Original Article

Care at critical care medical centers is associated with improved outcomes in patients with accidental hypothermia: a historical cohort study from the J-Point registry

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Aim: The recommendation that patients with accidental hypothermia should be transported to specialized centers that can provide extracorporeal life support has not been validated, and the efficacy remains unclear.

Methods: This was a multicenter retrospective cohort study of patients with a body temperature of ≤35°C presenting at the emergency department of 12 hospitals in Japan between April 2011 and March 2016. We divided the patients into two groups based on the point of care delivery: critical care medical center (CCMC) or non-CCMC. The primary outcome of this study was in-hospital death. In-hospital death was compared using a multivariable logistic regression analysis. Subgroup analyses were carried out according to patients with severe hypothermia (<28°C) or systolic blood pressure (sBP) of <90 mmHg.

Results: A total of 537 patients were included, 413 patients (76.9%) in the CCMC group and 124 patients (23.1%) in the non-CCMC group. The in-hospital death rate was lower in the CCMC group than in the non-CCMC group (22.3% versus 31.5%, $P < 0.001$). The multivariable logistic regression analysis showed that the adjusted odds ratio (AOR) of the CCMC group was 0.54 (95% confidence interval, 0.32–0.90). In subgroup analyses, patients with systolic blood pressure <90 mmHg in the CCMC group were less likely to experience in-hospital death (AOR 0.36; 95% CI, 0.23–0.56). However, no such association was observed among patients with severe hypothermia (AOR 1.08; 95% CI, 0.63–1.85).

Conclusions: Our multicenter study indicated that care at a CCMC was associated with improved outcomes in patients with accidental hypothermia.

Key words: Accidental hypothermia, critical care medical center, ER, specialized center

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INTRODUCTION

ACCIDENTAL HYPOTHERMIA (AH) is defined as an unintentional decrease in body temperature to ≤35°C.[1] A previous study reported that AH was the leading cause of weather-related deaths.[2] For example, the in-hospital mortality rate was approximately 30% in a Japanese report, and the in-hospital mortality rate among patients with moderate to severe AH was 40% in a report from the USA.[3,4] Therefore, it is important to develop strategies for improving the prognosis of patients with AH.

Towards improving the prognosis of critical diseases, several studies have reported the effectiveness of the treatment delivered in a specialized center.[5–7] For example, the treatment in a specialized center improved neurological outcomes after out-of-hospital cardiac arrest due to acute coronary syndrome[5] and the survival rate of patients that experienced severe trauma.[6] Moreover, a study reported that treatment within a stroke center reduced adverse outcomes associated with acute ischemic stroke.[7] Recently, some invasive and advanced treatments such as cardiopulmonary bypass or extracorporeal membrane oxygenation (ECMO) have attracted significant attention regarding their use for AH patients. In particular, the cardiopulmonary arrest guidelines of the European Resuscitation Council[8] recommended that patients with AH should be transported to specialized centers, which can provide extracorporeal life support, if the systolic blood pressure is below 90 mmHg, and there is ventricular arrhythmia, or the core temperature is <28°C.[8] However, this recommendation has not been validated, and its efficacy remains unclear.

We undertook a multicenter retrospective observational study using data obtained from the Japanese accidental hypothermia network registry (J-Point registry).[9] A total of 537 adult patients with AH were enrolled. Using the data from this registry, we aimed to evaluate the association between care at the critical care medical center (CCMC), which is a specialized center for critical illness in Japan and outcomes in patients with AH.

METHODS

Study design, patients, and setting

WE UNDERTOOK A multicenter, retrospective study of patients with AH using data from the J-Point registry. The period of this study was between 1 April, 2011 and 31 March, 2016. This study included hypothermic patients who were aged 18 years or older, and excluded those who did not visit an emergency department (ED), as well as those whose body temperature was unknown or over 35.0°C.

