Critical Care Medicine
July 2025 • Volume 53 • Number 7 • Pages e1416–e1425

CLINICAL INVESTIGATION

Association Between Rewarming Rate and Survival and Neurologic Outcome of Accidental Hypothermia

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OBJECTIVES: Accidental hypothermia has high mortality. Rewarming is the initial primary management strategy. However, detailed evidence on rewarming management is limited, that is, rewarming rate is unclear, particularly with noncardiac arrest. Here, we evaluated the association between rewarming rate in the early phase of rewarming and survival and neurologic outcomes in patients with accidental hypothermia.

DESIGN: A secondary analysis of a nationwide, multicenter, prospective, observational study—the Intensive Care with ExtraCorporeal membrane oxygenation Rewarming in Accidentally Severe Hypothermia (ICE-CRASH) study—including adult patients admitted with moderate-to-severe accidental hypothermia between 2019 and 2022.

SETTING: Emergency medical facilities in Japan ($n = 36$).

PATIENTS: Patients whose body temperature less than 32°C on arrival at the emergency department.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: The early phase of rewarming was defined as the time from arrival at the emergency department to achieving a body temperature of 33°C. Primary and secondary outcomes included 28-day survival after admission and favorable neurologic status at discharge (Cerebral Performance Category score of 1–2). The median rewarming rates in the early phase was 1.35°C/hr (interquartile range, 0.91–2.03°C/hr). Overall, the 28-day survival rate was 82.0% ($n = 324$), and the proportion of favorable neurologic outcome was 66.6% ($n = 263$). Multivariable logistic regression analysis showed that the rewarming rate was significantly associated with 28-day survival and favorable neurologic outcomes in the early phase (odds ratio [OR], 1.51; 95% CI, 1.10–2.09; $p = 0.011$ and OR, 1.32; 95% CI, 1.06–1.64; $p = 0.015$).

CONCLUSIONS: In the early phase, the rewarming rate was associated with survival and favorable neurologic outcomes.

KEYWORDS: accidental hypothermia; neurologic outcome; rewarming; rewarming rate; survival

Accidental hypothermia has high mortality (1, 2). Because hypothermia leads to hypotension, dysrhythmia, and cardiac arrest, rewarming is one of the main initial managements in patients with accidental hypothermia (1, 3–6).

Although rewarming procedures, such as passive or active external rewarming, internal rewarming, and extracorporeal rewarming, make it possible to rewarm earlier (7, 8), detailed evidence on rewarming management is limited,

DOI: 10.1097/CCM.0000000000006712

KEY POINTS

Question: Does the rewarming rate, especially early phase of rewarming, affect the outcome in patients with accidental hypothermia?

Findings: This prospective, multicenter observational study revealed that a faster rewarming rate in the early phase of rewarming was associated with 28-day survival and favorable neurologic outcomes in patients with accidental hypothermia.

Meaning: Our findings provide valuable data on the rewarming rate of accidental hypothermia, revealing that rapid passage of the early phase of rewarming is critical to the patient's outcome.

that is, rewarming rate is unclear. The current guidelines recommend rewarming to a temperature of 32°C for accidental hypothermia in patients with cardiac arrest. However, they do not specify an appropriate rewarming rate for patients with noncardiac arrest (9–11). Although several studies have found an association between the rewarming rate and outcome, the findings are inconclusive and include patients with cardiac arrest (12–14). Furthermore, these studies evaluated the association between the rewarming rate and outcomes for overall rewarming. Additionally, studies on targeted body temperature (BT) during rewarming are lacking.

Moderate-to-severe hypothermia can be life threatening (1, 4, 6, 15), but mild hypothermia is not a life-threatening condition (4). Therefore, we hypothesized that the management of rewarming consisted of two phases, that is, early phase of rewarming, which avoids severe/moderate hypothermia, and late phase of rewarming, which achieved normal temperature, of which early phase of rewarming could contribute to outcome. In this study, we aimed to evaluate the association between rewarming rate in the early phase of rewarming and survival and neurologic outcomes in patients with accidental hypothermia.

MATERIALS AND METHODS

Study Design and Setting

This was a secondary analysis of Intensive Care with ExtraCorporeal membrane oxygenation Rewarming in Accidentally Severe Hypothermia (ICE-CRASH) study–a nationwide multicenter, prospective, observational study in patients with accidental hypothermia (16). Detailed information regarding this registry is described in **Supplemental Methods** (https://links.lww.com/CCM/H723) and is also available in other studies (16).

Ethics Approval and Consent to Participate

The ICE-CRASH study was ethically approved by Asahikawa Medical University (approval no. 18194) and is registered with the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN000036132). The ICE-CRASH study was supported by the Japanese Association for Acute Medicine (approval no. 0005). In addition, the Institutional Review Board (IRB) of Hyogo Emergency Medical Center (Kobe, Japan) approved the current secondary analysis, entitled "Association between rewarming rate and survival and neurologic outcome of accidental hypothermia," on September 26, 2023, in accordance with the IRB ethical standards for human experimentation and the 1975 Declaration of Helsinki (approval no. 2023008). The local committee waived the requirement for patient consent due to the retrospective nature of the study.

