimated 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 finding the patient to the establishment of ECMO, if the location of cardiac arrest was a place other than an ambulance. Data on the complications during ECPR were also collected. A favorable neurological outcome was defined as a CPC score of 1 or 2, whereas an unfavorable outcome was defined as a CPC score of 3–5.

Missing value imputation

Missing values were imputed using the random forest method with the “missForest” package (version 1.4) in R software (version 4.1.2; R Foundation for Statistical Computing, Vienna, Austria).[6–8] Variables used for imputation included patient characteristics (age, sex, and comorbidities), cardiac arrest circumstances (location, incidence of witnessed arrest, bystander CPR, initial cardiac rhythm at the scene, use of defibrillation, prehospital airway management, cardiac rhythm before ECMO initiation, time course, and ROSC after hospital arrival), patient vital signs at hospital arrival, and outcomes (length of hospital stay, length of ICU stay, mortality at hospital discharge, and neurological outcomes).

Outcome measures

The primary outcome of this study was the mortality rate at hospital discharge. Secondary outcomes included unfavorable neurological outcomes based on the CPC.

Statistical analysis

Baseline characteristics and outcomes were summarized using descriptive statistics. Categorical variables are presented as proportions. Continuous variables are presented as medians and interquartile ranges (IQRs). Multivariable logistic regression analyses were performed to determine factors related to mortality and unfavorable neurological outcomes at hospital discharge. In the multivariable models, we adjusted for age, sex, BT, comorbidities, bystander CPR, and estimated low-flow time. We compared baseline characteristics, mortality, and CPC at hospital discharge between hypothermic and cardiogenic groups using the Mann–Whitney *U* test for continuous variables and Fisher’s exact or chi-square test for categorical variables, as appropriate. Considering the unbalanced characteristics of hypothermic and cardiogenic groups, we used propensity score matching analysis to compare the outcomes. A logistic regression model was applied to estimate the propensity score for each patient, predicting mortality based on age, sex, comorbidities, bystander CPR, initial cardiac rhythm, time from emergency medical services arrival at the scene to ECMO initiation, and estimated low-flow time. The propensity score matching extracted 1:1 matched pairs of patients with hypothermic and cardiogenic cardiac arrest using "MatchIt" package (version 4.5.5) in R software.[9] Matched pairs from the two groups were assessed using the absolute standardized mean difference. Values < 0.01 were considered acceptable. All statistical analyses were conducted with R software, and the level of significance was set at p-value < 0.05.

Results

Study participants

A flow diagram of the patient selection process is illustrated in Fig. 1. Among the 2,157 adult patients with OHCA who received ECPR in the SAVE-J II registry, a total of 1,748 patients were eligible for analysis. Of these, 102 and 1,646 patients had hypothermic and cardiogenic cardiac arrests, respectively.

Baseline characteristics of the hypothermic group

Characteristics of the patients in the hypothermic group are presented in Table 1. Briefly, their median [IQR] age was 68 [56–78] years; additionally, 65.7% were male, 46.1% had witnessed cardiac arrest, and 46.1% had received bystander CPR. Regarding prehospital intervention, 50% of the patients were defibrillated. The OHCA location is also listed in Table 1; the most common location was home (34.3%). The proportions of initial cardiac rhythms at the scene were 45.1%, 26.4%, and 27.4% for VF, pulseless electrical activity, and asystole, respectively. The BT median was 24.2 [22.4–26.5]. The median time from the call for an ambulance to ECMO was 73 [56–88] min, and the median estimated low-flow time was 69 [52–84] min. A histogram of the relationship between BT, number of survivors, and mortality cases is illustrated in Fig. 2. Notably, survival was observed even in cases of hypothermia below 18 °C, and there was no apparent correlation between survival and BT in the cardiac arrest group with hypothermia.

