

# Care at the Critical Care Medical Center is associated with improved outcomes in patients with accidental hypothermia: A report from the J-Point registry

**Yoshihiro Fujimoto**

Japanese Red Cross Kyoto Daiichi Hospital

**Tasuku Matsuyama** (✉ [task-m@koto.kpu-m.ac.jp](mailto:task-m@koto.kpu-m.ac.jp))

Kyoto Prefectural University of Medicine <https://orcid.org/0000-0003-4068-0306>

**Sachiko Morita**

Saiseikai Senri Hospital

**Naoki Ehara**

Japanese Red Cross Kyoto Daiichi Hospital

**Nobuhiro Miyamae**

Japanese Red Cross KyotoDaiichi Hospital

**Yohei Okada**

Japanese Red Cross Kyoto Daiichi Hospital

**Takaaki Jo**

Uji-Tokushukai Medical Center

**Yasuyuki Sumida**

Kyoto Prefectual University of Medicine

**Nobunaga Okada**

Kyoto Medical Center

**Makoto Watanabe**

Kyoto Prefectual University of Medicine

**Masahiro Nozawa**

Saiseikai Shiga Hospital

**Ayumu Tsuruoka**

Osaka City General Hospital

**Yoshiki Okumura**

Fukuchiyama City Hospital

**Tetsuhisa Kitamura**

Osaka University

**Tetsurou Takegami**

Japanese Red Cross Kyoto Daiichi Hospital

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## Research

**Keywords:** CCMC, specialized center, high volume, accidental hypothermia, mortality, outcome

**Posted Date:** February 3rd, 2020

**DOI:** <https://doi.org/10.21203/rs.2.22481/v1>

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## Abstract

**Background:** The recommendation that patients with accidental hypothermia (AH) should be transported to specialized centers which can provide extracorporeal life support has not been validated, and the efficacy still remains unclear.

**Methods:** This was a multicenter retrospective cohort study of patients with a body temperature of  $\leq 35^{\circ}\text{C}$  presenting at the emergency department of 12 hospitals in Japan between April 2011 and March 2016. We divided the patients into the 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 between AH patients at the CCMC and non-CCMC via a multivariable logistic regression analysis. Subgroup analyses were conducted according to patients with severe hypothermia ( $<28^{\circ}\text{C}$ ) or systolic blood pressure of  $<90 \text{ mmHg}$ .

**Results:** A total of 537 patients were included; 413 patients (76.9%) in the CCMC 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  $<90 \text{ mmHg}$  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 CCMC was associated with improved outcomes in patients with AH. Optimizing the transport of patients with AH to specialized centers is likely to be beneficial.

## Introduction

Accidental hypothermia (AH) is defined as an unintentional decrease in body temperature to  $\leq 35^{\circ}\text{C}$ .<sup>[i]</sup> A previous study reported that AH was the leading cause of weather-related deaths.<sup>[ii]</sup> For example, the in-hospital mortality rate was around 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 United States.<sup>[iii],[iv]</sup> 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.<sup>5-7</sup> For example, the treatment in a specialized center improved neurological outcomes after out of hospital cardiac arrest due to acute coronary syndrome<sup>[v]</sup> and the survival rate of patients that experienced severe trauma.<sup>[vi]</sup> Moreover, a study reported that treatment within a stroke center reduced adverse outcomes associated with acute ischemic stroke.<sup>[vii]</sup> Nowadays, some invasive and advanced treatments such as cardiopulmonary bypass or extracorporeal membrane oxygenation have attracted significant attention regarding their use for AH patients. In particular, the cardiopulmonary arrest guidelines of European resuscitation council<sup>[viii]</sup> 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.<sup>8</sup> However, this recommendation has not been validated, and its efficacy remains unclear.

