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Original Contribution

Prognostic factors for patients with accidental hypothermia: A multi-institutional retrospective cohort study

Yohei Okada [a,*], Tasuku Matsuyama [b], Sachiko Morita [c], Naoki Ehara [d], Nobuhiro Miyamae [e], Takaaki Jo [f], Yasuyuki Sumida [g], Nobunaga Okada [b,h], Tetsuhisa Kitamura [i], Ryoji Iiduka [a]

[a] Department of Emergency and Critical Care Medicine, Japanese Red Cross Society Kyoto Daini Red Cross Hospital, Japan
[b] Department of Emergency Medicine, Kyoto Prefectural University of Medicine, Kyoto, Japan
[c] Senri Critical Care Medical Center, SaiseikaiSenri Hospital, Suita, Japan
[d] Department of Emergency, Japanese Red Cross Society Kyoto Daiichi Red Cross Hospital, Kyoto, Japan
[e] Department of Emergency Medicine, Rakuwa-kai Otowa Hospital, Kyoto, Japan
[f] Department of Emergency Medicine, Uji-Tokushukai Medical Center, Uji, Japan
[g] Department of Emergency Medicine, North Medical Center, Kyoto Prefectural University of Medicine, Japan
[h] Department of Emergency and Critical Care Medicine, National Hospital Organization, Kyoto Medical Center, Kyoto, Japan
[i] Division of Environmental Medicine and Population Sciences, Department of Social and Environmental Medicine, Graduate School of Medicine, Osaka University, Japan

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ABSTRACT

Introduction: In cases of severe accidental hypothermia (AH) in urban areas, the prognostic factors are unknown. We identified factors associated with in-hospital mortality in patients with moderate-to-severe AH in urban areas of Japan.

Method: The J-Point registry database is a multi-institutional retrospective cohort study for AH in 12 Japanese emergency departments. From this registry, we enrolled patients whose core body temperature was 32 °C or less on admission. In-hospital death was the primary outcome of this study. We investigated the association between each candidate prognostic factor and in-hospital death by applying the multivariate logistic regression analyses with adjusted odds ratios (AORs) and their 95% confidence interval [CI] as the effect variables.

Results: Of 572 patients registered in the J-point registry, 358 hypothermic patients were eligible for analyses. Median body temperature was 29.2 °C (interquartile range, 27.0 °C–30.8 °C). In-hospital deaths comprised 26.3% (94/358) of all study patients. Factors associated with in-hospital death were age ≥ 75 years (AOR, 3.09; 95% CI, 1.31–7.27), need for assistance with activities of daily living (ADL; AOR, 3.06; 95% CI, 1.68–5.59), hemodynamic instability (AOR, 2.49; 95% CI, 1.32–4.68), and hyperkalemia (≥5.6 mEq/L; AOR, 2.65; 95% CI, 1.13–6.21).

Conclusion: The independent prognostic factors associated with in-hospital mortality of patients with moderate-to-severe AH in urban areas of Japan were age ≥ 75 years, need for assistance with ADL, hemodynamic instability, and hyperkalemia.

1. Introduction

Unintentional decrease in body temperature to 35 °C or less is defined as accidental hypothermia (AH) [1]. High risks of sudden cardiac arrest and consecutively high mortality rates are associated with especially severe hypothermia (body core temperature ≤ 28 °C) [1]. Because extracorporeal resuscitation and rewarming reportedly improve the prognosis for AH patients, those with moderate-to-severe AH (body core temperature ≤ 32 °C) should be transferred to institutions capable of these interventions [1]. However, these interventions are very invasive and require costly medical and human resources [2]. Without an immediate prediction of prognosis in moderate-to-severe AH cases, it is impossible to judge the appropriate indication for extracorporeal resuscitation.

