Original Article

Accidental hypothermia: characteristics, outcomes, and prognostic factors—A nationwide observational study in Japan (Hypothermia study 2018 and 2019)

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Aim: This study describes the clinical characteristics and outcomes as well as the prognostic factors of patients with accidental hypothermia (AH) using Japan's nationwide registry data.

Methods: The Hypothermia study 2018 and 2019, which included patients aged 18 years or older with a body temperature of 35°C or less, was a multicenter registry conducted at 87 and 89 institutions throughout Japan, with data collected from December 2018 to February 2019 and December 2019 to February 2020, respectively.

Results: In total, 1363 patients were enrolled in the registry, of which 1194 were analyzed in this study. The median (interquartile range) age was 79 (68–87) years, and the median (interquartile range) body temperature at the emergency department was $30.8^{\circ}C$ (28.4–33.6°C). Forty-three percent of patients with AH had a mild condition, 35.2° moderate, and 21.9° severe. AH occurred in an indoor setting in 73.4% and was caused by acute medical illness in 49.3% of patients. A total of 101 (8.5%) patients suffered from cardiopulmonary arrest on arrival at the hospital. The overall 30-day mortality rate was 24.5%, the median (interquartile range) intensive care unit stay was 4 (2–7) days, and the median (interquartile range) hospital stay was 13 (4–27) days. In the multivariable logistic analysis, the prognostic factors were age (\geq 75 years old), male, activities of daily living (needing total assistance), cause of AH (trauma, alcohol), Glasgow Coma Scale score, and potassium level (>5.5 mEq/L).

Conclusion: The mortality rate of AH was 24.5% in Japan. The prognostic factors developed in this study may be useful for the early prediction, prevention, and awareness of severe AH.

Key words: Accidental hypothermia, elderly, mortality, prehospital care, rewarming method

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INTRODUCTION

A CCIDENTAL HYPOTHERMIA (AH) is defined as a body core temperature below 35°C.¹ The prevalence of AH was recently reported to be 3.4–5.05 cases per 100,000 inhabitants per year in European countries.^{2,3} Severe AH is potentially life-threatening,^{4,5} so it is important to understand the clinical features of AH.

Previous studies^{6,7} have shown that in Japan, unlike in other countries, the occurrence of AH was high in the elderly and indoor settings, making it an important problem for a country facing an aging population. However, those studies mainly reported outcomes over a short duration⁶ or analyzed registry data limited to a small number of regions.⁷ In addition, studies regarding the prehospital management of AH are limited.^{8,9} Furthermore, with advances in technology, rewarming methods using intravascular catheters¹⁰ and extracorporeal membrane oxygenation (ECMO)^{11,12} for AH are becoming increasingly common. Nevertheless, studies on these treatments are still scarce.

To investigate these problems, we conducted a nationwide and multicenter study of patients with AH (Hypothermia study 2018 and 2019). We herein report the clinical characteristics, prehospital management, rewarming methods, and outcomes of patients with AH and explore the prognostic factors of patients with AH with the data from a Japanese nationwide observational study.

METHODS

Study setting and design

W E CONDUCTED A prospective, observational, multicenter registry of hypothermia: the Hypothermia study 2018 and 2019. This study was carried out from December 2018 to February 2019 and December 2019 to February 2020; 87 institutions participated in 2018 and 89 in 2019 from various regions in Japan.

This study was approved by the Ethics Review Board of Teikyo University Hospital, Japan (Approval No: 17-090-2). The requirement for informed consent was waived by the Ethics Review Board of Teikyo University Hospital because the study was an observational study. In addition, the review boards of each hospital listed in Appendix S1 approved this study.

Patient selection and data collection

Consecutive patients whose body temperature was below 35°C as measured by emergency medical services (EMSs) or at the emergency department (ED) were included in the

study. This study also included patients with cardiopulmonary arrest (CPA) on arrival at the hospital. We excluded patients aged <18 years. The following data were collected: age, sex, Charlson comorbidity index, Sequential Organ Failure Assessment (SOFA) score.¹³ activities of daily living (ADLs), lifestyle, location, causes underlying the hypothermia (acute medical illness, trauma [submersion, distress], alcohol intoxication, drugs), geographic information, prehospital data, temperature, Glasgow Coma Scale (GCS) score, laboratory data, blood pressure, heart rate, respiratory rate, cardiac arrest during prehospital, tracheal intubation, length of hospital stay, mortality, Cerebral Performance Category (CPC) score on day 30 after admission, and complications. The core temperature from the rectum, bladder, and esophagus was used to record the body temperature, if available; otherwise, the peripheral temperature from the axilla and ears was recorded. We classified the severity of hypothermia into mild (35-32°C), moderate (32-28°C), and severe (<28°C) according to body temperature.

