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## Clinical paper

# Extracorporeal membrane oxygenation improves outcomes of accidental hypothermia without vital signs: A nationwide observational study



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### Abstract

**Aim:** Patients with accidental hypothermia without vital signs increasingly receive venoarterial extracorporeal membrane oxygenation (VA-ECMO). However, there is limited knowledge regarding the efficacy of this advanced rewarming method. We aimed to determine whether VA-ECMO improved outcomes in patients with accidental hypothermia without vital signs, using a large nationwide inpatient database in Japan.

**Methods:** Using the Japanese Diagnosis Procedure Combination inpatient database from July 2010 to March 2017, we identified patients diagnosed with accidental hypothermia who received closed-chest cardiac massage in-hospital on the day of admission. Patients who received VA-ECMO on the day of admission were allocated to the VA-ECMO group, and those who received cardiopulmonary resuscitation (CPR) only were allocated to the conventional CPR group. The primary outcome was in-hospital mortality, and the secondary outcome was a Japan Coma Scale status of “alert consciousness” at discharge. Propensity score-matching analyses were performed to compare the outcomes.

**Results:** We identified 1661 eligible patients during the 81-month study period, and 318 (19%) received VA-ECMO on the day of admission. Crude in-hospital mortality was 65% in the VA-ECMO group and 84% in the conventional CPR group. Propensity score-matching analyses demonstrated significantly lower in-hospital mortality (risk difference: −13%; 95% confidence interval: −21% to −5.1%) and a higher proportion of “alert consciousness” at discharge (risk difference: 8.3%; 95% confidence interval: 1.9%–15%) in the VA-ECMO group compared with the conventional CPR group.

**Conclusion:** VA-ECMO was associated with higher survival and favourable neurological outcomes compared with conventional CPR alone in patients with accidental hypothermia without vital signs.

**Keywords:** Accidental hypothermia, Cardiac arrest, Cardiopulmonary resuscitation

## Introduction

Accidental hypothermia is a life-threatening condition associated with significant morbidity and mortality.<sup>1–3</sup> In 1967, the first successful use

of extracorporeal life support for accidental hypothermia with cardiac arrest was reported.<sup>4</sup> Since then, increasing numbers of patients with accidental hypothermia have received extracorporeal life support including venoarterial extracorporeal membrane oxygenation (VA-ECMO) and cardiopulmonary bypass (CPB).<sup>5–11</sup>

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<https://doi.org/10.1016/j.resuscitation.2019.08.041>

Received 17 May 2019; Received in revised form 17 August 2019; Accepted 25 August 2019

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Although over 50 years have elapsed since the first reported success of VA-ECMO in a patient with accidental hypothermia without vital signs, current knowledge on the efficacy of this advanced rewarming method remains limited. Previous case-series studies on patients with accidental hypothermia without vital signs treated by extracorporeal life support have tended to have relatively small sample sizes. Specifically, patient numbers have ranged from only a few patients to 68 patients and studies have involved heterogeneous cases with different causes of hypothermia, leading to a wide range of survival rates (11%–73%).<sup>9</sup> A previous meta-analysis of case-series of patients with accidental hypothermia treated with extracorporeal life support showed an overall survival rate of 54%.<sup>11</sup> Little is known about patients with accidental hypothermia without vital signs who are not treated with VA-ECMO or CPB.<sup>12–14</sup> Moreover, no studies have examined the efficacy of extracorporeal life support using experimental designs that attempt to replicate the ideal of randomised experiments when using observational data. Despite the limited evidence, the resuscitation guidelines from the European Resuscitation Council and the American Heart Association both recommend using extracorporeal life support in patients with accidental hypothermia without vital signs.<sup>15,16</sup>

The present study aimed to examine the effect of extracorporeal life support in patients with accidental hypothermia without vital signs by propensity score-matched analyses, using data from a Japanese nationwide inpatient database.

## Methods

The Institutional Review Board of the University of Tokyo approved this study. No identifying information for individual patients, hospitals or physicians was obtained. The requirement for informed consent was waived because of the anonymous nature of the data.