Certain prognostic factors in AH, such as hyperkalemia, pH, and hemodynamic instability, already have been investigated [3-18]. However, because these studies enrolled victims in specific situations, such as those experiencing mountain accidents or receiving extracorporeal membrane oxygenation (ECMO), the population included in these studies comprised mostly only the young generation and included only a few study patients [3-18]. On the other hand, the main victims of AH in the urban areas of developed countries were geriatric patients, found mostly in indoor settings [7, 19]. Little is known about the

* Corresponding author at: Department of Emergency and Critical Care Medicine, Japanese Red Cross Society Kyoto Daini Red Cross Hospital, Kamigyo-ku, Kyoto 602-8036, Japan.
E-mail address: okadayohei1127@yahoo.co.jp (Y. Okada).

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prognostic factors for AH in urban areas. Therefore, we identified, at admission, factors associated with in-hospital mortality in patients with moderate-to-severe AH in urban areas of Japan.

2. Methods

2.1. Study design and setting

We obtained epidemiologic information on cases of AH and their management at Japanese emergency departments by analyzing the Japanese AH network registry (J-Point registry) database, a multi-institutional retrospective cohort study. We retrospectively identified eligible patients using the International Classification of Diseases, Tenth Revision (ICD-10) code for T68 “Hypothermia” between April 1, 2011 and March 31, 2016, at eight Critical Care Medical Centers (CCMCs) and four non-CCMCs with departments for emergency treatments in the Kyoto, Osaka, and Shiga Prefectures in Japan. Median annual emergency department (ED) visit volume for participating institutions was 19,651 (interquartile range [IQR], 13,281–27,554). Those whose body temperature was unknown or > 35.0 °C, and those who refused or whose family members explicitly refused permission to be part of the registry were excluded from the registry. Registry data were collected by emergency physicians using a predefined uniform data sheet. The collected data were checked by the J-Point registry working group, and either confirmed or returned to each institution if there was any concern regarding their veracity. The ethics committee of each institution approved this study protocol.

2.2. Study patients

Patients whose core body temperature was 32 °C or less at admission from the J-point registry were included in our study, whereas those who were transferred from other hospitals and, therefore, whose body temperature was unknown were excluded.

2.3. Data collection

We collected from the registry baseline patient characteristics of sex, age, activities of daily living (ADL) before hypothermia (degree of independence and need for assistance), and a comprehensive past medical history, including cardiovascular diseases (ischemic heart diseases, heart failure, arrhythmia, hypertension, and other cardiovascular diseases), neurological diseases (stroke, epilepsy, Parkinson diseases or syndrome, and other neurological diseases), endocrine diseases (diabetes mellitus, thyroid diseases, adrenal insufficiency, and other endocrine diseases), psychiatric diseases (chronic alcoholism, depression, schizophrenia, and other psychiatric diseases), malignant diseases, dementia, and others.

Regarding in-hospital measurements, data collected included vital signs at hospital arrival (core body temperature [BT], systolic blood pressure [SBP], heart rate [HR], and Glasgow [GCS] and Japan [JCS] Coma Scales), biological data (serum pH and potassium [mEq/L]), external and minimally invasive rewarming methods (warm intravenous fluid, forced warm air, warm blanket, and others), active internal rewarming (lavage, intravascular rewarming device, and Veno-Venous and Veno-Arterial ECMO, and outcome).

2.4. Outcome measurements

In this study, the primary outcome was in-hospital death.

2.5. Statistical analysis

We divided the patient into two groups: survival-to-hospital discharge and in-hospital mortality groups. Patient characteristics and in-hospital information between the two groups were evaluated using the Wilcoxon signed-rank test for numeric variables and Pearson's χ^2 test for categorical variables. The association between each category of severity and in-hospital mortality was investigated by applying univariate and multivariate logistic regression analyses with adjusted odds ratios (AORs) and their 95% confidence interval (CI) as the effect variables. Basing our selection on previous studies on AH, we considered the potential confounders in multivariable models associated with in-hospital mortality to include age category (≤64, 65–74, and ≥75 years), sex (men or women), past medical history (yes or no), ADL (independent or in need of assistance), hemodynamic instability (unstable: cardiac arrest, SBP unmeasurable, SBP ≤ 60 mm Hg and HR ≤ 40 beats per minute [bpm]; or stable: other than those aforementioned), BT category (moderate, 32 °C–28.1 °C; severe, 28 °C–24.1 °C or profound, ≤24.0 °C), impaired consciousness category (mild, GCS 13–GCS 15; moderate, GCS 9–GCS 12; or severe, GCS ≤ 8), serum pH category (normal, pH ≥ 7.36; moderate acidemia, pH 7.21–pH 7.35; severe acidemia, pH ≤ 7.20 or unknown), and serum potassium category (hypokalemia, K ≤ 3.4 mEq/L; normal, 3.5–5.5 mEq/L, or hyperkalemia, ≥5.6 mEq/L). For each confounder, we defined these categories based on the normal limit, and we defined the temperature category based on the Swiss hypothermia grading scale. In the past medical history