Risk factors for mortality and unfavorable neurological outcome in patients with hypothermic cardiac arrest

The comparison between poor and favorable outcomes in the hypothermia group is shown in Supplementary Table 1 (survivors vs. non survivors) and Supplementary Table 2 (good vs. adverse neurological outcomes). In the multivariable logistic regression analysis, age (odds ratio [OR], 1.05 per year; p < 0.01) and estimated low-flow time (OR, 1.02 per minute; p = 0.04) were independent risk factors for in-hospital mortality in the hypothermia group (Table 2). In addition, the multivariable logistic regression analysis assessing adverse neurological outcomes showed a significant association with age (OR, 1.06 per year; p < 0.01; Table 3).

Comparison of outcomes between hypothermic and cardiogenic groups

Baseline characteristics of the study cohort before propensity score matching are presented in Table 1. The hypothermic group had a higher median age than the cardiogenic group. Moreover, the prevalence of VF was higher in the cardiogenic group than in the hypothermic group. Of the 102 OHCA patients with hypothermia, 31 (30%) had favorable neurological outcomes, whereas the rate of favorable neurological outcomes in the cardiogenic arrest group was 14%. Among patients with favorable CPC, the median low-flow time was 55 [45–66] min in the cardiogenic arrest group and 69 [52–84] min in the hypothermia group. Notably, the longest low-flow time for patients with favorable neurological outcome was 95 min in the cardiogenic arrest group and 160 min in the hypothermia group. Collectively, the hypothermia group showed better outcomes compared to

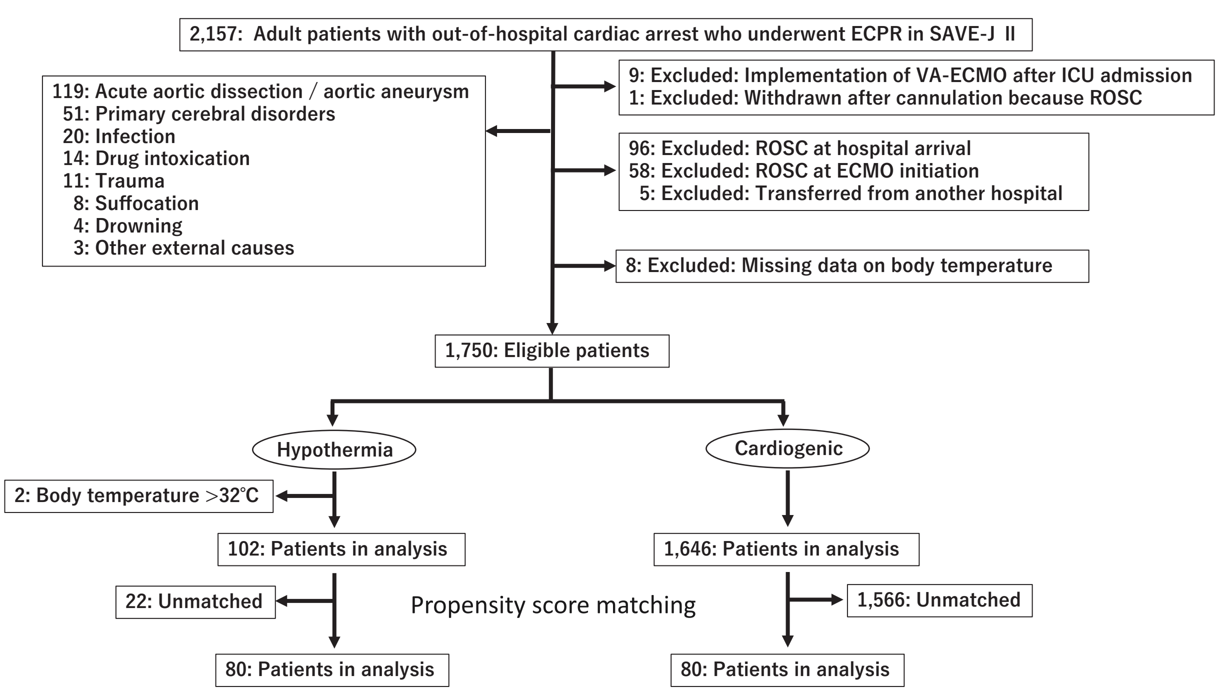

Fig. 1 – Study flow diagram. ECPR, extracorporeal cardiopulmonary resuscitation; VA-ECMO, veno-arterial extracorporeal membrane oxygenation; ROSC, return of spontaneous circulation.