### Data source

We used the Japanese Diagnosis Procedure Combination inpatient database, which includes discharge abstracts and administrative claims data for more than 1200 acute-care hospitals and covers approximately 90% of all tertiary-care emergency hospitals in Japan. The database includes data on age, sex, weight, height, level of consciousness, primary diagnosis, comorbidities at admission, postadmission complications, procedures, prescriptions and discharge status. To optimise the accuracy of the recorded diagnoses, the responsible physicians are required to record the diagnoses with reference to medical charts. The primary diagnosis, comorbidities at admission, and postadmission complications are recorded using International Classification of Diseases Tenth Revision (ICD-10) codes and text in Japanese. Furthermore, because the diagnostic records are linked to a payment system, the attending physicians are required to report objective evidence for the disease diagnosis for reimbursement of treatment costs.<sup>17</sup> A previous study evaluating the records of diagnoses and procedures in the database established the validity of the database.<sup>18</sup> In that study, the specificity of the diagnoses exceeded 96%, while the sensitivity was 50%–80%. The specificity and sensitivity of the procedures both exceeded 90%.

### Study population

Patients with accidental hypothermia without vital signs on admission were identified in the Japanese Diagnosis Procedure Combination

inpatient database from July 2010 to March 2017. We did not include patients who presented with deep accidental hypothermia without cardiopulmonary arrest.

We included all patients who were diagnosed with accidental hypothermia (ICD-10 code T68 as primary diagnosis or comorbidity on admission) who received closed-chest cardiac massage in hospital on the day of admission.<sup>3</sup> We did not include patients with a diagnosis of suspected accidental hypothermia.

The exclusion criteria were: (i) patients aged  $\leq 18$  years; (ii) diagnosis of aortic dissection, aortic aneurysm or advanced age (because of contraindications for VA-ECMO)<sup>19</sup>; (iii) patients who received open-chest cardiac massage on the day of admission (because only four patients received open-chest cardiac massage on the day of admission in our cohort); and (iv) patients who received CPB (because only one patient received CPB on the day of admission in our cohort).

Patients who received VA-ECMO on the day of admission were allocated to the VA-ECMO group, and those who received cardiopulmonary resuscitation (CPR) only were allocated to the conventional CPR group.

### Covariates and endpoints

Covariates included age, sex, quarters (1st: from 01 January, 2nd: from 01 April, 3rd: from 01 July and 4th: from 01 October), smoking history (nonsmoker, current/past smoker or missing data), body mass index at admission, Japan Coma Scale status (JCS) at admission,<sup>20</sup> Charlson comorbidity index,<sup>21</sup> comorbidity of dementia, comorbidity of malignancy, associated conditions (acute medical illness, trauma, poisoning, drowning and others) according to a previous study,<sup>3</sup> defibrillation on the day of admission, resuscitative drugs on the day of admission (antiarrhythmic medications [amiodarone, lidocaine or nifekalant], atropine, prefilled syringe of adrenaline (epinephrine)) and admission to a teaching hospital.

Body mass index was categorised as  $<18.5$ , 18.5–24.9, 25.0–29.9,  $\geq 30.0$  kg/m<sup>2</sup> or as missing data. JCS status was categorised as alert consciousness, confusion, somnolence, and coma. JCS status has been shown to be well correlated with the Glasgow Coma Scale.<sup>20</sup> The Charlson comorbidity index was scored by the diagnosis for each patient and categorised as 0, 1 or  $\geq 2$ .<sup>21</sup>

The primary outcome was in-hospital mortality. The secondary outcome was a JCS status of “alert consciousness” at discharge. Death on the day of admission and length of hospital stay were also evaluated.