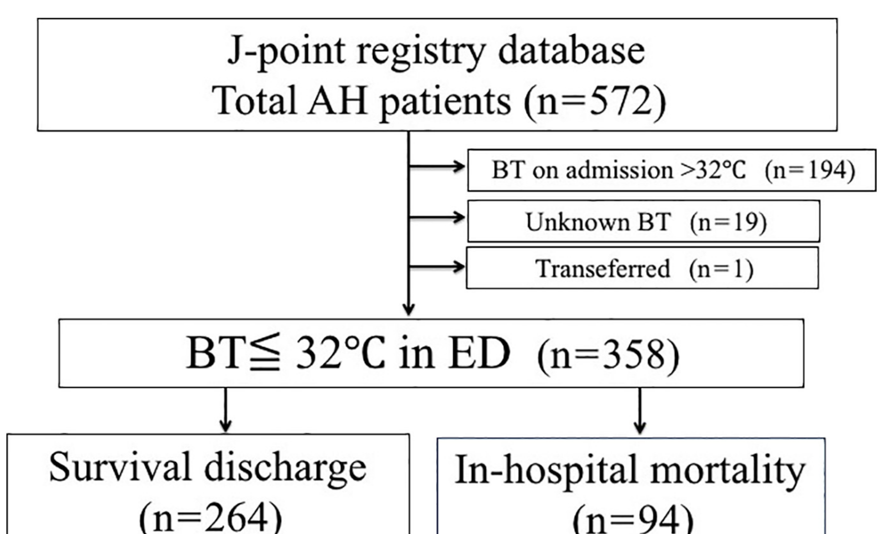

Fig. 1. Study flowchart. AH, accidental hypothermia; BT, body temperature; ED, emergency department.

Table 1
Patient characteristics.

	Total patients		Survival discharge		In-hospital death		p value[a]
	(n = 358)		(n = 264)		(n = 94)		
Male, n, (%)	184	(51.4)	132	(50.0)	52	(55.3)	0.38
Age, y	79	(67.8–87.3)	77.5	(65.3–87)	82	(75–88)	0.003
Median (IQR)							
Age category, n, (%)							
<65 years	73	(20.4)	64	(24.2)	9	(9.6)	
65–74	59	(16.5)	46	(17.4	13	(13.8)	
>75	226	(63.1)	154	(58.3)	72	(76.6)	
Activities of daily living, n, (%)							<0.001
Need for assist	112	(31.3)	69	(26.1)	43	(45.7)	
Pastmedical history, n, (%)	289	(80.7)	211	(79.9)	78	(83.0)	0.37
Cardiovascular	151	(42.2)	108	(40.9)	43	(45.7)	0.41
Neurological	66	(18.4)	51	(19.3)	15	(16.0)	0.47
Endocrine	80	(22.3)	60	(22.7)	20	(21.3)	0.77
Psychiatric	82	(22.9)	70	(26.5)	12	(12.8)	0.006
Malignant	40	(11.2)	29	(11.0)	11	(11.7)	0.84
Dementia	69	(19.3)	43	(16.3)	26	(27.7)	0.02
Other	72	(20.1)	52	(19.7)	20	(21.3)	0.74
Unknown	4	(1.1)	2	(0.8)	2	(2.1)	0.28