Table 1 – Characteristics of the patients.

Variables	Cardiogenic (n = 1646)	Hypothermic (n = 102)	SMD	P-value
Age, years old, median (IQR)	60 [49–68]	68 [56–78]	0.50	<0.01
Sex, male, n (%)	1392 (84.6)	67 (65.7)	0.44	<0.01
Presence of one or more comorbidities[†], n (%)	516 (31.3)	19 (18.6)	0.29	<0.01
BT on hospital arrival, Celsius, median (IQR)	35.2 [34.2–35.9]	24.2 [22.4–26.5]	4.30	<0.01
Initial cardiac rhythm, n (%)			0.07	0.65
Ventricular fibrillation	1097 (67.3)	46 (45.1)		
Ventricular tachycardia	34 (2.1)	0 (0)		
Pulseless electrical activity	369 (22.6)	27 (26.4)		
Asystole	130 (8)	28 (27.4)		
Bystander CPR, n (%)	947 (58.3)	47 (46.1)	0.22	0.02
Witness, n (%)	1291 (78.7)	47 (46.1)	0.71	<0.01
Location of cardiac arrest, n (%)			0.74	NA
Home	670 (40.7)	35 (34.3)		
Public place	292 (17.8)	14 (13.7)		
Street	232 (14.2)	12 (11.8)		
Ambulance	154 (9.4)	18 (17.6)		
Workplace	179 (10.9)	0 (0)		
Other	114 (7)	23 (22.6)		
Place of event, outdoor, n (%)	232 (14.1)	12 (11.7)	0.07	0.65
In-hospital mortality, n (%)	1198 (72.8)	53 (51.9)	0.44	<0.01
Defibrillation, n (%)	1057 (64.3)	50 (50.0)	0.30	<0.01
Complications during ECPR, n (%)				
Cannula malposition	81 (4.9)	8 (7.8)	0.12	0.28
Unsuccessful cannulation	11 (0.7)	0 (0)	0.12	1.00
Cannulation-related bleeding	268 (16.3)	10 (9.8)	0.19	0.09
Other	26 (1.6)	1 (0.9)	0.05	1.00
Ischemia	27 (1.6)	0 (0)	0.18	0.4
Neurological outcome at discharge, unfavorable, n (%)	1413 (85.9)	71 (69.9)	0.40	<0.01
Estimated low flow time, minute, median (IQR)	55 [45–66]	69 [52–84]	0.58	<0.01
Time from call ambulance to ECMO, minute, median (IQR)	56 [47–68]	73 [56–88]	0.68	<0.01
Length of hospital stays, days, median (IQR)	3 [1–19]	9 [2–39]	0.24	0.01
Cost, $\times$105, yen, median (IQR)	23.7 [11.9–38.9]	17.5 [9.2–34.5]	0.28	0.02

SMD, standard mean difference; IQR, interquartile range; BT, body temperature; CPR, cardiopulmonary resuscitation; ECPR, extracorporeal cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; SOFA, sequential organ failure assessment.

SAVE, survival after veno arterial-ECMO.

[†] Comorbidities: heart disease, cerebrovascular disease, chronic kidney disease.