The geographical region was divided into four areas: Northern, Eastern, Western, and Southern areas of Japan. The area was defined by the definition of the Japan Meteorological Agency.¹⁴

The prehospital data included the mode of arrival at hospital, body temperature at prehospital, presence or absence of shivering, and rewarming method used at the prehospital site.

The laboratory data measured at the ED consisted of the pH value, potassium level, lactate level, platelet count, prothrombin time-international normalized ratio (PT-INR) level, creatine phosphokinase level, blood urea nitrogen level, and creatinine level. As a rule, the pH value assessed with an arterial blood gas analysis and measured with venous blood gas was adjusted as described in a previous study.¹⁵

Complications were categorized as arrhythmia, pneumonia, pancreatitis, electrolyte abnormality, coagulopathy, or other. Pneumonia was defined as an evident shadow on a chest radiograph or computed tomography. Pancreatitis was defined if patients presented with at least two of the following conditions: (i) abdominal or back pain, (ii) elevated pancreatic enzyme levels in the blood, and (iii) pancreatic edema or peripancreatic effusion on ultrasound/computed tomography.

Rewarming methods were divided into active external rewarming (warmed blanket, forced warm air, heating pad, and warmed bath) and active internal rewarming (warmed fluid infusion, lavage, hemodialysis, intravascular catheter, and ECMO).

Outcome measures

The primary outcome in this study was the survival rate after 30 days of admission. The secondary outcomes were the

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Table 1. (Continued)							
Variable	Overall (n = 1194)	Missing	Survivors (n = 902)	Nonsurvivors $(n = 292)$	P-value		
Severity Sequential Organ Failure Assessment score (total)	5 (3–8)	210 (17.6)	4 (3–7)	8 (6–11)	<0.001		

The data are expressed as n (%) or median (interquartile range).

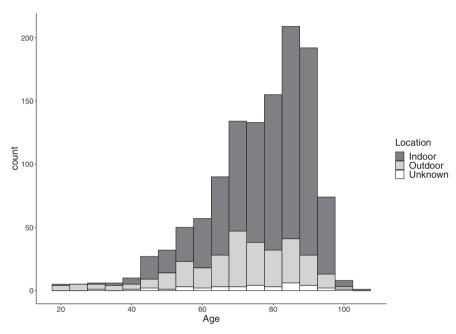


Fig. 1. The distribution of patients with accidental hypothermia, grouped by 5-year age intervals and by location (indoor or outdoor).

length of intensive care unit stay and hospital stay, CPC at 30 days after admission, and complications. A favorable outcome was defined as a CPC of 1 or 2, whereas an unfavorable outcome was defined as a CPC of 3-5.

Statistical analyses

Categorical variables were expressed as the n (%), and continuous variables were expressed as the median (interquartile range). Comparisons between groups were made by means of Fisher's exact test for categorical data and Mann–Whitney U test for continuous data. The comparisons between three groups were made by means of the Kruskal–Wallis test for continuous data. Prognostic factors were analyzed using multivariable logistic regression analyses. The following covariates were included in the multivariable model based on the relevant literature, $^{5,16-18}$ or the clinically important variables, which included age, sex, ADL, potassium level, causes underlying the hypothermia, GCS, location, temperature, systolic blood pressure, pH value, and PT-INR value. All tests were two-sided, and *P* values of <0.05 were considered statistically significant. All statistical analyses were performed with the R software program (version, 4.0.3; R Foundation for Statistical Computing, Vienna, Austria).