[a] Comparison between the 2 groups were evaluated with Wilcoxon signed-rank test for numeric variables and Pearson's X^2 test for categorical variables.

category, "yes" means patients who have the past medical history described in the characteristics, and "no" means patients who have no past medical history. We compensated for the lack of GCS score with the JCS score, because it was convertible to the GCS score [20] and was demonstrated to correlate with GCS categories in this registry by multiple linear regression analysis (data not shown). Two-sided P values < 0.05 were considered statistically significant. For all statistical analyses, we used the JMP® 13 (SAS Institute Inc., Cary, NC, USA).

3. Results

Of 572 hypothermic patients registered in the database, we excluded 194 whose BT was >32.0 °C, 19 with an unknown BT at admission, and one who was transferred from another hospital. This left 358 hypothermic patients whose BT was ≤32 °C available for analysis: 264 (73.7%) in the survival-to-hospital discharge group and 94 (26.3%) in the in-hospital death group (Fig. 1).

3.1. Patient characteristics

Approximately half of the patients were male (51.4%) and median age was 79 years (IQR, 67.8–87.3 years). The in-hospital death group included older patients and a higher proportion of patients needing assistance with ADL than the survival-to-hospital discharge group. The proportion of patients with a past medical history of psychiatric disease was lower, and that of patients with dementia was higher in the in-hospital death than in the survival-to-hospital discharge groups. No other characteristics were significantly different between the two groups (Table 1).

3.2. In-hospital data

Median BT was 29.2 °C (IQR, 27.0 °C–30.8 °C). A higher proportion of patients in the in-hospital death group were hemodynamically unstable and had an impaired consciousness level, acidemia, and hyperkalemia than those in the survival-to-hospital discharge group (Table 2). On the other hand, no significant difference in BT was found between the

Table 2
Vital signs and laboratory data on admission.

	All patients		Missing		Survival discharge		In-hospital death		p value[a]
	(n = 358)		(n, %)		(n = 264)		(n = 94)		
Heart rate (bpm) category			3	(0.8)					<0.001
≥60, n, (%)	183	(51.5)			147	(56.3)	36	(38.3)	
41–59	95	(26.8)			68	(26.1)	27	(28.7)	
≤40	61	(17.2)			40	(15.3)	21	(22.3)	
Systolic blood pressure (mm Hg) category			0						<0.001
≥90, n, (%)	236	(66)			188	(71.2)	48	(51.1)	
61–90	60	(16.8)			47	(17.8)	13	(13.8)	
≤60, unmeasurable	46	(12.8)			23	(8.7)	23	(24.5)	
Cardiac arrest	16	(4.5)			6	(2.3)	10	(10.6)	
Haemodynamically unstable[b], n, (%)	105	(29.3)			59	(22.4)	46	(48.9)	<0.001
Body temperature (°C), median, (IQR)	29.2	(27.0–30.8)	0		29.2	(27.3–30.9)	29.2	(26.2–30.7)	0.32
Body temperature category									0.56
32–28.1, n, (%)	229	(64.0)			173	(65.5)	56	(59.6)	
28–24.1	107	(29.9)			76	(28.8)	31	(33.0)	
≤24	22	(6.1)			15	(5.7)	7	(7.5)	
Glasgow coma scale, median, (IQR)	10	(7–13)	6	(1.7)	11	(8–13)	8	(3—11)	<0.001
Glasgow coma scale category									0.002
15–13, n, (%)	103	(29.3)			89	(34.4)	14	(15.2)	
12–9	124	(35.3)			93	(35.9)	31	(33.7)	
<9	124	(35.3)			77	(29.7)	47	(51.1)	
Serum pH, median, (IQR)	7.29	(7.20–7.35)	34	(9.5)	7.30	(7.24–7.35)	7.25	(7.06–7.33)	0.002
Serum pH category									<0.001
>7.35, n, (%)	80	(22.3)			63	(23.9)	17	(18.1)	
7.35–7.20	163	(45.5)			129	(48.9)	34	(36.2)	
<7.20	81	(22.6)			43	(16.3)	38	(40.4)	
Unknown	34	(9.5)			29	(11.0)	5	(5.3)	
Serum K^+ (mEq/l), median, (IQR)	4.1	(3.6–4.8)	4	(1.1)	4.0	(3.5–4.6)	4.5	(3.7–5.6)	<0.001
Serum K^+ (mEq/l) category									<0.001
<3.5, n, (%)	78	(22.0)			61	(23.2)	17	(18.7)	
3.5–5.5	236	(66.7)			185	(70.3)	51	(56.0)	
>5.5	40	(11.3)			17	(6.5)	23	(25.3)	