### Statistical analysis

We used propensity score-matching to compare outcomes between the VA-ECMO and conventional CPR groups.<sup>22,23</sup> A multivariable logistic regression model was used to predict patients' propensity scores for VA-ECMO treatment. Predictor variables included age, sex, quarter, smoking history, body mass index at admission, JCS at admission, Charlson comorbidity index, comorbidity of dementia, comorbidity of malignancy, associated conditions, defibrillation on the day of admission, resuscitative drugs on the day of admission and admission to a teaching hospital. One-to-one nearest-neighbour matching without replacement was performed for patients' estimated propensity scores using a caliper width set at 20% of the standard deviation for the logit of the propensity scores.<sup>22–24</sup> A caliper, which means the maximum tolerated difference between matched subjects

in a nearest-neighbour matching, is frequently set at 20% of the standard deviation for the logit of the propensity scores. The logit of a probability ( $p$ ) is defined as  $\ln[p/(1-p)]$ .

A standardised difference (SD) of  $\geq -10\%$  and  $\leq 10\%$  were considered to denote negligible imbalances in the variables between the propensity score-matched VA-ECMO and conventional CPR groups.<sup>25</sup> We performed propensity-score matching using the Stata (StataCorp, College Station, TX, USA) module, PSMATCH2, provided by Edwin and Barbara.<sup>26</sup>

We evaluated the crude and propensity score-matched outcomes in both groups. A JCS of “alert consciousness” at discharge was evaluated for all patients and survivors. Length of hospital stay was evaluated for the survivors.

We used a generalised estimating equation approach for comparisons of the primary and secondary outcomes, accompanied by cluster-robust standard errors that treated both propensity score-matched pairs and individual hospitals as clusters.<sup>27</sup> Risk differences, odds ratios and 95% confidence intervals (CIs) were calculated for the primary and secondary outcomes. These estimates were obtained by generalised estimating equation models with identity (for differences) and log (for ratios) link functions irrespective of outcome types.<sup>28</sup>

Continuous variables were presented as mean and standard deviation or median and interquartile range (IQR). All analyses were performed using STATA/MP 15.0 software (StataCorp).

## Results

A total of 1661 patients met our eligibility criteria during the 81-month study period. Of these, 318 (19%) received VA-ECMO on the day of admission (Fig. 1).

Table 1 shows patients’ baseline characteristics. Patients in the VA-ECMO group were more likely to: be younger, male and a current or past smoker; have poor consciousness at admission; have more

associated conditions of acute medical illnesses or poisoning; receive defibrillation, antiarrhythmic medications or a prefilled syringe of adrenaline and to be admitted to a teaching hospital. After propensity-score matching, the covariates were well-balanced between the two groups except for a JCS status of coma, at admission.

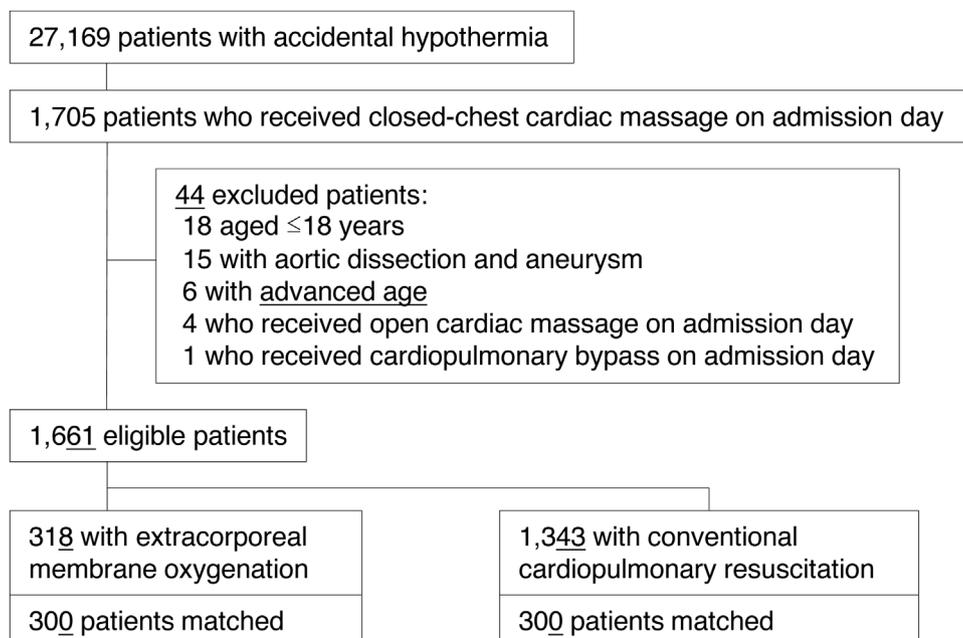
Table 2 shows the crude and matched cohort outcomes in the two groups. Crude in-hospital mortality was 65% in the VA-ECMO group and 84% in the conventional CPR group. The crude proportion of “alert consciousness” at discharge was 21% in the VA-ECMO group and 10% in the conventional CPR group. Among survivors, the crude proportion of “alert consciousness” at discharge was 62% in the VA-ECMO group and 62% in the conventional CPR group.