J-Point registry

The J-Point registry aimed to obtain descriptive information about AH towards understanding its management in the EDs of Japan, to improve patient outcomes. Details of the study methodology were described previously.[9] In brief, 12 acute care hospitals with EDs, including eight critical care medical centers, across the Kyoto, Osaka, and Shiga Prefectures in Japan joined the J-Point registry. We retrospectively enrolled eligible patients with the International Classification of Diseases, 10th Revision (ICD-10) code for hypothermia (T68) during the study period. The ethics committee of each participating institution approved this study.

Data collection and quality control

In this registry, data on the characteristics of the participants, clinical history, presentation, laboratory findings, and treatments were collected using a predefined uniform data sheet. All chart reviewers were emergency physicians who were trained for appropriate data review by face-to-face or web meetings. The collected data were reviewed by the working group and confirmed or returned to each institution in case of any problems.

Measurements

Baseline characteristic information included: sex, age, activities of daily living (ADL) before being hypothermic, residence, medical history (cardiovascular diseases, neurological diseases, endocrine diseases, psychiatric diseases, malignant diseases, dementia, mean outside temperature on the day of occurrence of AH, season, location, mode of arrival, vital signs on hospital arrival, biological data, exposure to cold, associated conditions, treatment process, and outcome. Sequential Organ Failure Assessment score was calculated only for patients admitted to the intensive care unit (ICU). Based on previous reports,[3,10] associated conditions were classified into internal diseases, trauma, alcohol intoxication, drowning, self-harm, and other factors. Rewarming procedures were divided into active external or minimally invasive rewarming and active internal rewarming. Other treatment information included tracheal intubation, use of catecholamine, and emergent transvenous cardiac pacing. Data regarding outcomes were in-hospital death, and length of hospital and ICU stay. The detailed information was described in a previous study.[9,11]

Key group definition

Acute care hospitals in this study were divided into two groups: CCMC or non-CCMC. The CCMC group included hospitals certified to provide intensive care, including ECMO, to all critically ill patients 24 h a day. The specialized centers were certified by the Japanese Ministry of Health, Labor, and Welfare.[12] To be certified as a specialized center, a hospital needs to have ≥20 beds and an ICU for critically ill patients. Non-specialized centers in this study are open and staffed 24 h a day. There were four non-CCMCs and eight CCMCs.

Outcomes

The primary outcome of this study was in-hospital death. The secondary outcomes were length of stay in the ICU and overall length of hospital stay.

Statistical analysis

Data were analyzed using the Mann–Whitney *U*-test for continuous variables and Fisher's exact test for comparing categorical variables between CCMC and non-CCMC. The association between care at CCMC and in-hospital death was analyzed by univariable and multivariable logistic regression. We calculated the odds ratios (ORs) and adjusted odds ratios (AORs) and their 95% confidence interval (CI) as the effect variables. Based on previous studies,[3,9,10] we selected potential confounders that are likely to be associated with clinical outcomes and adjusted for the following: age category (18–64 years, 65–74 years, and ≥75 years), sex (male or female), medical history (none, one, multiple, and unknown), ADL (independent, need some assistance, need total assistance, or unknown), systolic blood pressure category (cardiac arrest, unmeasurable, 40–90 mmHg, or >90 mmHg), exposure to cold (yes, no, or unknown), presence of associated internal diseases (yes or no), and active internal rewarming (yes or no). For subgroup analyses, the association between care at the specialized center and in-hospital death was investigated according to patients with severe hypothermia (<28°C), systolic blood pressure of <90 mmHg, active internal rewarming, ECMO, or care at ICU using univariable and multivariable logistic regression analysis adjusting for the same confounders described above. All *P*-values were two-sided, and <0.05 was considered statistically significant. All statistical analyses were undertaking using EZR software (version 1.36).