[a] Comparisons between the 2 groups were evaluated with Wilcoxon signed-rank test for numeric variables and Pearson's X2 test for categorical variables.
[b] Haemodynamically unstable: (HR ≤ 40 bpm, SBP ≤ 60 mm Hg, or cardiac arrest).

Table 3
Rewarming method.

Rewarming method	All patients (n = 358)		Survival discharge (n = 264)		In-hospital death (n = 94)		p value[a]
External and minimally invasive rewarming							
Warm intravenous fluid, n, (%)	274	(76.5)	207	(78.4)	67	(71.3)	0.16
Forced warm air	71	(19.8)	50	(18.9)	21	(22.3)	0.48
Warm blanket	247	(69.0)	186	(70.5)	61	(64.9)	0.32
Other	31	(8.7)	25	(9.5)	6	(6.4)	0.36
Active internal rewarming							
Lavage[b], n, (%)	39	(10.9)	26	(9.9)	13	(13.8)	0.29
Intravascular	3	(0.8)	2	(0.8)	1	(1.1)	NA
Hemodialysis	21	(5.9)	16	(6.1)	5	(5.3)	0.79
VV-ECMO	2	(0.6)	2	(0.8)	0	(0)	NA
VA-ECMO	18	(5.0)	9	(3.4)	9	(9.6)	0.02

VV-ECMO: Veno-venous Extracorporeal membrane oxygenation.
VA-ECMO: Veno-arterial Extracorporeal membrane oxygenation.
[a] Comparison between the 2 groups were evaluated with Pearson's X^2 test for categorical variables.
[b] Lavage: stomach, chest, bladder.

two groups. Regarding rewarming methods, fewer patients in the in-hospital death group were treated with V-A ECMO (3.4% vs. 9.6%, $P = 0.02$); no further differences were observed between the two groups (Table 3).

3.3. Outcome

The overall proportion of in-hospital death (primary outcome) was 26.3% (94/358). Multivariate logistic regression analysis showed that the factors independently associated with in-hospital death were age ≥ 75 years (AOR, 3.09; 95% CI, 1.31–7.27), need for assistance with ADL (AOR, 3.06; 95% CI, 1.68–5.59), hemodynamic instability (AOR, 2.49; 95% CI, 1.32–4.68), and hyperkalemia (≥5.6 mEq/L; AOR, 2.65; 95% CI, 1.13–6.21; Fig. 2).

4. Discussion

To the best of our knowledge, this study of moderate-to-severe AH in urban populations not only was the first multi-institutional study to assess the prognostic factors of moderate-to-severe AH victims over several years by multivariable analysis, but also one of the largest studies of AH in the world. We highlighted the fact that our findings are more applicable than those in previous literature to patients transported to EDs because of AH specifically in urban areas of developed countries.