Study Participants

This study included adult (≥ 18 yr old) patients with moderate-to-severe accidental hypothermia, defined as BT less than 32°C at the emergency department (ED) (4, 10). BT was measured at the bladder, rectum, axilla, esophagus, and other sites (blood and tympanum). Measurement site and timing was selected by the attending physician. Patients with cardiac arrest on arrival at the ED were excluded. Patients who received therapeutic hypothermia were excluded because it would affect rewarming rates (17–19). Patients without data on the rewarming rate and outcomes (28-day survival after admission and neurologic outcome at discharge) were excluded.

Data Collection

The following data were collected: age, sex, location of accidental hypothermia, causes of hypothermia, activities of daily living (ADL), Charlson Comorbidity Index

(CCI), BT on arrival at the ED, time course of rewarming, Glasgow Coma Scale (GCS) score, blood pressure, heart rate, laboratory data at the ED, Sequential Organ Failure Assessment (SOFA) score, rewarming procedure, rewarming rate, outcomes, and complications. Complications included events that occurred during rewarming and within 7 days.

Rewarming Procedures and Management

Rewarming procedures included warm blankets, warm parenteral fluids, warm baths, stomach tube, bladder wash, endovascular catheters, hemodialysis, extracorporeal membrane oxygenation (ECMO), and others. There was no established protocol for selecting the rewarming procedure, and targeted temperature, the course of action to achieve the targeted temperature and rewarming rate was at the physician's discretion (16).

Definition of Early Phase of Rewarming

The ICE-CRASH study included BT on arrival at the ED, time from arrival at the ED to achieving BT of 33°C, and time from BT of 33°C to achieving BT of 36°C. In this study, we focused on the early phase of rewarming, which could lead to physiologic changes (1, 3–5). The early phase of rewarming was defined as the time from arrival at the ED to achieving BT of 33°C. Therefore, the rewarming rate in the early phase of rewarming was calculated as follows: rewarming rate from arrival at the ED to 33°C (°C/hr) = difference in BT (33°C–BT on arrival at the ED)/time duration between arrival at the ED and 33°C.

Outcome Measures

The primary outcome in this study was 28-day survival after admission. The secondary outcome was favorable neurologic status at discharge. A favorable neurologic outcome was defined as a Glasgow-Pittsburgh Cerebral Performance Category (CPC) score of 1–2, and an unfavorable neurologic outcome was defined as a CPC score of 3–5 (20).

Statistical Analysis

Descriptive statistics were used to summarize the data on baseline characteristics, outcomes, and complications. We compared the baseline characteristics, outcomes, and complications according to each outcome, each rewarming procedure, and patients with/without ECMO, using a Mann-Whitney *U* test or a Kruskal-Wallis test for continuous variables and Fisher exact test or chi-square test for categorical variables. Multivariable logistic regression analysis was performed for the primary and secondary outcomes in the early phase of rewarming. We fitted logistic regression models with a generalized estimating equation (GEE) to account for patient clustering within a hospital. In the multivariable model, we adjusted for potential confounders, including age, GCS score, systolic blood pressure on arrival at the ED, and rewarming with ECMO (16, 21, 22). As recommended by clinical epidemiologists and statisticians, covariates were selected based on clinical plausibility and priori knowledge (23, 24). A cubic spline model was developed to illustrate the systemic associations between the rewarming rate in the early phase of rewarming and each outcome. To assess the robustness of our findings, we performed sensitivity and subgroup analyses. Additionally, we constructed fixed-effect models to account for variations in treatment protocols across hospitals. Detailed information on the statistical methods used for sensitivity and subgroup analyses is provided in the Supplemental Methods (https://links.lww.com/CCM/H723). To assess multicollinearity, the variance inflation factor (VIF) was calculated for all variables. All VIF values were within acceptable thresholds (VIF < 10) (25), indicating that no significant collinearity existed among the variables. Statistical analyses were performed using R, Version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria) and JMP Pro, Version 17 Statistical Software (SAS Institute, Cary, NC). All *p* values were two-sided, and *p* values of less than 0.05 were statistically significant. Missing data were excluded from the analysis.

RESULTS

Of the 499 patients who underwent rewarming for accidental hypothermia in ICE-CRASH, 395 were included for analysis. (**Fig. 1**).

Baseline Characteristics of the Study Population

The median age of the patients was 81 years (interquartile range, 70–88 yr). The median BT on arrival at the ED was 28.6°C (27.2–30.2°C). The proportion of