RESULTS

A TOTAL OF 572 patients were registered in our hypothermia study. After excluding 15 patients who were below 18 years of age, as well as 12 patients with unknown body temperature, and eight patients whose body temperature was >35.0°C, 537 patients were enrolled. There were 413 patients (76.9%) in the CCMC and 124 patients (23.1%) in the non-CCMC group (Fig. 1).

Table 1 shows the characteristics of AH patients. Compared with the non-CCMC group, the CCMC group had a

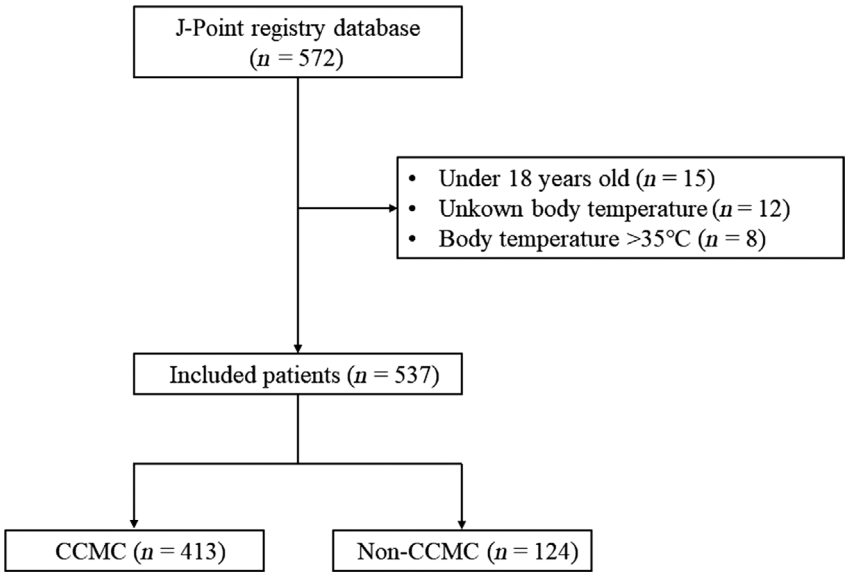

Fig. 1. Patient flow of this study. CCMC, critical care medical center; J-Point, Japanese accidental hypothermia network.

Table 1. Baseline characteristics of Japanese patients with hypothermia, grouped according to point of care delivery: critical care medical center (CCMC) or non-CCMC

	Non-CCMC (n = 124)	CCMC (n = 413)	P-value
Men	59 (48)	214 (52)	0.415
Age, years; median (IQR)	82.5 (68–88)	79 (67–86)	0.082
Activities of daily living			
Independent	74 (60)	299 (72)	0.036
Need for some assistance	40 (32)	90 (22)	
Need for total assistance	10 (8)	22 (5)	
Unknown	0 (0)	2 (1)	
Residence			
Home			
Living alone	44 (36)	167 (40)	0.435
Not living alone	62 (50)	206 (50)	
Nursing home	11 (9)	21 (5)	
Homeless	1 (1)	5 (1)	
Unknown	6 (5)	14 (3)	
Season			
Spring (March–May)	24 (19)	72 (17)	0.976
Summer (June–August)	4 (3)	15 (4)	
Autumn (September–November)	16 (13)	55 (13)	
Winter (December–February)	80 (65)	271 (66)	
Temperature, °C, median (IQR)	6.6 (4–11)	6 (4–11)	0.592
Mode of arrival			
Ambulance	117 (94)	391 (95)	0.824
Walk-in	7 (6)	22 (5)	
Medical history			
Cardiovascular diseases	48 (39)	189 (46)	0.181
Neurological diseases	27 (22)	66 (16)	0.138
Endocrine diseases	22 (18)	109 (26)	0.056
Psychiatric diseases	23 (19)	97 (24)	0.27
Malignant diseases	9 (7)	45 (11)	0.344
Dementia	39 (32)	69 (17)	<0.001
Other	24 (19)	70 (17)	0.59
Unknown	0 (0)	8 (2)	0.208
Patient volume, persons/year/hospital	10.3	6.2	<0.001

Values are expressed as number (%) unless indicated otherwise.
IQR, interquartile range.

higher proportion of patients with independent ADL and lower proportion of patients with dementia. No significant differences were observed between the groups in terms of age, sex, mean outside temperature, or medical history other than dementia.