Table 3 shows the results of the propensity score-matching analyses. The propensity score-matching analyses demonstrated significantly lower in-hospital mortality (risk difference,  $-13\%$ ; 95% CI,  $-21\%$  to  $-5.1\%$ ) and a significantly higher proportion of “alert consciousness” at discharge (risk difference:  $8.3\%$ ; 95% CI:  $1.9\%$ – $15\%$ ) in the VA-ECMO group compared with the conventional CPR group. Among survivors, the proportion of “alert consciousness” at discharge did not differ significantly between the two groups (risk difference:  $2.7\%$ ; 95% CI,  $-14\%$ – $19\%$ ).

## Discussion

Our study demonstrated that VA-ECMO was significantly associated with decreased in-hospital mortality and favourable neurological outcomes compared with conventional CPR in accidental hypothermia patients without vital signs.

VA-ECMO has several pathophysiological advantages compared with other rewarming methods. Specifically, it is the fastest method for rewarming, it provides adequate and immediate circulatory support, it can rapidly correct metabolic and electrolyte derangements and it rewarms the heart before the rest of the body, preventing shock from peripheral vasodilatation.<sup>1,29</sup>



**Fig. 1 – Patient flowchart.**

**Table 1 – Comparisons of patients' baseline characteristics in the original cohort and propensity score-matched cohort.**

Characteristic	Original cohort			Matched cohort		
	Conventional CPR	VA-ECMO	SD	Conventional CPR	VA-ECMO	SD
	(n = 1343)	(n = 318)		(n = 300)	(n = 300)	
Age (years), median (IQR)	79 (67, 85)	71 (58, 80)	−50	72 (61, 82)	72 (60, 81)	−1
Male, n (%)	721 (54)	196 (62)	16	168 (56)	181 (60)	9
Quarters, n (%)						
1st: from 01 January	792 (59)	199 (63)	7	184 (61)	186 (62)	1
2nd: from 01 April	110 (8)	31 (10)	6	35 (12)	30 (10)	−5
3rd: from 01 July	26 (2)	3 (1)	−8	2 (1)	3 (1)	4
4th: from 01 October	415 (31)	85 (27)	−9	79 (26)	81 (27)	2
Smoking history, n (%)						
Nonsmoker	489 (36)	122 (38)	4	125 (42)	113 (38)	−8
Current or past smoker	144 (11)	49 (15)	14	42 (14)	44 (15)	2
Unknown	710 (53)	147 (46)	−13	133 (44)	143 (48)	7
Body mass index (kg/m <sup>2</sup> ), n (%)						
<18.5	189 (14)	46 (15)	1	49 (16)	45 (15)	−4
18.5–24.9	320 (24)	115 (36)	27	111 (37)	105 (35)	−4
25.0–29.9	53 (4)	25 (8)	17	17 (6)	21 (7)	6
≥30.0	9 (1)	6 (2)	11	5 (2)	4 (1)	−3
Missing data	772 (58)	126 (40)	−36	118 (39)	125 (42)	5
Japan Coma Scale at admission, n (%)						
Alert	90 (7)	15 (5)	−9	12 (4)	15 (5)	5
Confusion	79 (6)	9 (3)	−15	13 (4)	9 (3)	−7
Somnolence	77 (6)	13 (4)	−8	7 (2)	13 (4)	11
Coma	1097 (82)	281 (88)	19	268 (89)	263 (88)	−5
Charlson comorbidity index, n (%)						
0	1006 (75)	253 (80)	11	235 (78)	238 (79)	2
1	224 (17)	45 (14)	−7	42 (14)	43 (14)	1
2	113 (8)	20 (6)	−8	23 (8)	19 (6)	−5
Dementia as comorbidity, n (%)	58 (4)	10 (3)	−6	10 (3)	10 (3)	0
Malignancy as comorbidity, n (%)	34 (3)	4 (1)	−9	6 (2)	4 (1)	−5
Associated conditions, n (%)						
Acute medical illness	644 (48)	173 (54)	13	157 (52)	160 (53)	2
Trauma	122 (9)	37 (12)	8	33 (11)	35 (12)	2
Poisoning	36 (3)	16 (5)	12	16 (5)	15 (5)	−2
Drowning	58 (4)	16 (5)	3	13 (4)	15 (5)	3
Other	483 (36)	76 (24)	−27	81 (27)	75 (25)	−5
Defibrillation, n (%)	445 (33)	193 (61)	57	176 (59)	175 (58)	−1
Resuscitative drugs, n (%)						
Antiarrhythmic medications	170 (13)	84 (26)	35	77 (26)	75 (25)	−2
Atropine	140 (10)	24 (8)	−10	22 (7)	24 (8)	3
Prefilled syringe of adrenaline (syringe), median (IQR)	2 (0, 4)	2 (0, 6)	14	2 (0, 5)	2 (0, 5)	−8
Admission to a teaching hospital, n (%)	1254 (93)	312 (98)	24	295 (98)	294 (98)	−3