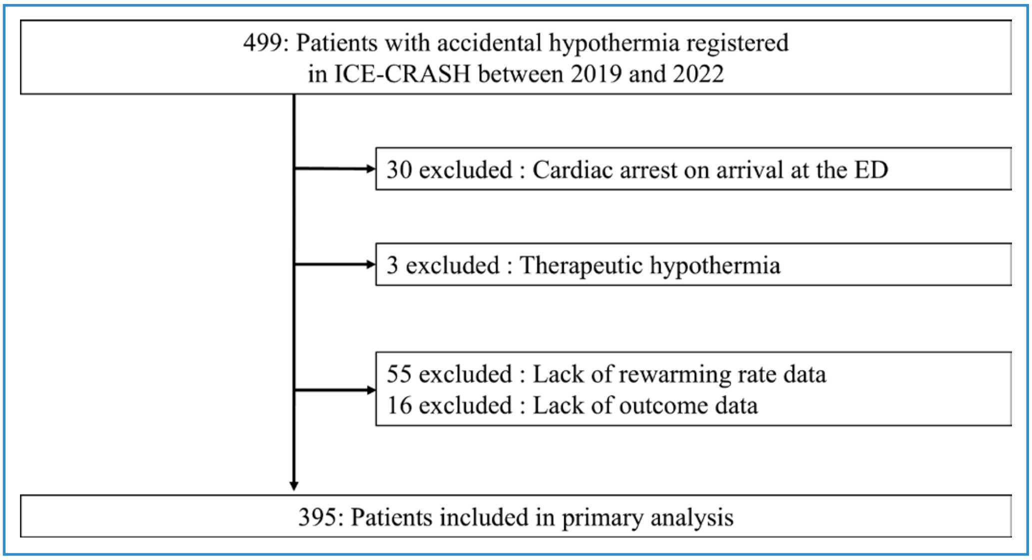


Figure 1. Flow diagram of the study population. ED = emergency department, ICE-CRASH = Intensive Care with ExtraCorporeal membrane oxygenation Rewarming in Accidentally Severe Hypothermia.

patients with BT less than 28°C was 36.2% (n = 143) (**Table 1**). The proportion of patients who underwent ECMO as a rewarming procedure was 7.3% (n = 29) (**Table 2**). The baseline characteristic was shown for each outcome, each rewarming procedure, and patients rewarmed with/without ECMO (**Supplemental Tables 1–3**, https://links.lww.com/CCM/H723).

The median rewarming rate in the early phase of rewarming was 1.35°C/hr (0.91–2.03°C/hr) (Table 2). The distribution of rewarming rates and outcomes were shown in **Supplemental Figure 1** (https://links.lww.com/CCM/H723). The distribution of cases in each institution and the rewarming rate in each center volume groups were shown in **Supplemental Figure 2** and **Supplemental Table 4** (https://links.lww.com/CCM/H723), respectively.

Association Between Rewarming Rate and Outcome

The 28-day survival rate was 82.0% (n = 324), and the proportion of favorable neurologic outcome was 66.6% (n = 263) (**Table 3**). According to the GEE analysis, in the early phase of rewarming, the rewarming rate was significantly associated with 28-day survival and favorable neurologic outcomes (odds ratio [OR], 1.51; 95% CI, 1.10–2.09; $p = 0.011$ and OR, 1.32; 95% CI, 1.06–1.64; $p = 0.015$) (**Fig. 2**). Significant association between rewarming rate in the early phase of rewarming and each outcome are persisted in a fixed-effect model (**Supplemental Table 5**, https://links.lww.com/CCM/H723).

In the early phase of rewarming, the association between the rewarming rate and 28-day survival and favorable neurologic outcomes increased; however, for each outcome, the slope of improvement declined slowly once the rewarming rate reached approximately 3°C/hr (**Fig. 3**).

Sensitivity and Subgroup Analyses

In sensitivity analysis, the significant association between the rewarming rate in the early phase of rewarming and each outcome persisted in each model (Fig. 2). In subgroup analysis, significant association between the rewarming rate in the early phase of rewarming and each outcome persisted in the severe hypothermia subgroup, with the exception of patients rewarmed using ECMO and SOFA score greater than or equal to 7 group (Fig. 2).

DISCUSSION

In this study, we classified rewarming phases by targeted BT and found that a faster rewarming rate in the early phase of rewarming was associated with 28-day survival and favorable neurologic outcomes in patients with accidental hypothermia.

The current guidelines recommend rewarming to a temperature of 32°C for accidental hypothermia in patients with cardiac arrest. However, they do not specify a suitable rewarming rate for patients with noncardiac arrest (9). Therefore, the appropriate rewarming strategy for these patients is still unknown. Studies on the association between the rewarming rate and outcomes in patients with accidental hypothermia are limited. One study reported that rewarming rate (< 5°C/hr) was associated with a favorable neurologic outcome (12). However, that study was conducted using an individual patient data meta-analysis that only rewarmed using ECMO. In that study, 83% of patients had cardiac arrest. Another systematic review on

TABLE 1.
Baseline Characteristics of the Study Population

Variables	Total ($n = 395$)
Age (yr)	81 (70–88)
Male (%)	206 (52.2)
The location: indoor (%)	313 (79.2)
Causes (%)	
Internal cause	
Cerebrovascular disease	21 (5.3)
Endocrine disease	54 (13.7)
Infection	78 (19.7)
Cardiovascular disease	14 (3.5)
External cause	
Intoxication	30 (7.6)
Trauma	28 (7.1)
Others	84 (21.3)
Unknown	86 (21.8)
Charlson Comorbidity Index	1 (0–2)
Activities of daily living: independence (%)	231 (58.5)
Body temperature (°C)	28.6 (27.2–30.2)
Severe hypothermia (%)	143 (36.2)
Glasgow Coma Scale score	7 (10–12)
Systolic blood pressure (mm Hg)	111 (85–137)
Hemodynamic instability (%)	149 (37.8)
Heart rate (beats/min)	65 (48–82)
Laboratory data at the emergency department	
K (mmol/L)	4.1 (3.6–4.7)
Lactate (mmol/dL)	2.9 (1.4–6.2)
pH	7.29 (7.19–7.34)
SOFA score	6 (4–9)
SOFA score < 7	203 (52.7)
SOFA score ≥ 7	292 (47.3)
5A score	4 (3–5)

SOFA = Sequential Organ Failure Assessment.
Severe hypothermia was defined as body temperature on arrival at the emergency department (ED) < 28°C.
Hemodynamic instability at the ED was defined as either heart rate < 60 beats/min or systolic blood pressure < 90 mm Hg. 5A score, based on age, activities of daily living, arrest, acidemia, and albumin, predicts mortality after accidental hypothermia.
Our dataset lacked albumin data, so the 5A score was modified to exclude albumin from its calculation.
Data are presented as medians (interquartile range) for continuous variables and *n* (%) for categorical variables.