We performed a multicenter retrospective observational study using data obtained from the Japanese accidental hypothermia network registry (J-Point registry).[ix] 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, patient, and setting

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

### The Japanese accidental hypothermia network registry (J-Point registry)

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.<sup>9</sup> In brief, twelve 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, Tenth 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

The Baseline characteristic information was following: sex, age, activities of daily living (ADL) before being hypothermic (independent, need some assistance, and need total assistance), residence (living

alone at home, not living alone at home, nursing home, and homelessness), past medical history (cardiovascular diseases [ischemic heart diseases, heart failure, arrhythmia, hypertension, and other cardiovascular diseases], neurological diseases [stroke, epilepsy, Parkinson disease 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, mean outside temperature of the day upon the occurrence of AH, season, location (indoor and outdoor), mode of arrival (walk-in and via ambulance), vital signs upon hospital arrival (body temperature, blood pressure, heart rate, and Glasgow Coma scale [GCS] score), biological data (serum pH, HCO<sub>3</sub> [mEq/L], lactate [mmol/L], sodium [mEq/L], potassium [mEq/L], and glucose [mg/dL] levels), exposure to cold, associated conditions, treatment process, and outcome. Sequential organ failure assessment (SOFA) score was calculated only for patients admitted to the ICU. Based on previous reports,<sup>3,[i]</sup> associated conditions were classified into internal diseases (stroke, seizure, Parkinson disease, thyroid diseases, hypoglycemia, infectious diseases, acute pancreatitis, uremia, malignant disease, bowel ischemia, rhabdomyolysis, or other internal diseases), trauma (fall [injury in the head, spine, and extremity], motor vehicle accident, or other traumatic injuries), alcohol intoxication, drowning (indoor or outdoor), self-harm (drug or external), and other factors (iatrogenic, mountain incident, burn, malnutrition/infirmity, or others). Rewarming procedures were divided into active external or minimally invasive rewarming (warm intravenous fluids, warm blanket, forced warm air, heating pads, and warm bath) and active internal rewarming (lavage [stomach, chest, and bladder], intravascular rewarming, hemodialysis, and extra corporeal membrane oxygenation [ECMO]). 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.

## Key Group Definition

Acute care hospitals in this study were divided into the 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.<sup>[ii]</sup> To be certified as a specialized center, a hospital needs to have ≥20 beds and an intensive care unit for critically ill patients. Non-specialized centers in this study are open and staffed 24 h a day. There were 4 non-CCMCs and 8 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 analysed 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 analysed via 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,<sup>3,9,10</sup> 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  $\geq 75$  years), sex (male or female), past 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 ( $<28^{\circ}\text{C}$ ) or systolic blood pressure of  $<90$  mmHg via 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 conducted the EZR software (version 1.36).

## Results

A total of 572 patients were registered in our hypothermia study. After excluding 24 patients whose body temperature was  $>35.0^{\circ}\text{C}$ , as well as 3 patients with unknown body temperature, and 8 patients who were below 18 years, 537 patients were enrolled. There were 413 patients (76.9%) in the CCMC and 124 patients (23.1%) in non-CCMC group (Figure 1).

Table 1 shows the characteristics of AH patients. Compared with the non-CCMC group, the CCMC group had a 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, and past history other than dementia.

**Table 1. Baseline Characteristics**

	non-CCMC	CCMC		<i>P</i> Values
	(n=124)	(n=413)		
Men	59 (48)	214 (52)		0.415
Age, y, 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
living not alone	62 (50)	206 (50)		
Nursing home	11 (9)	21 (5)		
Homelessness	1 (1)	5 (1)		
Unknown	6 (5)	14 (3)		
Season				
spring (3-5 month)	24 (19)	72 (17)		0.976
summer (6-8 month)	4 (3)	15 (4)		
autumn (9-11 month)	16 (13)	55 (13)		
winter (12-2 month)	80 (65)	271 (66)		
temperature, y, 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)		
Past 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

Values are expressed as numbers (percentages) unless indicated otherwise.