VA-ECMO, venoarterial extracorporeal membrane oxygenation; CPR, cardiopulmonary resuscitation; SD, standardised difference; IQR, interquartile range.

In-hospital mortality for the VA-ECMO group in our cohort (65%) was higher than that in a previous meta-analysis (54%).<sup>11</sup> This inconsistency could have arisen because the population of accidental hypothermia patients in our study differed from those in the studies included in the meta-analysis. The proportion of older patients was much higher in our study compared with previous studies (median age: 71 years vs. 36 years, respectively). A previous study using a multicentre accidental hypothermia registry in Japan showed that the median patients' age was 79 years (IQR, 67–87 years), and that 30% of the patients had impaired activities of daily living before admission.<sup>3</sup> The authors found that older age and impaired activities of daily living were significantly associated with mortality. The authors also found that 50% of the patients had an acute medical illness at admission, and that 78% of the patients developed accidental hypothermia in an

indoor setting.<sup>3</sup> A previous systematic review found that patients with purely hypothermic arrest from cold exposure had lower mortality than patients with primary hypoxia or cardiogenic arrest accompanying hypothermia.<sup>5</sup> Differences in study populations may also explain the higher mortality in the VA-ECMO group in our study compared with the mortalities reported in the previous studies.

To date, there are limited available data for patients with accidental hypothermia without vital signs who did not receive VA-ECMO or CPB. The survival rate was reported to be less than 37%,<sup>12–14</sup> and neurological outcomes have not been well studied. Our study showed that the neurological prognosis among survivors after conventional CPR only was comparable with that of survivors after VA-ECMO, suggesting that patients who were successfully resuscitated by conventional CPR may not require additional extracorporeal life

**Table 2 – Outcomes in the original cohort and propensity score-matched cohort.**

Outcome	Original cohort		Matched cohort	
	Conventional CPR (n= 1343)	VA-ECMO (n= 318)	Conventional CPR (n= 300)	VA-ECMO (n= 300)
In-hospital mortality, n (%)	1131 (84)	208 (65)	237 (79)	198 (66)
Death on the day of admission, n (%)	961 (72)	131 (41)	189 (63)	127 (42)
Japan Coma Scale at discharge, n (%)				
Alert consciousness	131 (10)	68 (21)	36 (12)	61 (20)
Confusion	50 (4)	33 (10)	16 (5)	33 (11)
Somnolence	11 (1)	3 (1)	4 (1)	3 (1)
Coma	20 (2)	6 (2)	7 (2)	5 (2)
Japan Coma Scale at discharge among survivors, n (%) <sup>a</sup>				
Alert consciousness	131/212 (62)	68/110 (62)	36/63 (57)	61/102 (60)
Confusion	50/212 (24)	33/110 (30)	16/63 (25)	33/102 (32)
Somnolence	11/212 (5)	3/110 (3)	4/63 (6)	3/102 (3)
Coma	20/212 (9)	6/110 (6)	7/63 (11)	5/102 (5)
Length of hospital stay among survivors (days), median (IQR) <sup>a</sup>	30 (14, 50)	35 (22, 61)	28 (15, 47)	36 (22, 63)