ECMO-treated patients with accidental hypothermia reported that rewarming rate (1.5–4°C/hr) was associated with survival (14). In that study, 75.5% of patients had cardiac arrest. Watanabe et al (13) showed that in-hospital mortality rates increased with each 0.5°C/hr decrease in rewarming rate, and a slower rewarming rate (< 0.5°C/hr) was associated with increased in-hospital mortality. In that study, 3.7% of patients underwent ECMO as a rewarming procedure, and 2.5% of patients had cardiac arrest. Furthermore, these studies

TABLE 2.
Rewarming Information

Variables	Total ($n = 395$)
Rewarming procedure (%)	
Blankets	292 (73.9)
Warm parenteral fluids	330 (83.5)
Warm baths	17 (4.3)
Stomach tube	3 (0.8)
Bladder wash	10 (2.5)
Endovascular catheters	39 (9.9)
Hemodialysis	12 (3.0)
Extracorporeal membrane oxygenation	29 (7.3)
Others	41 (10.4)
Rewarming rate in the early phase (°C/hr)	1.35 (0.91–2.03)

Early phase of rewarming was defined as time from arrival at the emergency department to achieving a body temperature of 33°C.
Data are presented as medians (interquartile range) for continuous variables and *n* (%) for categorical variables.

TABLE 3.
Outcomes and Complications in the Study Population

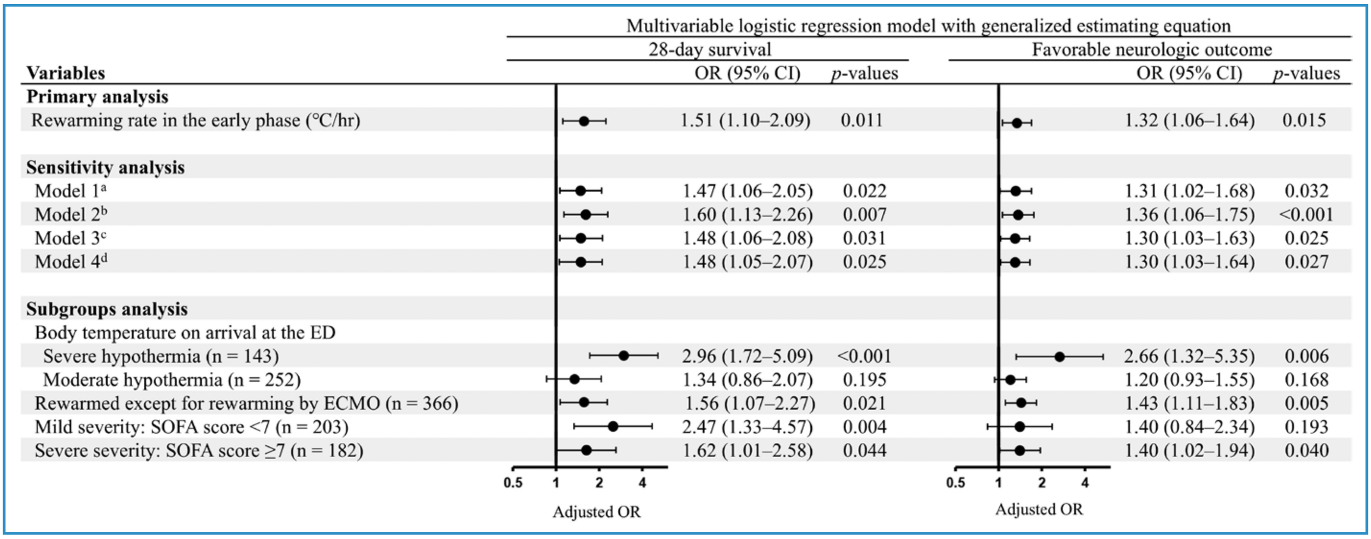
Variables	Total ($n = 395$)
Outcomes (%)	
28-d survival	324 (82.0)
Neurologic outcome at discharge	
Favorable neurologic outcome: CPC 1–2	263 (66.6)
Unfavorable neurologic outcome: CPC 3–5	132 (33.4)
Complications (%)	
Ventricular fibrillation	13 (3.3)
Hemorrhage	91 (23.0)
Pneumonia	85 (21.5)
Pancreatitis	13 (3.3)
Acute kidney injury	79 (20.0)
Others	51 (12.9)

CPC = Cerebral Performance Category.
Data are presented as *n* (%) for categorical variables.

did not specify the targeted BT or evaluate the association between the rewarming rate and outcomes for overall rewarming, as the phase of rewarming was not classified and examined. Therefore, a strength of our study was that we focused on the association between the rewarming rate in the early phase of rewarming and outcomes, classifying the phase of rewarming by targeted BT in accidental hypothermia patients with noncardiac arrest.