Table 2.	Acute medical	illness	causing	accidental	hypother-
mia					

Variable	Overall (<i>n</i> = 1194
Infection	116 (9.7)
Cerebrovascular disease	72 (6.0)
Hypoglycemia	65 (5.4)
Gastrointestinal disease	61 (5.1)
Malnutrition	52 (4.4)
Cardiac failure	45 (3.8)
Hyperglycemia	44 (3.7)
Ischemic cardiac disease	36 (3.0)
Renal disease	28 (2.4)
Endocrine disease (except for diabetes mellitus)	14 (1.2)
Epilepsy	5 (0.4)
Arrhythmia	5 (0.4)
Others	151 (12.7)

Table 3.	Prehospital	records	of	patients	with	accidental
hypotherr	mia					

Variable	Overall
	(<i>n</i> = 1194)
Mode of arrival at hospital	
Ambulance	1077 (90.2)
Medical helicopter	44 (3.7)
Walk-in	21 (1.8)
Others	44 (3.7)
Body temperature at prehospital	32.0 (28.6–34.5
Unknown body temperature	379 (31.7)
Shivering	
Present	57 (4.9)
Absent	797 (66.8)
Unknown	339 (28.4)
Time from awareness to arrival at	39 (30–51)
hospital (min)	
Rewarming methods	
Blanket	717 (60.1)
Warmed fluid infusion	24 (2.0)
Others	4 (0.3)
Nothing or unknown	419 (35.1)

Data are expressed as *n* (%) or median (interquartile range)

RESULTS

T HIS STUDY ENROLLED 1363 patients, including 656 in 2018 and 707 in 2019. Of these, 169 were excluded from the study because of body temperature >35°C (n = 23), unknown temperature (n = 123), or unknown outcome (n = 23). The remaining 1194 patients were analyzed in this study.

Baseline characteristics of the study population

Among the 1194 patients, the median patient age was 79 (68–87) years (Table 1). The distribution of patients' ages is shown in Figure 1. Nearly 81% of patients with AH were aged over 65 years. The incidence of AH was more likely to occur in an indoor setting, where it was noted in 867 (73.4%) patients. The most prevalent cause of hypothermia was acute medical illness, being seen in 595 (49.3%) patients. The acute medical illness causing hypothermia consisted of infection, cerebrovascular disease, hypoglycemia, gastrointestinal disease, malnutrition, cardiac failure, hyperglycemia, ischemic cardiac disease, renal disease, endocrine disease, epilepsy, arrhythmia, and others (Table 2). The rates of hypothermia in the northern areas of Japan (Figure S1).

Prehospital management

The number of patients whose body temperature at the prehospital setting was unknown or could not be measured was 379 (31.7%). Absence of shivering was seen in 797 (66.8%). The use of active rewarming method was limited, as a total of 419 (35.1%) patients were either not given rewarming or their treatment was unknown (Table 3).

Clinical and laboratory data of the study population

Among the 1194 cases, the core body temperature was measured in 739 cases (61.9%). The sites of measurement were as follows: rectal temperature, 202 (27.3%); bladder temperature, 494 (66.8%); and esophageal temperature, 43 (5.8%). Table 4 shows the comparison of clinical and laboratory data between nonsurvivors and survivors. In the univariate analysis, the nonsurvivors had more severe hypothermia, a lower GCS level, lower blood pressure, lower pH value, lower platelet count, higher potassium level, higher lactate level, higher PT-INR level, higher blood urea nitrogen level, and higher creatinine level than the survivors.