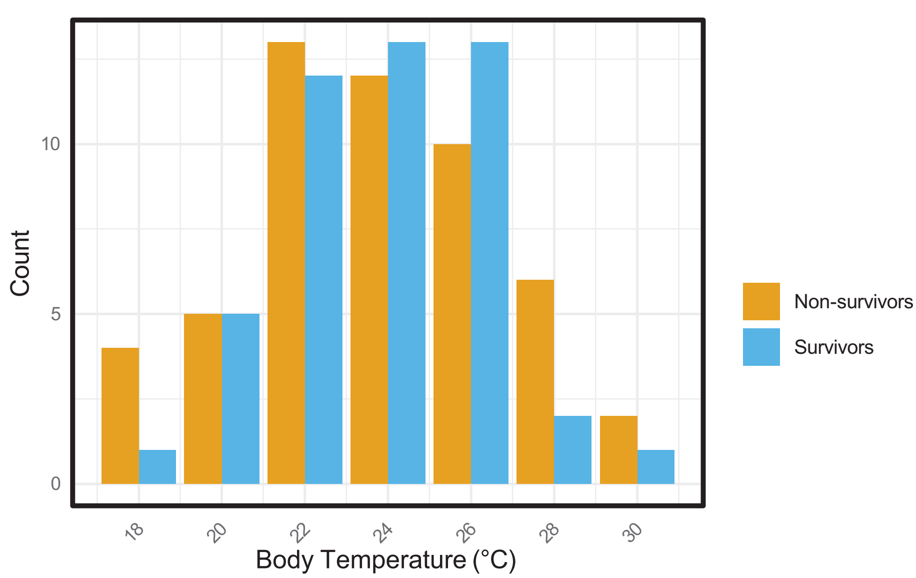

Fig. 2 – Histogram depicting the distribution of initial body temperatures, grouped by 2 °C intervals, and the proportions of survivors and non-survivors in the hypothermic cardiac arrest group.

Table 2 – Multivariable logistic regression analyses of mortality in the hypothermic cardiac arrest group.

Variables	OR (95%CI)	P-value
Age per year	1.05 (1.01–1.09)	<0.01
BT on hospital arrival per degree	1.05 (0.88–1.23)	0.59
Male sex	1.12 (0.38–3.27)	0.83
Presence of one or more comorbidities[†]	1.16 (0.35–3.79)	0.8
Bystander CPR	0.84 (0.31–2.3)	0.74
Estimated low-flow time per minute	1.02 (1–1.03)	0.04

OR, odds ratio; BT, body temperature; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation

[†] Comorbidities: heart disease, cerebrovascular disease, chronic kidney disease.

Table 3 – Multivariable logistic regression analyses of unfavorable neurological outcome at discharge in the hypothermic cardiac arrest group.

Variables	OR (95% CI)	P-value
Age per year	1.06 (1.02–1.9)	<0.01
BT on hospital arrival per degree	1.01 (0.85–1.20)	0.96
Male sex	1.51 (0.48–4.75)	0.47
Presence of one or more comorbidities[†]	2.30 (0.55–9.57)	0.25
Bystander CPR	0.71 (0.24–2.06)	0.53
Estimated low-flow time per minute	1.01 (0.99–1.02)	0.36

OR, odds ratio; BT, body temperature; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation

[†] Comorbidities: heart disease, cerebrovascular disease, chronic kidney disease.

the cardiogenic CA group, despite their longer low-flow time before adjustment for baseline characteristics using propensity scores. Kaplan–Meier curves illustrating the timing of mortality in both groups are also shown in Supplementary Fig. 1.

Based on propensity score matching analysis, 80 matched pairs were selected using a one-to-one matching process. The baseline characteristics of patients in the propensity score-matched cohort are presented in Table 4. The mortality rate and unfavorable neurological outcomes were lower in the hypothermic group than in the cardiogenic group (46.2% vs. 77.5%; $p < 0.01$), (62.5% vs. 87.5%; $p < 0.01$, respectively). We also plotted histograms showing the distribution of the relationship between low-flow time and in-hospital mortality and neurological outcome in Supplementary Figs. 2 and 3, respectively. The analysis showed that, compared with the cardiogenic arrest group, the hypothermia group not only had a higher number of cases with favorable outcomes, but there were also cases with favorable outcomes among those with prolonged low-flow time.

Discussion

The present study provides detailed descriptive statistics of patients with hypothermic cardiac arrest who underwent ECPR. The results indicate that the patient demographics and outcomes of hypothermic cardiac arrest cases differ significantly from those of cardiogenic cardiac arrest cases. In addition, older age and prolonged low-flow time, but not BT, were identified as significant predictors of mortality in patients undergoing ECPR for hypothermic cardiac arrest. Furthermore, after adjusting for multiple factors using propensity score matching, patients with hypothermic cardiac arrest had lower mortality rates and a lower incidence of adverse neurological outcomes compared with patients with cardiogenic cardiac arrest.