In this study, the rewarming rate in the early phase of rewarming contributed to survival. Hypothermia leads to hypotension, bradycardia, dysrhythmia, lethal arrhythmias, and cardiac arrest (1, 6). Furthermore, the risk of adverse events may increase with lower BT (1, 3–5). Particularly, these physiologic effects are more pronounced in severe hypothermia compared with moderate hypothermia (6, 25, 26). Our findings suggest that a faster rewarming rate in the early phase of rewarming is crucial to prevent life-threatening conditions during the initial management, particularly in patients with severe hypothermia. Hypothermia also has detrimental effects on multiple organs, including the heart, brain, and kidneys as well as blood coagulation and potentially the immune system (3–5). With respect to brain damage, mild-to-moderate hypothermia can offer neuroprotection by reducing cerebral metabolic rate and cerebral oxygen consumption (27). In contrast, severe hypothermia or hypothermia-induced low cardiac output, blood pressure, and cerebral blood flow reduces cerebral perfusion (28–31). Prolonged exposure to severe hypothermia with hypotension can deteriorate cerebral circulation and lead to neuronal damage. A faster rewarming rate in the early phase also reduces the duration of susceptibility to potentially harmful physiologic effects that could lead to neurologic damage. This suggests that a quicker rewarming rate in the early phase is not only associated with survival but also with favorable neurologic outcome. Consistently, this study showed a strong association between rewarming rate and outcome in the severe hypothermia group. Faster rewarming rate might contribute more to improving the outcomes, especially in patients with severe hypothermia.

Regarding the optimal rewarming rate, the side effects of rapid rewarming were reported. Rapid rewarming might promote outgassing––the decrease in jugular bulb venous oxygen saturation––reducing internal jugular venous oxygen hemoglobin saturation, a mismatch between oxygen supply and demand, or intracranial hypertension (32–34). Indeed, our cubic spline modeling results showed that the rewarming rate and predicted probability of each outcome increased



Variables	28-day survival OR (95% CI)	28-day survival p-values	Favorable neurologic outcome OR (95% CI)	Favorable neurologic outcome p-values
Primary analysis				
Rewarming rate in the early phase (°C/hr)	1.51 (1.10–2.09)	0.011	1.32 (1.06–1.64)	0.015
Sensitivity analysis				
Model 1[a]	1.47 (1.06–2.05)	0.022	1.31 (1.02–1.68)	0.032
Model 2[b]	1.60 (1.13–2.26)	0.007	1.36 (1.06–1.75)	<0.001
Model 3[c]	1.48 (1.06–2.08)	0.031	1.30 (1.03–1.63)	0.025
Model 4[d]	1.48 (1.05–2.07)	0.025	1.30 (1.03–1.64)	0.027
Subgroups analysis				
Body temperature on arrival at the ED				
Severe hypothermia (n = 143)	2.96 (1.72–5.09)	<0.001	2.66 (1.32–5.35)	0.006
Moderate hypothermia (n = 252)	1.34 (0.86–2.07)	0.195	1.20 (0.93–1.55)	0.168
Rewarmed except for rewarming by ECMO (n = 366)	1.56 (1.07–2.27)	0.021	1.43 (1.11–1.83)	0.005
Mild severity: SOFA score <7 (n = 203)	2.47 (1.33–4.57)	0.004	1.40 (0.84–2.34)	0.193
Severe severity: SOFA score ≥7 (n = 182)	1.62 (1.01–2.58)	0.044	1.40 (1.02–1.94)	0.040

Figure 2. Primary, sensitivity, and subgroup analyses in the early phase of rewarming. Primary analysis was adjusted for age, Glasgow Coma Scale (GCS) score, systolic blood pressure (SBP), and rewarming with extracorporeal membrane oxygenation (ECMO). [a]Model 1 was adjusted for age, GCS score, SBP, and the type of rewarming procedure (e.g., passive rewarming, active external rewarming, active internal rewarming, ECMO, and others). [b]Model 2 was adjusted for age, rewarming with ECMO, Sequential Organ Failure Assessment (SOFA) score (< 7 or ≥ 7), body temperature, heart rate, and blood gas analysis results at the emergency department (ED) (e.g., K, lactate levels, and pH). [c]Model 3 was adjusted for age, GCS score, SBP, rewarming with ECMO, and patient characteristics (e.g., location and cause of accidental hypothermia, Charlson Comorbidity Index, and activities of daily living). [d]Model 4 was adjusted for GCS, rewarming with ECMO, 5A score, body temperature, heart rate, and blood gas analysis results at the ED (e.g., K and lactate levels). The subgroup analysis was adjusted for age, GCS score, SBP, and rewarming with ECMO. The confounders used for subgrouping were excluded from the subgroup analysis. Early phase of rewarming was defined as the time from arrival at the ED to achieving a body temperature of 33°C. Causes of hypothermia were categorized as internal, external, others, and unknown. 5A score, based on age, activities of daily living, arrest, acidemia, and albumin, predicts mortality after accidental hypothermia. Our dataset lacked albumin data, so the 5A score was modified to exclude albumin from its calculation. Severe hypothermia was defined as a body temperature on arrival at the ED less than 28°C. Moderate hypothermia was defined as a body temperature on arrival at the ED greater than or equal to 28°C and less than 32°C. A favorable neurologic outcome was defined as Cerebral Performance Category score of 1–2 at discharge. OR = odds ratio.