Table 2 shows the in-hospital data. There was no difference between the two groups in terms of vital signs on hospital admission. Regarding biological data, the CCMC group had lower HCO_3 and glucose and higher lactate level. The CCMC group also had a higher proportion of cold exposure, alcohol intoxication, and catecholamine use. Regarding the rewarming procedure, warm i.v. fluid, forced warm air, and active internal rewarming including ECMO were more frequent in the specialized center group.

In terms of the primary outcome, the in-hospital death rate was lower in the CCMC group than in the non-CCMC group (22.3% [92/413] versus 31.5% [39/124], P = 0.043). In the multivariable logistic regression analysis, care at a CCMC was associated with a lower likelihood of in-hospital mortality (AOR 0.54; 95% CI, 0.288–0.998) (Table 3). In terms of secondary outcomes, the length of ICU stay was longer in the non-CCMC group, and there was no significant difference in

Table 2. In-hospital data for Japanese patients with hypothermia, grouped according to point of care delivery: critical care medical center (CCMC) or non-CCMC

	Non-CCMC (n = 124)	CCMC (n = 413)	P-value
Body temperature, °C; median (IQR)	31.0 (28.8–32.8)	30.7 (28.0–32.6)	0.128
Systolic blood pressure category			0.055
Cardiac arrest	4 (3)	17 (4)	
Unmeasurable	6 (5)	30 (7)	
40–90 mmHg	20 (16)	87 (21)	
>90 mmHg	94 (76)	279 (68)	
Heart rate, b.p.m.; median (IQR)	64 (49–82)	65 (46–83)	0.967
Glasgow Coma Scale, median (IQR)	11 (8–14)	11 (7–14)	0.639
Biological data			
Serum pH, median (IQR)	7.33 (7.27–7.37)	7.31 (7.22–7.37)	0.052
Serum HCO_3, mEq/L; median (IQR)	22.3 (17.7–26.3)	20.1 (14.6–25.2)	0.008
Serum lactate, mmol/L; median (IQR)	2.1 (1.2–4.1)	3.2 (1.4–7.1)	0.006
Serum sodium, mEq/L; median (IQR)	139 (134–142)	140 (136–143)	0.076
Serum potassium, mEq/L; median (IQR)	4.1 (3.6–3.6)	4.0 (3.5–4.7)	0.910
Serum glucose, mg/dL; median (IQR)	109 (78–178)	132 (98–194)	0.018
SOFA score[†]	4 (2–6)	5 (3–8)	0.084
Cold exposure	99 (80)	340 (82)	0.019
Associated condition			
Internal diseases	60 (48)	211 (51)	0.610
Trauma	21 (17)	52 (13)	0.232
Alcohol intoxication	4 (3)	46 (11)	0.007
Drowning including immersion	4 (3)	29 (7)	0.140
Self-harm	6 (5)	28 (7)	0.532
Other	15 (12)	43 (10)	0.558
Rewarming procedure			
Active external or minimally invasive	117 (94)	389 (94)	1.000
Warm i.v. fluids	51 (41)	342 (83)	<0.001
Warm blanket	105 (85)	268 (65)	<0.001
Forced warm air	6 (5)	76 (18)	<0.001
Heating pads	6 (5)	17 (4)	0.800
Warm bath	0 (0)	16 (4)	0.030
Active internal	11 (9)	80 (19)	0.006
Lavage	7 (6)	38 (9)	0.268
Intravascular	0 (0)	4 (1)	0.580
Hemodialysis	4 (3)	22 (5)	0.475
ECMO	0 (0)	22 (5)	0.004
Other treatment			
Intubation	5 (4)	30 (7)	0.298
Catecholamine	14 (11)	85 (21)	0.018
Emergent transvenous cardiac pacing	1 (1)	6 (2)	1.000
Rewarming rate, median (IQR)[‡]	0.66 (0.41–1.02)	0.89 (0.54–1.40)	<0.001
Admission ward			0.087
No admission	12 (10)	23 (6)	
General ward	61 (49)	181 (44)	
Intensive care unit	51 (41)	209 (51)	