AH involves an unintentional decrease in core BT below 35.[1] Therefore, in moderate-to-severe hypothermia with BT less than 32, the risk of arrhythmia and cardiac arrest increases.[1] A recent nationwide study of AH in Japan indicated that 21% of patients with AH had severe hypothermia, with a mortality rate as high as 29%.[10] Veno-arterial ECMO has several pathophysiological advantages over other rewarming methods. Specifically, it is the fastest method for rewarming, provides adequate and immediate circulatory support, rapidly corrects metabolic and electrolyte derangements, and rewarms the heart before the rest of the body, preventing shock from peripheral vasodilatation.[11,12]

Several previous studies have reported beneficial outcomes of using ECMO for hypothermia treatment.[12,3,4] However, these studies either included mixed conventional CPR and ECMO cases or had limited ECMO-only cases. Moreover, only a few studies examined large numbers of ECMO-only cases. In contrast, in the present study, we performed extensive analyses of a relatively large number of patients with AH undergoing ECPR. We identified age and estimated low-flow time as factors influencing the mortality rate after ECPR. Neither temperature nor initial cardiac rhythm was significantly associated with the prognosis in the present study. Furthermore, previous studies support our finding that the core temperature is not associated with in-hospital mortality.[13,14] The present study, along with previous literature,[12,3,4] also demonstrates that ECMO may prove beneficial in hypothermic cardiac arrest cases. However, the optimal timing for its initiation and the specific indicated cases have not yet been thoroughly investigated, especially in OHCA patients with hypothermia. Therefore, further research is required to address these issues.

Hypothermia increases the tolerance of the brain to ischemia by slowing down metabolic processes and reducing oxygen consumption.[11] To the best of our knowledge, this is the first study to demon-

Table 4 – Characteristics of the patients after propensity score matching.

Variables	Cardiogenic (n = 80)	Hypothermic (n = 80)	SMD	P-value
Age, years old, median (IQR)	67 [54–73]	66 [54–76]	0.01	0.93
Sex, male, n (%)	58 (72.5)	56 (70)	0.05	0.86
Presence of one or more comorbidities[†], n (%)	15 (18.8)	14 (17.5)	0.03	1.00
BT on hospital arrival, Celsius, median (IQR)	35.1 [33.7–35.7]	24.6 [22.4–26.7]	4.40	<0.01
Place of event, outdoor, n (%)	9 (11.2)	10 (12.5)	0.03	1.00
Initial cardiac rhythm, n (%)			0.42	0.06
Ventricular fibrillation	39 (48.8)	40 (50)		
Ventricular tachycardia	2 (2.5)	0 (0)		
Pulseless electrical activity	28 (35)	19 (23.8)		
Asystole	11 (13.8)	21 (26.2)		
Bystander CPR, n (%)	36 (45.0)	38 (47.5)	0.05	0.87
Witness, n (%)	69 (86.2)	35 (43.8)	0.99	<0.01
In-hospital mortality, n (%)	62 (77.5)	37 (46.2)	0.68	<0.01
Complications during ECPR, n (%)				
Cannula malposition	3 (3.8)	5 (6.2)	0.11	0.71
Unsuccessful cannulation	0 (0)	0 (0)	NA	NA
Cannulation-related bleeding	12 (15)	5 (6.2)	0.28	0.12
Other	5 (6.2)	1 (1.2)	0.26	0.21
Ischemia	3 (3.8)	0 (0)	0.27	0.24
Neurological outcome at discharge, unfavorable, n (%)	70 (87.5)	50 (62.5)	0.60	<0.01
Estimated low flow time, minute, median (IQR)	64 [54–82]	68 [49–81]	0.02	0.68
Time from call ambulance to ECMO, minute, median (IQR)	67 [56–86]	71 [55–83]	<0.01	0.96
Length of hospital stays, days, median (IQR)	4 [1–17]	14 [2–39]	0.33	0.01
Cost, ×105, yen, median (IQR)	2.3 [1.0–3.6]	2.0 [12.9–35.9]	0.20	0.55

IQR, interquartile range; BT, body temperature; CPR, cardiopulmonary resuscitation; ECPR, extracorporeal cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; SOFA, sequential organ failure assessment.