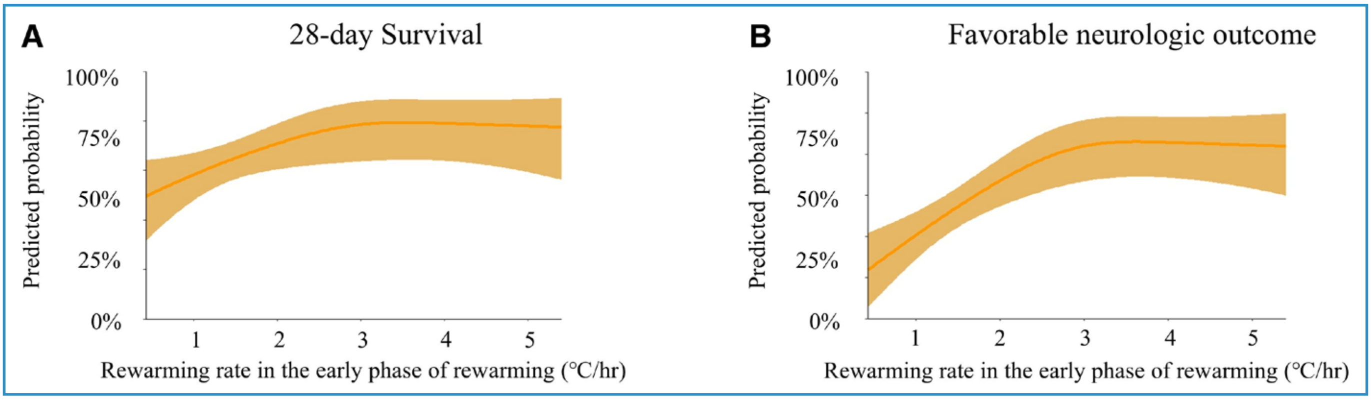


Figure 3. Rewarming rate in the early phase of rewarming (°C/hr) and probability of 28-d survival and favorable neurologic outcomes at discharge. Cubic spline regression modeling of estimated probability (with 95% CI) of survival and favorable neurologic outcomes according to the rewarming rate. Early phase of rewarming was defined as the time from arrival at the emergency department (ED) to body temperature of 33°C. The rewarming rate was calculated as the rate of increase in body temperature to 33°C on arrival at the ED. A favorable neurologic outcome was defined as Cerebral Performance Category score of 1–2 at discharge.

significantly up to 3°C/hr, but when the rewarming rate exceeded 3°C/hr, the predicted probability of each outcome was almost constant. Considering the side effects of rapid rewarming, when the rewarming rate exceeded a threshold, the advantages of fast rewarming may be limited, that is, the disadvantages of fast rewarming might appear. Further studies are required to determine the optimal rewarming rate.

The current study included patients with a median age of 81 years, and most of them were found indoors (79.2%). This study was conducted in Japan, where the population is rapidly aging, and the targeted population was older than that in many other countries (35). In addition, compared with previous studies from other countries, the proportion of patients found indoors and those with hypothermia caused by endogenous diseases was higher in this study (36, 37). This suggests that our dataset included several patients with secondary accidental hypothermia, which may have contributed to the higher mortality rates. Therefore, our findings, that is, early rewarming, might easily affect mortality. To account for this, we performed a sensitivity analysis considering the location of accidental hypothermia and patient characteristics. The association between rewarming rate and outcome remained significant. However, country-specific factors may have influenced the results. Owing to a limited number of cases, we were unable to conduct subgroup analyses focusing on younger patients or those with primary hypothermia occurring outdoors. Thus, direct generalization of our results to the entire accidental hypothermia population may be hard. Therefore, external validation of effect of early phase of rewarming in different populations is warranted.

The type of rewarming procedure and rewarming rate were determined at the discretion of the attending physician, given the observational nature of the study, which might have introduced selection bias. ECMO may have influenced the outcomes (7). In this study, 71.4% of patients who underwent rewarming with ECMO exhibited circulatory instability, and 86.2% of these patients had severe hypothermia. Thus, ECMO should be considered for patients with severe hypothermia. However, some key data, such as the reasons for ECMO use, timing, and vital signs before ECMO initiation, were unavailable, which is a major limitation. To reduce the impact of ECMO on the outcomes, we performed multivariable analysis adjusted for ECMO use and a subgroup analysis limited to patients who were rewarmed without ECMO. Despite these efforts, further research focusing on ECMO-treated patients is warranted. There was no evidence of a significant association between other rewarming procedures and outcomes (38). However, the selection of rewarming procedures may have also introduced bias. Therefore, we conducted another analysis on rewarming procedures, but we could not examine the detailed effects of other rewarming methods on outcomes due to the small sample size.

Our findings suggest that rapid passage of the early phase of rewarming is important for rewarming, and its effect may depend on the severity of hypothermia. Clinically, considering the adverse effects of rapid rewarming, it is important to closely monitor hemodynamic and blood gas data and minimize the systemic effects of hypothermia and complications associated with rewarming (3, 39–41). Further research is needed to determine whether rewarming strategies with phase classification are effective and to identify the optimal rewarming rate threshold using a larger sample size.