One strength of our study is its population and sample size. Previous studies investigating prognostic factors in AH were concerned mostly with a young generation treated with extracorporeal rewarming or those performing outdoor activities involving avalanches, climbing, and submersion (Table 4) [3-19]. On the other hand, in urban areas with super-aging societies, AH patients generally presenting to EDs are geriatric, and their AH occurs mostly in indoor settings [7, 19]. Therefore, the

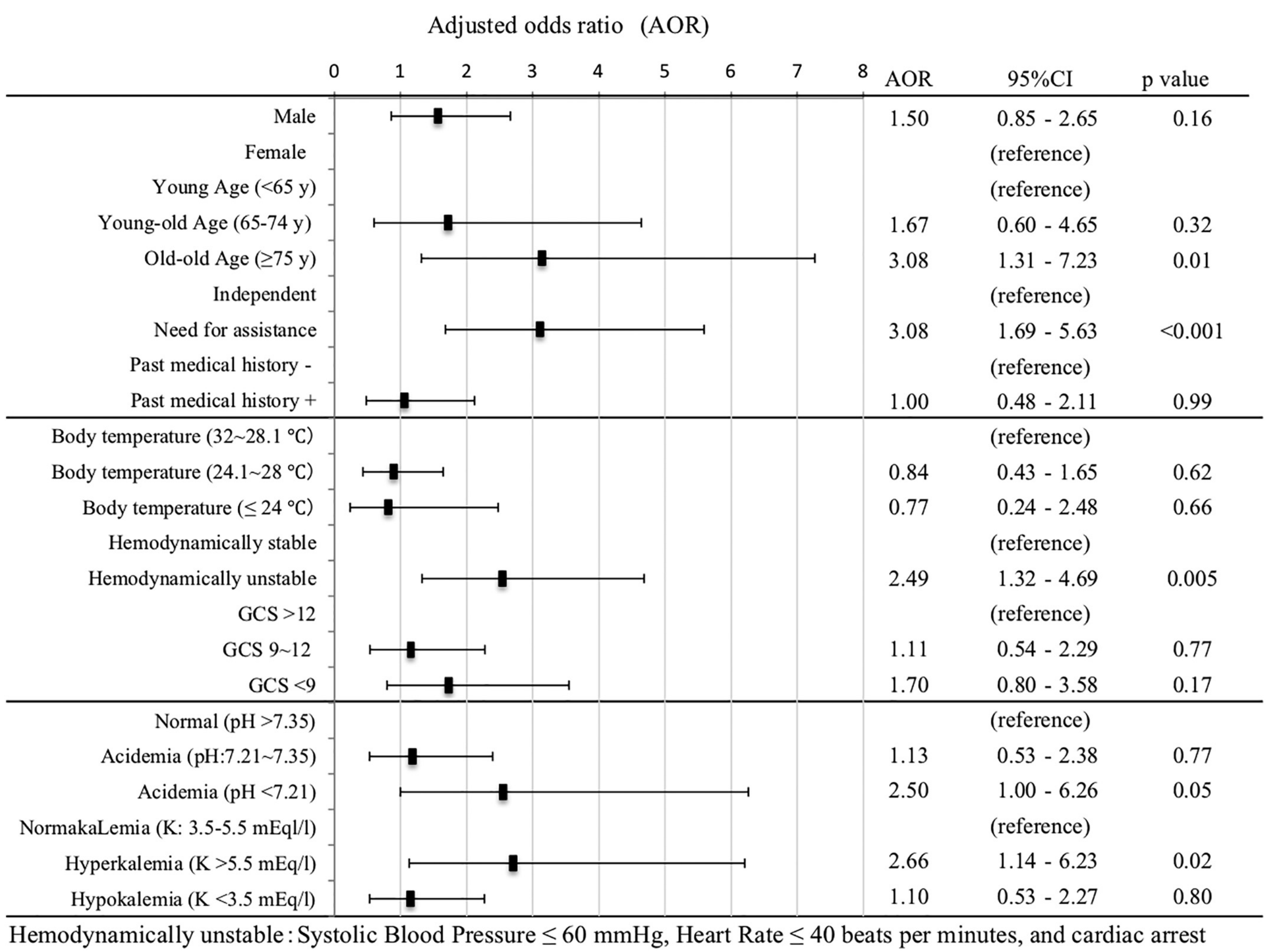

Fig. 2. Multivariate logistic regression analysis demonstrated that the factors associated with in-hospital death were age ≥ 75 years (AOR, 3.09; 95% CI, 1.31–7.27), need for assistance with ADL (AOR, 3.06; 95% CI, 1.68–5.59), hemodynamic instability (AOR, 2.49; 95% CI, 1.32–4.68), and hyperkalemia (≥5.6 mEq/L; AOR, 2.65; 95% CI, 1.13–6.21).