SAVE, survival after veno arterial-ECMO.

[†] Comorbidities: heart disease, cerebrovascular disease, chronic kidney disease.

strate that the use of ECMO for hypothermic cardiac arrest is associated with lower mortality rates and unfavorable neurological outcomes compared to its use for cardiogenic cardiac arrest. Direct comparisons between these groups are challenging due to differences in the study populations. However, in our study, 48% of patients in the hypothermia group survived with ECPR using ECMO, including OHCA patients, while 30% achieved favorable neurological outcomes. In addition, favorable neurological outcomes were observed even in some cases with a low-flow time of up to 160 min. Although there are no definitive criteria, it is prudent to use ECPR more aggressively for hypothermic cardiac arrest than for cardiogenic cardiac arrest.

Moreover, because ECMO is an invasive treatment with more complications than conventional CPR, it is necessary to strictly select patients for whom ECMO is indicated. ECMO-related complications include bleeding, unsuccessful cannulation, infection, ischemia, and hemolysis.[15–17] Among ECPR-related complications, the most common is bleeding, with rates of 8%–70% in previous studies.[18,19] Hypothermia decreases platelet function and clotting factor activity, resulting in abnormal coagulation.[20] However, in our study, patients with hypothermic cardiac arrest did not show a higher rate of bleeding complication than patients with cardiogenic cardiac arrest (9.8% vs. 16.3%; p = 0.09). This result persisted even with propensity score matching cohort (6.2% vs. 15%, p = 0.12). The lack of a uniform definition of hemorrhagic complications across institutions and differences in patient body mass index compared to those in Western countries may have influenced the results. However, the findings of the present study suggest that is no need to hesitate to use ECPR in cases of hypothermic cardiac arrest due to concerns about the bleeding risk.

Limitations

The present study had some limitations. First, this was a retrospective study with variations in the inclusion criteria across participating institutions. Second, the backgrounds of cardiogenic and hypothermic cases were different. Accordingly, performing propensity score matching reduced the sample size. Third, although the cause of AH was considered a prognostic factor,[11] the cause of hypothermia was not investigated in the present study. Fourth, there was no control group. Ideally, to assess the utility of ECPR for hypothermia, patients with hypothermic cardiac arrest treated with ECPR should be compared to those treated with conventional CPR. However, this was impossible because we used data from an OHCA registry. Conversely, compared to the ICE-CRASH[4] and other studies, the present study analyzed more ECPR cases, enabling the examination of detailed background factors and prognostic determinants. Finally, confounders of the time course, such as the number of ROSCs and total ROSC time until ECMO establishment, could not be obtained from this dataset. Thus, the estimated low-flow time may differ from the actual low-flow time.

Conclusions

In this large cohort study, we comprehensively examined the epidemiological characteristics of patients with hypothermia undergoing

ECPR and demonstrated that age and estimated low-flow time significantly influenced patient outcomes. Among patients receiving ECPR, those with hypothermic cardiac arrest have a better prognosis than those with cardiogenic cardiac arrest. Overall, these results suggest that ECPR is a promising strategy for managing patients with hypothermic cardiac arrest.

Funding

This study was supported by the Japan Society for the Promotion of Science (JSPS) KAKENHI (Grant-in-Aid for Scientific Research [C]) [grant number JP19K09419]. The funding source had no role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

CRediT authorship contribution statement

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

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.