CCMC indicates critical care medical center, IQR; interquartile range

Table 2 shows the in-hospital data. There was no difference between the 2 groups in terms of vital signs on hospital admission. Regarding biological data, the CCMC group had lower HCO<sub>3</sub> and glucose and higher lactate level. the CCMC group also had higher proportion of cold exposure, alcohol intoxication, and catecholamine use. Regarding the rewarming procedure, warm intravenous fluid, forced warm air, and active internal rewarming including ECMO were more frequent in the specialized center group.

**Table 2. In-hospital data**

	non-CCMC (n=124)	CCMC (n=413)	P Values
Body temperature,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)	
40-90mmHg	20 (16)	87 (21)	
>90mmHg	94 (76)	279 (68)	
Heart Rate, 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 HCO3 (mEq/L), Median (IQR)	22.3 (17.7-26.3)	20.1 (14.5-25.2)	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)	0.91
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)	0.61
Trauma	21 (17)	52 (13)	0.232
Alcohol intoxication	4 (3)	46 (11)	0.007
Drowning including immersion	4 (3)	29 (7)	0.14
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
Warm intravenous 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)	0.8
Warm bath	0 (0)	16 (4)	0.03
Active internal	11 (9)	80 (19)	0.006
Lavage	7 (6)	38 (9)	0.268
Intravascular	0 (0)	4 (1)	0.58
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
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 numbers (percentages) unless indicated otherwise.

CCMC indicates critical care medical center, ECMO; extra-corporeal membrane oxygenation, IQR; interquartile range, SOFA; sequential organ failure assessment

†Calculated with patients admitting to ICU.

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 the CCMC group was associated with a lower likelihood of in-hospital mortality (AOR 0.54, 95% CI 0.32-0.90). As for secondary outcomes, the length of ICU stay was longer in the non-CCMC group, and there was no significant difference in the length of hospital stay among the survivors in the 2 groups (Table 3).

**Table 3. Outcomes**

Characteristics	non-CCMC (n=124)	CCMC (n=413)	P Values
<b>Primary outcome</b>			
In-hospital death	39 (32)	92 (22)	0.043
Crude Odds Ratio (95%CI)	Reference	0.63 (0.40-0.98)	
Adjusted Odds Ratio (95%CI)	Reference	0.54 (0.32-0.90)	
<b>Secondary outcomes</b>			
hospital stay	13 (2-34)	12 (3-30)	0.955
ICU stay†	4 (2-7)	3 (2-5)	0.005

Values are expressed as numbers (percentages) unless indicated otherwise.

\*Adjusted for age category, sex, number of past history, systolic blood pressure category, activities of daily living category, cold exposure, active internal rewarming, internal disease etiology

CI; confidence interval, CCMC; critical care medical center

†calculated with patients admitting to ICU.

In the sub-group 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 0.36, 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) (Table 4).

**Table 4.** In-hospital death according to the body temperature or hemodynamic status

Characteristics	non-CCMC	CCMC
severe hypothermia	9/21 (43)	29/108 (27)
Crude OR (95%CI)	Reference	0.71 (0.50-1.09)
Adjusted OR (95%CI)	Reference	1.08 (0.63-1.85)
sBP<90mmHg	18/30 (60)	44/134 (33)
Crude OR (95%CI)	Reference	0.37 (0.25-0.56)
Adjusted OR (95%CI)	Reference	0.36 (0.23-0.56)

Values are expressed as numbers (percentages) unless indicated otherwise.

\*Adjusted for age category, sex, number of past history, systolic blood pressure category, activities of daily living category, cold exposure, active internal rewarming, internal disease etiology

CI; confidence interval, CCMC; critical care medical center, OR; odds ratio. sBP; systolic blood pressure.