Variable	Overall $(n = 1194)$	Missing	Survivors $(n = 902)$	Nonsurvivors $(n = 292)$	P-value
Temperature	30.8 (28.4–33.6)	0	31.3 (28.7–33.8)	30.5 (27.4–33.4)	0.003
	513 (43.0)		394 (43.7)	119 (40.8)	0.002
Mild (35–32°C)					
	420 (35.2)		332 (36.8)	88 (30.1)	
Moderate (32–28°C)					
	261 (21.9)		176 (19.5)	85 (29.1)	
Severe (<28°C)					
Glasgow Coma Scale score	11 (7–14)	106 (8.9)	11 (8–14)	7 (3–11)	< 0.001
Cardiac arrest on arrival at hospital	101	2 (0.2)	27 (3.0)	74 (25.4)	< 0.001
Systolic blood pressure (mmHg)	120 (93–148)	130 (10.9)	123 (98–149)	103 (78–143)	< 0.001
Diastolic blood pressure (mmHg)	69 (53–87)	149 (12.5)	71 (55–88)	64 (41–86)	< 0.001
Heart rate	72 (54–90)	74 (6.2)	73 (55–90)	70 (51–88)	0.084
Respiratory rate	18 (15–22)	153 (12.8)	18 (15–22)	20 (15–24)	0.074
рН	7.30 (7.19–7.37)	96 (8.0)	7.32 (7.22–7.38)	7.24 (7.01–7.34)	< 0.001
Potassium (mEq/L)	4.2 (3.7–4.9)	25 (2.1)	4.2 (3.7–4.7)	4.7 (3.9–5.7)	< 0.001
Lactate (mmol/L)	3.4 (1.7–7.6)	180 (15.1)	3.1 (1.6–6.4)	5.9 (2.3–11.8)	< 0.001
Platelet ($\times 10^4/\mu$ L)	18.7 (12.7–25.1)	31 (2.6)	19.6 (14.0–25.9)	14.4 (10.0–22.5)	< 0.001
Prothrombin time-international normalized ratio	1.12 (1.00–1.33)	132 (11.1)	1.08 (0.98–1.25)	1.27 (1.11–1.55)	< 0.001
Creatine phosphokinase (U/L)	328 (128–1136)	103 (8.6)	321 (127–1131)	348 (142–1212)	0.400
Blood urea nitrogen (mg/dL)	30.1 (18.2–53)	29 (2.4)	28.0 (17.4–48.0)	40.4 (22.8–70.5)	< 0.001
Creatinine (mg/dL)	1.1 (0.7–1.8)	31 (2.6)	1.0 (0.7–1.6)	1.4 (0.9–2.7)	< 0.001

The data are expressed as n (%) or median (interquartile range).

Variable	Overall (<i>n</i> = 1194)	Mild (n = 513)	Moderate $(n = 420)$	Severe (<i>n</i> = 261)	P-value
Active external rewarming					
Warmed blanket	416 (34.8)	143 (27.9)	170 (40.5)	103 (39.5)	< 0.001
Forced warm air	601 (50.3)	159 (31.0)	282 (67.1)	160 (61.3)	< 0.001
Heating pad	48 (4.0)	10 (1.9)	20 (4.8)	18 (6.9)	0.002
Warmed bath	20 (1.7)	O (O)	12 (2.9)	8 (3.1)	<0.001
Active internal rewarming					
Warmed fluid infusion	716 (60.0)	210 (40.9)	315 (75.0)	191 (73.2)	< 0.001
Lavage	29 (2.4)	O (O)	9 (2.1)	20 (7.7)	< 0.001
Hemodialysis	10 (0.8)	5 (1.0)	1 (0.2)	4 (1.5)	0.155
Intravascular catheter	21 (1.8)	3 (0.6)	6 (1.4)	12 (4.6)	< 0.001
Extracorporeal membrane oxygenation	35 (2.9)	2 (0.4)	6 (1.4)	27 (10.3)	< 0.001
Others	19 (1.6)	4 (0.8)	6 (1.4)	9 (3.4)	0.026
Nothing	203 (17.0)	177 (34.5)	17 (4.0)	9 (3.4)	<0.001

Variable	Overall (n = 1194)	Survivors $(n = 902)$	Nonsurvivors $(n = 292)$	P-value
Return home as outpatients	115 (9.6)	115 (12.7)	_	
Died at emergency department	43 (3.6)	—	43 (14.7)	
Admission	1027 (86.0)	783 (87.2)	244 (85.0)	0.369
Length of stay at intensive care unit	4 (2–7)	4 (2–7)	2 (1-4)	< 0.001
Length of stay at hospital	13 (4–27)	7 (1–16)	2 (0–3)	< 0.001
Cerebral Performance Category at 30 days	5			
Good (1–2)	353	353 (64.4)		< 0.001
Poor (3–5)	363	195 (35.6)	168 (100)	
Complication				
Arrhythmia	21	11 (1.2)	10 (3.4)	0.022
Pneumonia	5	2 (0.2)	3 (1.0)	0.097
Pancreatitis	1	1 (0.1)	0 (0)	1.000
Electrolyte abnormalities	4	0 (0)	4 (1.4)	0.004
Coagulopathy	6	0 (0)	6 (2.1)	< 0.001
Other	9	4 (0.4)	5 (1.7)	0.044

Data are expressed as n (%) or median (interquartile range).