CPR, cardiopulmonary resuscitation; VA-ECMO, venoarterial extracorporeal membrane oxygenation; IQR, interquartile range.  
<sup>a</sup> The number of survivors in the conventional CPR and VA-ECMO groups was 212 and 110 patients in the crude cohort and 63 and 102 patients in the propensity score-matched cohort, respectively.

**Table 3 – Comparison of primary and secondary outcomes between the two groups in the matched cohort using a generalised estimating equation.**

Outcome	Conventional CPR (n= 300)	VA-ECMO (n= 300)	Risk difference (95% CI)	Relative risk (95% CI)
In-hospital mortality, n (%)	237 (79)	198 (66)	–13 (–21 to –5.1)	0.84 (0.75–0.94)
Alert consciousness at discharge, n (%)	36 (12)	61 (20)	8.3 (1.9–15)	1.69 (1.13–2.54)
Alert consciousness at discharge among survivors, n (%) <sup>a</sup>	36/63 (57)	61/102 (60)	2.7 (–14 to 19)	1.05 (0.79–1.34)

CPR, cardiopulmonary resuscitation; VA-ECMO, venoarterial extracorporeal membrane oxygenation; CI, confidence interval.  
<sup>a</sup> The number of survivors in the conventional CPR and VA-ECMO groups was 63 and 102 patients in the propensity score-matched cohort, respectively.

support. These findings provide additional evidence for the importance of high-quality CPR in patients with accidental hypothermia when extracorporeal life support is not available.

The present study has several limitations. Results from observational database studies require careful interpretation. First, because of data unavailability, we were unable to evaluate patients' core temperatures at admission. Some patients may have had mild (35 °C–32 °C) or moderate (32 °C–28 °C) hypothermia. However, the registry in Japan found no significant difference between core temperature and in-hospital mortality in patients with accidental hypothermia.<sup>3</sup> Core temperature can thus be considered a weak unmeasured confounder in this Japanese patient sample. Although, our patient sample included more indoor, older and sicker patients, compared to European studies which include mainly outdoor, younger and previously healthier patients.<sup>30–32</sup> Therefore, our findings need to be corroborated with similar patients from other settings (e.g. Europe and North America). Second, the assignment of VA-ECMO was not random. We used propensity score-matched analyses to control for possible measured confounders, but our results may have been biased by major unmeasured confounders such as core temperature or “do not resuscitate” orders. Third, the diagnosis of accidental hypothermia based on diagnostic codes has not been well validated. Fourth, we were unable to access data on how the patients in the conventional CPR group were rewarmed. Fifth, we could not include some variables used in the Hypothermia Outcome Prediction after ECLS (HOPE) survival probability score such as CPR duration or

serum potassium level, which might have influenced our results.<sup>33,34</sup> Sixth, we used JCS status instead of Cerebral Performance Category as our neurological outcome scale for post-cardiac arrest patients because of data unavailability.

## Conclusion

This large retrospective study provides evidence that VA-ECMO is significantly associated with higher survival and favourable neurological outcomes compared with conventional CPR alone in patients with accidental hypothermia without vital signs.

## Conflicts of interest

None.

## Acknowledgements

This work was supported by grants from the Ministry of Health, Labour and Welfare of Japan (H30-Policy-Designated-004 and H29-ICT-General-004); Ministry of Education, Culture, Sports, Science and Technology of Japan (17H04141); and the Japan Agency for Medical Research and Development. This funding source had no role in the design of this study

and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

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