## Discussion

Our multi-center study found that AH patients receiving care at the CCMC had lower likelihood of mortality compared to those receiving care at non-specialized centers. Moreover, although there was no significant difference in mortality rate among patients with severe hypothermia between the two groups, among patients with blood pressure of <90 mmHg, the CCMC group had lower mortality rate. 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-threatening 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 specialized center for patients with critical diseases such as AMI, stroke, and severe trauma.<sup>5-7</sup> Regarding AH, the severe hypothermia center has been established to improve outcomes of AH patients in Poland.[i] However, there has been no study to assess the impact of a specialized center on AH outcomes. One of the important functions about specialized center for AH is to perform ECMO. In this study, the proportion of CCMCs performing 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.<sup>12</sup> The consolidation of AH patients is expected to result in higher hospital patient volume. The higher hospital patient volume could increase staff knowledge, standardize response, as well as improve the performance of 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 may be key to improving prognosis.

In the sub-group analysis, there was no significant difference in mortality rate between severe hypothermia group and non-severe hypothermia group as analyzed by multivariable logistic regression. Unlike other studies that the predominant condition associated with secondary hypothermia was cold

alcohol or drug intoxication,<sup>4,[ii]</sup> 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, [iii],[iv] there might be little difference in the quality of care for patients with internal diseases between the specialized center and non-specialized center in this study. In contrast, among patients with systolic blood pressure of <90 mmHg, care at the specialized center 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.[v] Indeed, severe hypothermic patients are more likely to have lower blood pressure.<sup>1,10</sup> However, unstable hemodynamic status may 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 the specialized center.

In the field of ACS, stroke, and severe trauma, improvement of prognosis has been reported by patient consolidation.<sup>5-7</sup> Based on the results of our study, it is reasonable to promote the consolidation of AH patients, but the specialized center for AH seems not to be cost-effective due to the small number of cases in Japan due to the not so cold climate. Furthermore, this study did not assess the effect of bypass emergency medical system transport on prognosis, and further research is needed to investigate as to whether the transport all AH patients with circulatory failure to the 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 2 groups seemed balanced. Finally, we included patients with ICD 10 code, and we could have lost the populations of AH patients without ICD 10 code.

## Conclusions

Our multicenter study indicated that Care at CCMC was associated with improved outcomes in patients with AH. Optimizing the transport of AH to the specialized center is likely to be beneficial.

## Abbreviations

AH: accidental hypothermia; AOR: adjusted odds ratio; CI: confidence interval; ED: emergency department; CCMC: critical care medical center; ECMO: extra corporeal membrane oxygenation; ICD-10: the International Classification of Diseases, Tenth Revision; ADL: activities of daily living; GCS: Glasgow Coma Scale; SOFA: Sequential organ failure assessment; ICU: intensive care unit; VF: ventricular fibrillation; VT: ventricular tachycardia

# **Declarations**

## **Ethics approval and consent to participate**

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. Because of the retrospective study and de-identification of personal data,

each committee waived the need for informed consent.

## **Consent for publication**

Not applicable.

## **Availability of supporting data**

The data that support the findings of this study are available from Kyoto Prefectural

University of Medicine, but the availability of these data were restricted. However, data

are available from TM upon reasonable request and with permission of the institutions.

## **Conflict of interest statement**

The authors declare that they have no conflicts of interest.

## **Funding sources**

None

## **Authors' contributions**

FY and TM designed the study, analyzed the data, and wrote the first draft of the manuscript. SM, NE, NM, YO, TJ, YS, NO, MW, MN, AT, and YO extracted the data, interpreted the data, and critically revised the manuscript. TK reviewed all statistical analyses and critically revised the manuscript. TT supervised the analysis of the data and critically revised the manuscript. All the authors read and approved the final manuscript.

## Acknowledgements

We are deeply indebted to all members of the J-Point registry group for their contribution. We also thank Ms Marie Hara for study support.

## Author's information

No additional information.