This study had several limitations. First, several system-related factors, such as the rewarming protocol (including targeted temperature) and ICU management, could have confounded the results. Unfortunately, these factors could not be analyzed due to the lack of data. If the targeted BT varied between institutions, the definition of early rewarming might also have differed. Furthermore, there was no significant difference between rewarming rate and each institution, which were divided into five groups based on experience patient's number. Furthermore, GEE analysis and the fixed-effect model within hospitals involved could be performed to minimize the differences in rewarming strategies and ICU management between institutions. However, the results should be interpreted with caution. Additionally, decisions regarding the restriction of treatment, such as withdrawal or withholding of care, were made through discussions between the physician and the patients' family, in accordance with institutional policies, which could have affected the outcomes. Second, a significant proportion of patients (21.8%) had accidental hypothermia of unknown cause. Furthermore, the neurologic status before the onset of accidental hypothermia was not confirmed. To reduce this potential bias, we conducted another sensitivity analysis that considered the effect of the causes of hypothermia and patient characteristics, such as CCI and ADL. Third, the rewarming rate was calculated using three points such as arrival at the ED, reaching 33°C, and 36°C only; thus, other set points of the phase could not be examined. Fourth, the dataset did not include continuous or detail vital sign and hemodynamic parameters, such as cardiac output, blood pressure, heart rate, GCS, echocardiogram findings, blood gas data, and urine output, before or during rewarming. Although, we attempted to reduce these factors using several models, we could not examine the detailed association between hemodynamic status and the rewarming rate. Despite these limitations, we believe that our findings provide valuable data on the rewarming rate of accidental hypothermia in a multicenter cohort.

CONCLUSIONS

We examined the management of rewarming during accidental hypothermia and classified the phase based on the targeted BT. In the early phase of rewarming, the rewarming rate was associated with survival and favorable neurologic outcomes. Furthermore, according to our data on survival and neurologic outcomes, a rewarming rate of approximately 3°C/hr may be more reasonable. This association was particularly observed in the severe hypothermia group. This result could help in the management of rewarming in accidental hypothermia. Further prospective and larger studies are warranted to clarify the optimal rewarming rates and targeted BT for accidental hypothermia.

ACKNOWLEDGMENTS

We are deeply indebted to all members of the Intensive Care with ExtraCorporeal membrane oxygenation Rewarming in Accidentally Severe Hypothermia (ICE-CRASH) study group for their contribution.

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Drs. Hara and Taira contributed equally to this work.

Dr. Ijuin received support for article research from the National Institutes of Health. The remaining authors have disclosed that they do not have any potential conflicts of interest.

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REFERENCES

1. 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; 37:565–570
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; 81:1550–1555
3. Polderman KH: Mechanisms of action, physiological effects, and complications of hypothermia. *Crit Care Med* 2009; 37:S186–S202
4. Paal P, Pasquier M, Darocha T, et al: Accidental hypothermia: 2021 update. *Int J Environ Res Public Health* 2022; 19:501
5. Brown DJ, Brugger H, Boyd J, et al: Accidental hypothermia. *N Engl J Med* 2012; 367:1930–1938
6. Zafren K, Giesbrecht GG, Danzl DF, et al; Wilderness Medical Society: Wilderness Medical Society practice guidelines for the out-of-hospital evaluation and treatment of accidental hypothermia: 2014 update. *Wilderness Environ Med* 2014; 25:S66–S85
7. Prekker ME, Rischall M, Carlson M, et al: Extracorporeal membrane oxygenation versus conventional rewarming for severe hypothermia in an urban emergency department. *Acad Emerg Med* 2023; 30:6–15
8. Morita S, Inokuchi S, Yamagiwa T, et al: Efficacy of portable and percutaneous cardiopulmonary bypass rewarming versus that of conventional internal rewarming for patients with accidental deep hypothermia. *Crit Care Med* 2011; 39:1064–1068
9. Lott C, Truhlář A, Alfonzo A, et al; ERC Special Circumstances Writing Group Collaborators: European Resuscitation Council Guidelines 2021: Cardiac arrest in special circumstances. *Resuscitation* 2021; 161:152–219
10. Musi ME, Sheets A, Zafren K, et al: Clinical staging of accidental hypothermia: The Revised Swiss System: Recommendation of the International Commission for Mountain Emergency Medicine (ICAR MedCom). *Resuscitation* 2021; 162:182–187
11. Dow J, Giesbrecht GG, Danzl DF, et al: Wilderness Medical Society clinical practice guidelines for the out-of-hospital evaluation and treatment of accidental hypothermia: 2019 update. *Wilderness Environ Med* 2019; 30:S47–S69
12. Saczkowski R, Kuzak N, Grunau B, et al: Extracorporeal life support rewarming rate is associated with survival with good neurological outcome in accidental hypothermia. *Eur J Cardiothorac Surg* 2021; 59:593–600
13. Watanabe M, Matsuyama T, Morita S, et al: Impact of rewarming rate on the mortality of patients with accidental hypothermia: Analysis of data from the J-Point registry. *Scand J Trauma Resusc Emerg Med* 2019; 27:105
14. Austin MA, Maynes EJ, O'Malley TJ, et al: Outcomes of extracorporeal life support use in accidental hypothermia: A systematic review. *Ann Thorac Surg* 2020; 110:1926–1932
15. Paal P, Gordon L, Strapazzon G, et al: Accidental hypothermia-an update: The content of this review is endorsed by the International Commission for Mountain Emergency Medicine (ICAR MEDCOM). *Scand J Trauma Resusc Emerg Med* 2016; 24:111
16. 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