Values are expressed as number (%) unless indicated otherwise.
ECMO, extracorporeal membrane oxygenation; IQR, interquartile range; SOFA, sequential organ failure assessment.
[†]Including patients admitted to the intensive care unit.
[‡]Data not available for 493 patients.

Table 3. In-hospital death among Japanese patients with hypothermia, according to hospital characteristics

Characteristic	*n*/*N* (%)	Crude odds ratio (95% CI)	Adjusted odds ratio† (95% CI)
Primary outcome			
Non-CCMC	39/124 (32)	Reference	Reference
CCMC	92/413 (22)	0.63 (0.402–0.977)	0.54 (0.288–0.998)
Explanatory variables			
Age category (years)			
<65	17/113 (15)	Reference	Reference
65–74	16/86 (18.6)	1.29 (0.61–2.73)	1.53 (0.64–3.66)
>74	98/337 (29)	2.32 (1.31–4.08)	3.11 (1.53–6.34)
Men			
No	57/262 (22)	Reference	Reference
Yes	74/272 (27)	1.36 (0.91–2.02)	1.61 (1.3–253)
Number of previous significant medical conditions			
0	22/97 (23)	Reference	Reference
1	47/188 (25)	1.14 (0.64–2.03)	1.15 (0.60–2.18)
>1	62/251 (25)	1.12 (0.64–1.95)	1.01 (0.54–1.90)
ADL category			
Independent	72/372 (19)	Reference	Reference
Need some assistance	46/130 (35)	2.28 (1.47–3.55)	1.98 (1.19–3.28)
Need for total assistance	13/32 (41)	2.85 (1.35–6.04)	2.49 (1.03–6.05)
Unknown	0/2 (0)	<0.01 (0–inf)	<0.01 (0–inf)
Patient volume category			
1–4	61/262 (23)	Reference	Reference
5–8	47/186 (25)	1.11 (0.72–1.73)	0.93 (0.51–1.68)
9–12	23/88 (26)	1.17 (0.67–2.03)	1.1 (0.54–2.25)
sBP category			
>90	69/372 (19)	Reference	Reference
<90	31/107 (29)	0.45 (0.15–1.37)	0.25 (0.07–0.91)
Unmeasurable	17/36 (47)	0.20 (0.08–0.55)	0.08 (0.03–0.27)
Arrest	14/21 (67)	0.11 (0.04–0.29)	0.05 (0.02–0.15)
Cold exposure			
No	25/98 (26)	Reference	Reference
Yes	100/421 (24)	0.91 (0.55–1.51)	1.24 (0.66–2.33)
Unknown	6/17 (35)	1.59 (0.53–4.75)	1.69 (0.50–5.74)
Internal etiology			
No	46/265 (17)	Reference	Reference
Yes	85/271 (31)	2.18 (1.45–3.27)	2.58 (1.60–4.14)
Active internal rewarming			
No	104/456 (23)	Reference	Reference
Yes	27/80 (34)	1.72 (1.03–2.88)	1.31 (0.71–2.44)

Values are expressed as number (%) unless indicated otherwise.
ADL, activities of daily living; CCMC, critical care medical center; CI, confidence interval; inf, infinity; sBP, systolic blood pressure.
†Adjusted for age category, sex, number of previous significant medical conditions, systolic blood pressure category, activities of daily living category, cold exposure, active internal rewarming, internal disease etiology, patient volume.