applicability of previous studies to patients with AH in urban settings was in doubt. Moreover, in similar previous studies, the number of study patients was limited, and almost all studies used only univariate analysis (Table 4). Therefore, the possibility exists that a major confounder might have influenced the prognostic factors reported. A few reports used multivariate analysis [6, 7, 10, 13], but these analyses also included a limited number of patients, which might have led to overfitting. Our study well represents general AH patients of urban areas in developed countries, and our results will be useful for aging societies.

We demonstrated age ≥ 75 years and disturbance of ADL as prognostic factors. These populations were thought to be particularly vulnerable to AH, because of malnutrition, hypoactivity, and a decrease in muscle and fat [21]. Moreover, in emergency and critical care, age, frailty, and disturbance of ADL are well-known prognostic factors for in-hospital death [22,23]. Similarly, we judged these factors to be valid as prognostic factors for AH.

A hemodynamic instability, including unmeasurable SBP, SBP ≤ 60 mm Hg, HR ≤ 40 bpm, and cardiac arrest also were identified as prognostic factors. Generally, hypothermia provokes hypotension, bradycardia, arrhythmia, and cardiac arrest, with the disturbance of organ perfusion apparently causing organ failure and death. Thus, for patients with hypothermia and cardiac instability who are unresponsive to medical management, ECMO should be recommended [24]. Therefore, hemodynamic instability could be an important prognostic factor.

We also indicated hyperkalemia as an independent factor associated with in-hospital mortality. Many reports cite hyperkalemia as the main prognostic factor [3, 5, 6, 9, 13, 15, 16], and treatment guidelines have described it as an indicator to withdraw resuscitation [23]. Hypothermia may cause hypokalemia and hyperkalemia [5]. Hypokalemia was observed particularly in cases of therapeutic hypothermia, and the reported mechanism was potassium transportation into the cell or cold diuretic [24]. On the other hand, hyperkalemia may have been caused by inhibition of potassium transportation because of the disturbance to the ion channel on the cell membrane caused by hypothermia [25]. Moreover, it also was caused by organ hypoperfusion and dysfunction due to hemodynamic instability brought about by hypothermia [25]. Based on these mechanisms, hyperkalemia may reasonably be well associated with in-hospital death.

BT and pH were not demonstrated to be factors associated with in-hospital death. A previous study also did not report BT as a prognostic factor [7]. The exact mechanism was unclear, but according to one plausible explanation, the oxygen consumption of each organ might be decreased by severe hypothermia even in an unstable hemodynamic state, and this decrease could buy time, delaying organ failure. Guided by multivariate analysis, we also did not select pH as a factor. Serum pH, like serum potassium, apparently resulted from hypoperfusion and organ failure and was reported to be associated with prognosis by univariate analysis. However, in these studies, patients with severe acidemia (<pH 7.0 or <pH 6.8) were mostly avalanche victims or people suspected of asphyxiation [5, 6, 9, 11, 12, 15, 16]. These acidemia cases were related to hypoxia and respiratory acidosis caused by sudden airway obstruction rather than hypoperfusion due to AH. Our study included no avalanche victims and only a small number of immersion patients, which may explain why serum pH was not selected.

Our findings may have important implications for the clinical care of patients with AH. For AH patients with hemodynamic instability or hyperkalemia, invasive treatment, such as V-A ECMO, or intensive care is necessary to save their lives. On the other hand, for AH patients with age ≥ 75 years and disturbance of ADL, invasive treatment is likely to be lethal; therefore, it is necessary to determine carefully the indication for invasive treatments based on their baseline characteristic and prognosis. However, because these interventions and decision were not included in our analysis, further studies are necessary for the appropriate decision.