Acknowledgments

We thank all the members of the SAVE-J II study group: Hirotaka Sawano, M.D., Ph.D. (Osaka Saiseikai Senri Hospital); Yuko Egawa, M.D., Shunichi Kato, M.D. (Saitama Red Cross Hospital); Kazuhiro Sugiyama, M.D., Maki Tanabe, M.D. (Tokyo Metropolitan Bokutoh Hospital); Naofumi Bunya, M.D., Takehiko Kasai, M.D. (Sapporo Medical University); Shinichi Ijuin, M.D., Shinichi Nakayama, M.D., Ph.D. (Hyogo Emergency Medical Center); Jun Kanda, M.D., Ph.D., Seiya Kanou, M.D. (Teikyo University Hospital); Toru Takiguchi, M.D., Shoji Yokobori, M.D., Ph.D. (Nippon Medical School); Hiroaki Takada, M.D., Kazushige Inoue, M.D. (National Hospital Organization Disaster Medical Center); Ichiro Takeuchi, M.D., Ph.D., Hiroshi Honzawa, M.D. (Yokohama City University Medical Center); Makoto Kobayashi, M.D., Ph.D., Tomohiro Hamagami, M.D. (Toyooka Public Hospital); Wataru Takayama, M.D., Yasuhiro Otomo, M.D., Ph.D. (Tokyo Medical and Dental University Hospital of Medicine); Kunihiko Maekawa, M.D. (Hokkaido University Hospital); Takafumi Shimizu, M.D., Satoshi Nara, M.D. (Teine Keijinkai Hospital); Michitaka Nasu, M.D., Kuniko Takahashi, M.D. (Urasoe General Hospital); Yoshihiro Hagiwara, M.D., M.P.H. (Imperial Foundation Saiseikai, Utsunomiya Hospital); Shigeki Kushimoto, M.D., Ph.D. (Tohoku University Graduate School of Medicine); Reo Fukuda, M.D. (Nippon Medical School Tama Nagayama Hospital); Takayuki Ogura, M.D., Ph.D. (Japan Red Cross Maebashi Hospital); Shinichiro Shiraishi, M.D. (Aizu Central Hospital); Ryosuke Zushi, M.D. (Osaka Mishima Emergency Critical Care Center); Norio Otani, M.D., Hiroshi Okamoto, M.D, M.P.H. (St. Luke's International Hospital); Migaku Kikuchi, M.D., Ph.D. (Dokkyo Medical University); Kazuhiro Watanabe, M.D. (Nihon University Hospital); Takuo Nakagami, M.D. (Omihachiman Community Medical Center); Nobuya Kitamura, M.D., Ph.D. (Kimitsu Chuo Hospital); Takayuki Otani, M.D. (Hiroshima City Hiroshima Citizens Hospital); Yoshinori Matsuoka, M.D., Ph.D. (Kobe City Medical Center General Hospital); Makoto Aoki, M.D., Ph.D. (Gunma University Graduate School of Medicine); Masaaki Sakuraya, M.D., M.P.H. (JA Hiroshima General Hospital Hiroshima); Hideki Arimoto, M.D. (Osaka City General Hospital); Koichiro Homma, M.D., Ph.D. (Keio University School of Medicine); Hiromichi Naito, M.D., Ph.D. (Okayama University Hospital); Shunichiro Nakao, M.D., Ph.D. (Osaka University Graduate School of Medicine); Tomoya Okazaki, M.D., Ph.D., Jun Kunikata, M.D., Ph.D., Hideto Yokoi, M.D., Ph.D. (Kagawa University Hospital); and Yoshio Tahara, M.D., PhD (National Cerebral and Cardiovascular Center).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resplu.2024.100705.

Author details

on behalf of theSAVE-J II study group [a] *Emergency and Critical Care Centre, Tokyo Women's Medical University Adachi Medical Centre, 4-33-1, Kohoku, Adachi, Tokyo 123-8558, Japan* [b] *Department of Acute Critical Care and Disaster Medicine, Tokyo Medical and Dental University Hospital, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8510, Japan* [c] *Department of Emergency and Critical Care Medicine, Hyogo Emergency Medical Centre, 1-3-1 Wakinohamakaigandori, Chuo, Kobe, Hyogo 651-0073, Japan* [d] *Department of Emergency and Critical Care Medicine, St. Luke's International Hospital, 9-1 Akashi-cho, Chuo-ku, Tokyo 104-8560, Japan* [e] *Department of Emergency Medicine, Teikyo University School of Medicine, 2-11-2 Kaga, Itabashi, Tokyo 173-8606, Japan* [f] *Department of Emergency Medicine, Kagawa University School of Medicine, 1750-1 Ikenobe, Miki, Kita, Kagawa 761-0793, Japan*