the length of hospital stay among the survivors in the two groups (Table 4). In the subgroup analyses, among patients with systolic blood pressure of <90 mmHg, the CCMC group experienced a lower likelihood of in-hospital death than did the non-specialized center group (AOR 0.29; 95% CI, 0.09–0.9). However, no such association was observed among patients with severe hypothermia (AOR 0.34; 95% CI, 0.08–1.45), active internal rewarming (AOR 0.38; 95% CI, 0.01–10.2), ECMO (AOR not applicable; 95% CI, not applicable), or care at ICU (AOR 0.74; 95% CI, 0.31–1.78) (Table 5).

Table 4. Secondary outcomes among Japanese patients with hypothermia, grouped according to point of care delivery: critical care medical center (CCMC) or non-CCMC

Characteristic	Non-CCMC (n = 124)	CCMC (n = 413)	P-value
Hospital stay, days	13 (2–34)	12 (3–30)	0.955
ICU stay[†]	4 (2–7)	3 (2–5)	0.005

Data are shown as median (interquartile range).
[†]Patients admitted to intensive care unit (ICU).

Table 5. In-hospital death among Japanese patients with hypothermia: subgroup analysis according to point of care delivery (critical care medical center [CCMC]) or non-CCMC

Characteristic	Non-CCMC	CCMC
Severe hypothermia	9/21 (43)	29/108 (27)
Crude OR (95% CI)	Reference	0.49 (0.19–1.28)
Adjusted OR[†] (95% CI)	Reference	0.34 (0.08–1.45)
sBP < 90mmHg	18/30 (60)	44/134 (33)
Crude OR (95% CI)	Reference	0.33 (0.14–0.74)
Adjusted OR[†] (95% CI)	Reference	0.29 (0.09–0.90)
Active internal rewarming	5/9 (56)	22/71 (31)
Crude OR (95% CI)	Reference	0.36 (0.09–1.47)
Adjusted OR[†] (95% CI)	Reference	0.38 (0.01–10.2)
ECMO	0/0	11/22 (50)
Crude OR (95% CI)	Reference	n/a
Adjusted OR[†] (95% CI)	Reference	n/a
ICU	16/51 (31)	50/209 (24)
Crude OR (95% CI)	Reference	0.69 (0.35–1.35)
Adjusted OR[†] (95% CI)	Reference	0.74 (0.31–1.78)

Values are expressed as number (%) unless indicated otherwise.
CI, confidence interval; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; n/a, not applicable; OR, odds ratio; sBP, systolic blood pressure.
[†]Adjusted for age category, sex, number of previous significant medical conditions, systolic blood pressure category, activities of daily living category, cold exposure, active internal rewarming, internal disease etiology, patient volume.

DISCUSSION

OUR MULTICENTER STUDY found that AH patients receiving care at a CCMC had lower likelihood of mortality compared to those receiving care at non-specialized centers. Moreover, among patients with blood pressure of <90 mmHg, the CCMC group had a lower mortality rate, although there was no significant difference in mortality rates between the two groups in terms of severe hypothermia, active internal rewarming, severe hypothermia, and care in ICU. To the best of our knowledge, this is the first study investigating the impact of receiving care at a specialized center for AH patients, and our findings provide important information to inform better strategies for this life-threating illness.