Rewarming treatment

Table 5 shows the relationship between the rewarming method and the severity of AH. Among patients with mild AH, 34.5% did not use any rewarming method, whereas patients with moderate to severe AH often used warm fluids (73.2%, 73.5%), warmed blankets (40.5%, 39.5%), or forced warm air (67.1%, 61.3%). ECMO rewarming was used in only 2.9% of overall patients with AH but in 10.3% of those with severe AH.

Outcomes

The overall 30-day mortality rate was 24.5% (292/1194). The median intensive care unit stay was 4 (2–7) days, the median hospital stay was 13 (4–27) days, and 64.4% (353/902) of the survivors had a good neurological prognosis (CPC 1–2). None of the complications had a high incidence (Table 6). A subgroup analysis showed that CPA on arrival at the hospital was observed in 101 patients (8.5%), and the survival rate was 26.7% (27/101; Table S1).

Prognostic factors associated with mortality

In a multivariable logistic analysis, independent predictors of mortality were age (\geq 75 years old; odds ratio [OR], 1.90;

95% confidence interval [CI], 1.04–3.50), male (OR, 1.86; 95% CI, 1.24–2.79), ADL (needing total assistance; OR, 2.66; 95% CI, 1.25–5.62), cause of AH (trauma; OR, 0.39; 95% CI, 0.18–0.83), alcohol (OR, 0.12; 95% CI, 0.02–0.90), GCS (OR, 0.84; 95% CI, 0.79–0.88), and potassium level (>5.5 mEq/L; OR, 2.46; 95% CI, 1.43–4.24; Table 7). Furthermore, in a multivariable logistic analysis with the exclusion of patients with cardiac arrest, the prognostic factors associated with mortality showed a similar tendency (Table S2).

DISCUSSION

T HIS STUDY SHOWED that 81% of patients with AH were aged over 65 years, 73.4% of cases occurred in an indoor setting, and 49.3% were caused by an acute medical illness. The overall mortality rate of AH in this study was 24.5%, and the poor prognostic factors of patients with AH included an older age (\geq 75 years old), a male sex, ADL (needing total assistance), a low GCS, and a high potassium level. By contrast, hypothermia caused by trauma and high intoxication of the patient at presentation to the hospital were good prognostic factors.

In this study, the mortality rate of AH was similar to or slightly higher than that in other studies.^{2,3,5,7} Regarding the reasons for this, first, this study included patients who had CPA on arrival, and 3.6% died at the ED without admission.

Variable	Odds ratio	95% confidence interval	P- value
Age category			
<65 years	Reference		—
65–74 years	1.17	0.59–2.32	0.651
≥75 years	1.90	1.04–3.50	0.038
Male	1.86	1.24–2.79	0.003
Activities of daily living			
Independent	Reference		—
Almost independent	0.82	0.43–1.58	0.558
Needing some	1.14	0.61–2.13	0.690
assistance			
Almost needing	1.47	0.86–2.52	0.162
assistance			
Needing total	2.66	1.25–5.62	0.001
assistance			
Potassium category			
3.5–5.5 mEq/L	Reference		
>5.5 mEq/L	2.46	1.43-4.24	0.001
<3.5 mEq/L	1.05	0.61–1.80	0.867
Causes underlying the hy	pothermia		
Acute medical illness	Reference		
Trauma, submersion,	0.39	0.18–0.83	0.014
and distress			
Alcohol intoxication	0.12	0.02–0.90	0.039
Drug	0.51	0.13–1.98	0.330
Unknown	0.62	0.39–0.98	0.042
Glasgow Coma Scale	0.84	0.79–0.88	< 0.001
(per 1 point)			
Location			
Outdoor	Reference		
Indoor	1.16	0.65–2.05	0.615
Temperature (per 1°C)	1.05	0.98–1.12	0.199
Systolic blood pressure c	ategory		
>90 mmHg	Reference		
Cardiac arrest	2.46	0.48–12.7	0.282
30–90 mmHg	1.31	0.84–2.04	0.227
рН	0.31	0.09–1.09	0.069
Prothrombin time-	0.99	0.91–1.07	0.746
international	0.77		
normalized ratio			

 Table 7. Results of a multivariable logistic regression analy

 sis for factors associated with mortality

Second, the institutions that participated in this study were mainly tertiary-care centers and treated patients with severe AH. Third, the patients in this study were older than those in studies from other countries,^{2,3} which may have influenced the results.