REFERENCES

1. Brown DJ, Brugger H, Boyd J, et al. Accidental hypothermia. N Engl J Med 2012;367:1930–8.
2. van der Ploeg GJ, Goslings JC, Walpoth BH, et al. Accidental hypothermia: Rewarming treatments, complications and outcomes from one university medical centre. Resuscitation 2010;81:1550–5.
3. Lott C, Truhlář A, Alfonzo A, et al. European Resuscitation Council Guidelines 2021: cardiac arrest in special circumstances. Resuscitation 2021;161:152–219.

4. Takauji S, Hayakawa M, Yamada D, et al. Outcome of extracorporeal membrane oxygenation use in severe accidental hypothermia with cardiac arrest and circulatory instability: A multicentre, prospective, observational study in Japan (ICE-CRASH study). Resuscitation 2023;182:109663.
5. 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 Car 2022;26:129.
6. Kojima M, Endo A, Shiraishi A, et al. Association between the plasma-to-red blood cell ratio and survival in geriatric and non-geriatric trauma patients undergoing massive transfusion: a retrospective cohort study. J Intensive Care 2022;10:2.
7. Waljee AK, Mukherjee A, Singal AG, et al. Comparison of imputation methods for missing laboratory data in medicine. BMJ Open 2013;3:e002847.
8. Stekhoven DJ, Bühlmann P. MissForest—non-parametric missing value imputation for mixed-type data. Bioinformatics 2012;28:112–8.
9. Ho D, Imai K, King G, Stuart EA. MatchIt: Nonparametric preprocessing for parametric causal inference. J Stat Soft 2011;42:1–28.
10. Takauji S, Hifumi T, Saijo Y, et al. Accidental hypothermia: characteristics, outcomes, and prognostic factors—A nationwide observational study in Japan (Hypothermia study 2018 and 2019). Acute Med Surg 2021;8:e6949.
11. Walpoth BH, Walpoth-Aslan BN, Mattle HP, et al. Outcome of survivors of accidental deep hypothermia and circulatory arrest treated with extracorporeal blood warming. N Engl J Med 1997;337:1500–5.
12. Ohbe H, Isogai S, Jo T, et al. Extracorporeal membrane oxygenation improves outcomes of accidental hypothermia without vital signs: A nationwide observational study. Resuscitation 2019;144:27–32.
13. Kornberger E, Mair P. Important aspects in the treatment of severe accidental hypothermia: the Innsbruck experience. J Neurosurg Anesthesiol 1996;8:83–7.
14. Okada Y, Matsuyama T, Morita S, et al. Prognostic factors for patients with accidental hypothermia: a multi-institutional retrospective cohort study. Am J Emerg Med 2019;37:565–70.
15. Paden ML, Conrad SA, Rycus PT, et al. Extracorporeal life support organization registry report 2012. ASAIO J 2013;59:202–10.
16. Bisdas T, Beutel G, Warnecke G, et al. Vascular complications in patients undergoing femoral cannulation for extracorporeal membrane oxygenation support. Ann Thorac Surg 2011;92:626–31.
17. Inoue A, Hifumi T, Sakamoto T, et al. Extracorporeal cardiopulmonary resuscitation for out-of-hospital cardiac arrest in adult patients. J Am Heart Assoc 2020;9:e015291.
18. Otani T, Sawano H, Natsukawa T, et al. D-dimer predicts bleeding complication in out-of- hospital cardiac arrest resuscitated with ECMO. Am J Emerg Med 2018;36:1003–8.
19. Kashiura M, Sugiyama K, Tanabe T, et al. Effect of ultrasonography and fluoroscopic guidance on the incidence of complications of cannulation in extracorporeal cardiopulmonary resuscitation in out-of-hospital cardiac arrest: a retrospective observational study. BMC Anesthesiol 2017;17:4.
20. Levi M. Hemostasis and thrombosis in extreme temperatures (hypo- and hyperthermia). Semin Thromb Hemost 2018;44:651–5.