The present study showed that AH patients receiving care at the CCMC had lower likelihood of mortality compared to those receiving care at non-CCMCs. Previous studies have highlighted several benefits in treatments delivered at a specialized center for patients with critical diseases such as acute myocardial infarction, stroke, and severe trauma.[5–7] Regarding AH, a Severe Accidental Hypothermia Center has been established to improve outcomes for AH patients in Poland.[13] However, there has been no study to assess the impact of a specialized center on AH outcomes. One of the important functions about a specialized center for AH is to undertake ECMO.[13] In this study, the proportion of CCMCs carrying out ECMO was only 5.3%, which was higher compared to the non-CCMCs. Another important function is that the specialized center in Poland is expected to improve patient outcomes through education, coordination, and use of contemporary equipment.[13] After adjusting for "patient volume", the CCMC group still had an association with lower mortality. Rather than the higher patient volume itself, multiple factors such as the education, coordination, equipment, number of staff, and system that can provide intensive care 24 h a day might be more effective for decreasing AH patients' mortality rate. The CCMC could increase staff knowledge, standardize response, as well as improve the implementation of active internal rewarming, including ECMO, at the time of circulatory failure. These effects could lead to an improvement in patients' prognosis. The consolidation of AH patients into the specialized center could be key to improving prognosis.

In the subgroup analysis, there was no significant difference in mortality rates in the CCMC group regarding severe hypothermia, active internal rewarming, and ICU care as analyzed by multivariable logistic regression. Unlike other studies that reported the predominant conditions associated with secondary hypothermia were cold and alcohol or drug intoxication,[4,12] more than half of the patients in this study had internal diseases, which should be treated alongside rewarming. Considering that the cause of death of patients with secondary hypothermia is often an underlying disease, rather than the hypothermia itself,[14,15] there might be little difference in the quality of care for patients with internal diseases between the specialized centers and non-specialized centers in this study.

In contrast, among patients with systolic blood pressure of <90 mmHg, care at the specialized centers had a positive association with improved outcome. Circulatory support such as ECMO for unstable patients often requires time-sensitive procedures and human or medical resources.[11,16] Indeed, severe hypothermic patients are more likely to have lower blood pressure.[1,10] However, unstable hemodynamic status could have greater impact on the outcomes of patients with AH than decreased body temperature itself. Thus, unstable hemodynamic status should be the best indicator of the need for the transportation of AH patients to a specialized center.

In the field of acute coronary syndrome, stroke, and severe trauma, improvement of prognosis has been reported by patient consolidation.[5–7] Based on the results of our study, it is reasonable to promote the consolidation of AH patients, but a specialized center for AH does not appear to be cost-effective due to the small number of cases in Japan, because of its mild climate. Furthermore, this study did not assess the effect of bypass emergency medical system transport on prognosis, and further research is needed to investigate whether the transportation of all AH patients with circulatory failure to a specialized center is effective or not.

Limitation

In this study, some inherent limitations should be noted. First, this is an observational study, and although we adjusted for as many confounders as possible, there may still be residual confounding factors. Second, the reasons for the visit or how the AH patients visited or were transported to a hospital was unknown, and selection bias might exist. However, basic information or status on hospital arrival of the included patients between the two groups seemed balanced. Finally, we included patients with an ICD-10 code, and we could have lost the groups of AH patients without an ICD-10 code.

CONCLUSIONS

OUR MULTICENTER STUDY indicated that care at a CCMC was associated with improved outcomes in patients with AH. Optimizing the transportation of patients with AH to a specialized center is likely to be beneficial.

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DISCLOSURE

Approval of the Research Protocol: The Ethics Committee of each institution (Kyoto Prefectural University of Medicine, Japanese Red Cross Kyoto Daiichi Hospital, Saiseikai Senri Hospital, Rakuwa-kai Otowa Hospital, Japanese Red Cross Society Kyoto Daini Red Cross Hospital, Uji-Tokushukai Medical Center, North Medical Center, Kyoto Prefectural University of Medicine, Kyoto Medical Center, Saiseikai Shiga Hospital, Kyoto Min-iren Chuo Hospital, Yodogawa Christian Hospital, and Fukuchiyama City Hospital) approved this study protocol.
Informed Consent: Due to the retrospective nature of the study and deidentification of personal data, each committee waived the need for informed consent.
Registry and the Registration no. of the Study/trial: N/A.
Animal Studies: N/A.
Conflict of Interest: None.

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