17. Dankiewicz J, Cronberg T, Lilja G, et al; TTM2 Trial Investigators: Hypothermia versus normothermia after out-of-hospital cardiac arrest. *N Engl J Med* 2021; 384:2283–2294
18. Lascarrou JB, Merdji H, Le Gouge A, et al; CRICS-TRIGGERSEP Group: Targeted temperature management for cardiac arrest with nonshockable rhythm. *N Engl J Med* 2019; 381:2327–2337
19. Cho E, Lee SE, Park E, et al: Pilot study on a rewarming rate of 0.15°C/hr versus 0.25°C/hr and outcomes in post cardiac arrest patients. *Clin Exp Emerg Med* 2019; 6:25–30
20. Cummins RO, Chamberlain DA, Abramson NS, et al: Recommended guidelines for uniform reporting of data from out-of-hospital cardiac arrest: The Utstein Style. A statement for health professionals from a task force of the American Heart Association, the European Resuscitation Council, the Heart and Stroke Foundation of Canada, and the Australian Resuscitation Council. *Circulation* 1991; 84:960–975
21. 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:e694
22. Vassal T, Benoit-Gonin B, Carrat F, et al: Severe accidental hypothermia treated in an ICU: Prognosis and outcome. *Chest* 2001; 120:1998–2003
23. Harrell FE: *Regression Modeling Strategies: With Applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis*. Cham, Switzerland, Springer International Publishing, 2015
24. VanderWeele TJ, Shpitser I: A new criterion for confounder selection. *Biometrics* 2011; 67:1406–1413
25. Cappaert TA, Stone JA, Castellani JW, et al; National Athletic Trainers' Association: National Athletic Trainers' Association position statement: Environmental cold injuries. *J Athl Train* 2008; 43:640–658
26. Mallet ML: Pathophysiology of accidental hypothermia. *QJM* 2002; 95:775–785
27. Fernando SM, Di Santo P, Sadeghirad B, et al: Targeted temperature management following out-of-hospital cardiac arrest: A systematic review and network meta-analysis of temperature targets. *Intensive Care Med* 2021; 47:1078–1088
28. Kim JJ, Yang HJ, Lim YS, et al: Effectiveness of each target body temperature during therapeutic hypothermia after cardiac arrest. *Am J Emerg Med* 2011; 29:148–154
29. Greeley WJ, Kern FH, Meliones JN, et al: Effect of deep hypothermia and circulatory arrest on cerebral blood flow and metabolism. *Ann Thorac Surg* 1993; 56:1464–1466
30. Rees K, Beranek-Stanley M, Burke M, et al: Hypothermia to reduce neurological damage following coronary artery bypass surgery. *Cochrane Database Syst Rev* 2001; 2001:CD002138
31. Bor-Seng-Shu E, Kita WS, Figueiredo EG, et al: Cerebral hemodynamics: Concepts of clinical importance. *Arq Neuropsiquiatr* 2012; 70:352–356
32. Engelman R, Baker RA, Likosky DS, et al; Society of Thoracic Surgeons: The Society of Thoracic Surgeons, The Society of Cardiovascular Anesthesiologists, and The American Society of ExtraCorporeal Technology: Clinical practice guidelines for cardiopulmonary bypass—temperature management during cardiopulmonary bypass. *Ann Thorac Surg* 2015; 100:748–757
33. Kawahara F, Kadoi Y, Saito S, et al: Slow rewarming improves jugular venous oxygen saturation during rewarming. *Acta Anaesthesiol Scand* 2003; 47:419–424
34. Grigore AM, Grocott HP, Mathew JP, et al; Neurologic Outcome Research Group of the Duke Heart Center: The rewarming rate and increased peak temperature alter neurocognitive outcome after cardiac surgery. *Anesth Analg* 2002; 94:4–10, table of contents
35. Weuster M, Brück A, Lippross S, et al; TraumaRegister DGU: Epidemiology of accidental hypothermia in polytrauma patients: An analysis of 15,230 patients of the TraumaRegister DGU. *J Trauma Acute Care Surg* 2016; 81:905–912
36. Petrone P, Marini CP, Miller I, et al: Factors associated with severity of accidental hypothermia: A cohort retrospective multi-institutional study. *Ann Med Surg (Lond)* 2020; 55:81–83
37. Kosiński S, Darocha T, Gałązkowski R, et al: Accidental hypothermia in Poland—estimation of prevalence, diagnostic methods and treatment. *Scand J Trauma Resusc Emerg Med* 2015; 23:13
38. Sugiyama K, Nomura O, Irie J, et al: Effects of rewarming therapies on outcomes in accidental hypothermia: A secondary analysis of a multicenter prospective study. *Am J Emerg Med* 2024; 79:91–96
39. Lu X, Ma L, Sun S, et al: The effects of the rate of postresuscitation rewarming following hypothermia on outcomes of cardiopulmonary resuscitation in a rat model. *Crit Care Med* 2014; 42:e106–e113
40. Choi R, Andres RH, Steinberg GK, et al: Intraoperative hypothermia during vascular neurosurgical procedures. *Neurosurg Focus* 2009; 26:E24
41. Matsushita Y, Bramlett HM, Alonso O, et al: Posttraumatic hypothermia is neuroprotective in a model of traumatic brain injury complicated by a secondary hypoxic insult. *Crit Care Med* 2001; 29:2060–2066