There are some limitations of this study. The first limitation was its retrospective nature as a cohort study. Second, treatment and intervention were decided individually by each physician, allowing for the possibility that the decision might have influenced the prognosis. (For instance, old age with disturbance of ADL in a patient might have influenced the decision to perform an invasive intervention, such as extracorporeal rewarming.)

5. Conclusions

Age ≥ 75 years, need for assistance with ADL, hemodynamic instability (unmeasurable SBP, SBP ≤ 60 mm Hg, HR ≤ 40 bpm, and cardiac arrest), and hyperkalemia (K ≥ 5.6 mEq/L) were independent prognostic

Table 4
Prognostic factors which have been reported.

Factor	Settings	N	Age[a]	BT[a]	ECMO or ECC	Outdoor activity[b]	Method of analysis	Ref
K+, Ammonia, Fibrinogen	Oregon	11	15 (15–17)	7.1 (6.4–19.7)	91%	100%	Descriptive	3
No factor	Multi-city	401	53.8 ± 20.0	30.5 ± 3.5	4%	Unknown	Univariate analysis	4
pH, K+	Switzerland	24	42 (27–50.5)	29.2 (27–31.2)	25%	63%	Univariate analysis	5
pH, K+, ACT	Austria	22	25 (?-?)	24 (?-?)	100%	87%	Multivariate analysis[c]	6
Shock	France	47	61.7 ± 16	28.8 ± 2.5	Unknown	Unknown	Multivariate analysis	7
Aspyxia, CPR-time	Norway	26	26.7 (3.8–44.5)	23.3 ± 3.3	100%	69%	Univariate analysis	8
pH, PaCO2, K+	Helsinki	23	50 (37–63.5)	24.4 (22.4–26.8)	100%	48%	Univariate analysis	9
Asphyxia, ECMO	Austria	59	31 ± 18	24.5 ± 3.7	100%	49%	Multivariate analysis[c]	10
Age, BT, Lac, INR, pH, PaCO2, BE	Amsterdam	84	47 (29–63.8)	31.6 ± 2.6	1%	47%	Univariate analysis	11
Cardiac rhythm, pH, Lac, Aspyxia	Japan	26	50.5 (28.5–58.8)	24.4 (22.2–26.5)	100%	54%	Univariate analysis	12
K+	Norway	34	27.5 (?-?)	24(?-?)	100%	24%	Multivariate analysis[c]	13
Intoxication, Osborn J, Lac	Vienna	18	50 (38–64)	24 (23–26)	50%	Unknown	Univariate analysis	14
pH, Lac, Na+, K+, Cr, PT, ACT	French Alps	48	46 (26–66)	26 (24–27.2)	48%	44%	Univariate analysis	15
Sex, BT, pH, K+, CPR time	Norway	68	30 (?-?)	24 (?-?)	100%	72%	Univariate analysis	16
NSE, S100b	Denmark	34	33 (20–56)	24.6 (15.5–31.9)	79%	56%	Univariate analysis	17
HD, Organ hypo perfusion	Poland	13	60 (56–66)	25.8 (20.7–29.0)	100%	Unknown	Descriptive	18
Age, ADL, HD, K+	Multi-city	358	79 (67.8–87.3)	29.2 (27.0–30.8)	5%	2.80%	Multivariate analysis	This study

BT: body temperature, ECMO: Extracorporeal membrane oxygenation, ECC: Extra corporeal circulation, ACT: activated whole blood clotting time, INR: international normalized ratio, HD: Hemodynamic state, NSE: Neuron specific enolase, ADL: Activity of daily living, Lac: lactate, IQR: interquartile range, SD: standard deviation.
[a] Age: years old, median (IQR) or average ± SD, BT: °C, median (IQR), or average ± SD.
[b] Associated with outdoor activity: Avalanche, climbing, and submersion/immersion in the sea or river.
[c] Stepwise logistic regression analysis.

factors associated with in-hospital mortality of moderate-to-severe AH patients in urban areas of Japan. Our findings suggested that these factors may be useful to determine the indication for intensive care and invasive treatment, or withdrawal of aggressive treatment.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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