In the prehospital setting, the body temperature was unclear or could not be measured in 379 (31.7%) patients. This may be because measurement of the body core temperature by EMS is legally difficult in Japan, or the body peripheral temperature could not be successfully measured as the body temperature was too low. In cases of mountain rescue, the "Swiss" hypothermia classification is used to judge the severity of AH based on a clinical examination, such as shivering and consciousness, without measuring the body temperature.¹⁹ In the present study, however, the proportion of patients with no or unclear shivering was high, so the use of "Swiss" classification was not appropriate. The use of warmed fluid infusion was limited in the prehospital setting. To date, no study has provided any evidence regarding the optimal method of rewarming in the prehospital setting,⁸ therefore it is important to develop protocols for rewarming of AH patients and to consider advanced medical procedures that can be performed by EMS.

Recently, the intravascular catheter¹⁰ and ECMO^{11,12} have become available for use in rewarming patients with severe AH. The HOPE score²⁰ was suggested to be useful for deciding whether or not to initiate ECMO rewarming in AH. However, the indications for ECMO remain unclear. In this study, the physician at each institution decided whether or not to use ECMO rewarming, so an elderly age or the presence of certain underlying diseases may have prevented patients from being selected for ECMO as a rewarming procedure. The intensive care with ECMO rewarming in accidentally severe hypothermia (ICE-CRASH) study is being performed to evaluate the efficacy and safety of ECMO for AH as research supported by the Japanese Association for Acute Medicine (UMIN Clinical Trials Registry; UMIN000036132. Registered April 1, 2019), and results are awaited.

The strength of this study is that it was a nationwide study conducted by the Japanese Association of Acute Medicine and is the largest of all studies of hypothermia in Japan conducted to date. Therefore, we were able to clarify the characteristics of hypothermia. In addition, this study collected data regarding the prehospital setting. No similar study has analyzed data from the prehospital setting, which may be useful for the future development of consistent management protocols from prehospital to in-hospital treatment.

However, several limitations associated with this study warrant mention. First, this study is biased toward patients with severe AH who were transported to a tertiary emergency center and did not include patients who were dead at discovery but not transported to a hospital. Second, this study only collected data during or after rewarming, so data on complications that occurred in the late phases were missing. Therefore, the incidence of complications in this study

may have been underestimated compared with other studies.⁵ Third, because the registry had many missing values, we were unable to analyze some variables, such as the rewarming rate. Despite these limitations, the results of this study have implications for future research and clinical practice in AH.

CONCLUSION

T HIS STUDY CLARI fied that the mortality rate of AH was 24.5%. A multivariable logistic analysis showed that poor prognostic factors were an older age (\geq 75 years old), a male sex, ADL (needing total assistance), a low GCS, and a high potassium level. By contrast, hypothermia caused by trauma and the patient being highly intoxicated at presentation to hospital were factors for good prognosis. The present findings will be useful for facilitating the prevention and awareness of AH. The development of AH protocols that cover prehospital to in-hospital treatment is needed.

FUNDING INFORMATION

N O FUNDING INFORMATION provided.

DISCLOSURE Approval of the research protocol with approval No. and

committee Name: The study was approved by the Ethics Review Board of Teikyo University Hospital in Japan (Approval No: 17-090-2). The requirement for informed consent was waived by the Ethics Review Board of Teikyo University Hospital because of the observational nature of this study. In addition, the institutional review boards of each of the hospitals listed in Appendix S1 approved this study. Registry and the Registration No. of the study/Trial: N/A. Animal Studies: N/A.

Conflict of Interest: None declared.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Fig S1. The geographic area and severity of patients with accidental hypothermia.

Table S1. The comparison between CPA and non-CPA patients with accidental hypothermia.

Table S2. The multivariable logistic regression analysis to identify factors associated with mortality, with the exclusion of patients with cardiac arrest.

Appendix S1. List of hospitals participating in the present study.