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## Figures

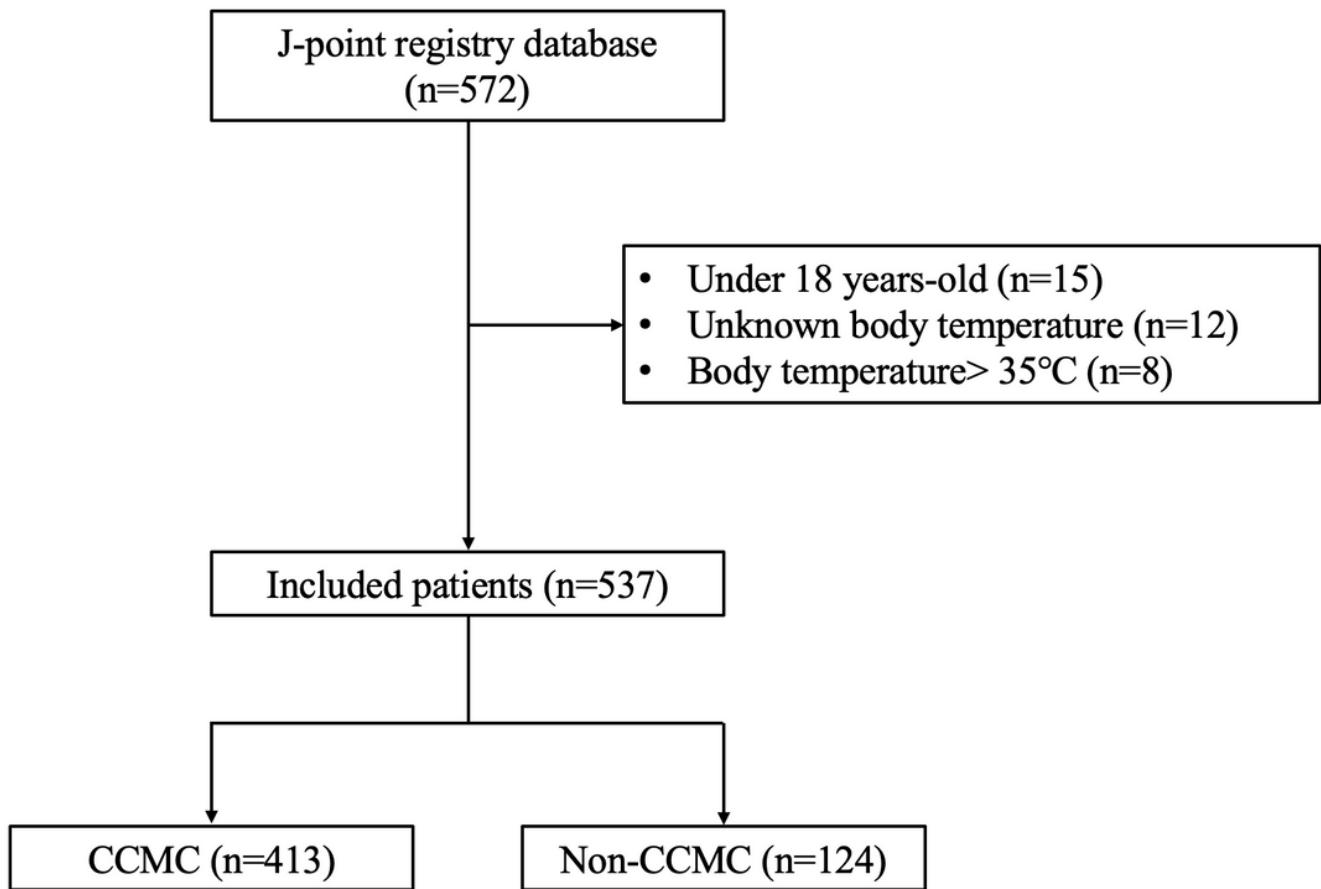


Figure 1

Patient flow of this study CCMC, critical care medical center.