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Incidence of hypothermia in critically ill patients receiving continuous renal replacement therapy in Siriraj Hospital, Thailand

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Background: Hypothermia is a relatively common complication in patients receiving continuous renal replacement therapy (CRRT). However, few studies have reported the factors associated with hypothermia.

Methods: A retrospective cohort study was performed in five intensive care units (ICUs) to evaluate the incidence of hypothermia and the predictive factors for developing hypothermia during CRRT, with hypothermia defined as a time-weighted average temperature <36 °C.

Results: From January 2020 to December 2021, 300 patients were enrolled. Hypothermia developed in 23.7% of them within the first 24 hours after CRRT initiation. Compared to non-hypothermic patients, hypothermic patients were older and had lower body weight, more frequent acidemia, and higher ICU and 30-day mortality rates. In the multivariate analysis, age >70 years (odds ratio [OR], 2.59; 95% CI, 1.38–4.98; P=0.004), higher positive fluid balance on the day before CRRT (OR, 1.11; 95% CI, 1.02–1.22; P=0.02), and CRRT dose (OR, 1.003; 95% CI, 1.00–1.01; P=0.04) were significantly associated with hypothermia. Conversely, a higher body weight was independently associated with mitigated risk of hypothermia (OR, 0.89; 95% CI, 0.81–0.97; P=0.01). Moreover, a higher coefficient of variance of temperature was associated with greater ICU mortality (OR, 1.41; 95% CI, 1.13–1.78; P=0.003).

Conclusions: Hypothermia during CRRT is a relatively common occurrence, and factors associated with hypothermia onset in the first 24 hours include older age, lower body weight, higher positive fluid balance on the day before CRRT, and higher CRRT dose. Greater temperature variability was associated with increased ICU mortality.

Key Words: acute kidney injury; continuous renal replacement therapy; hypothermia; mortality

INTRODUCTION

Continuous renal replacement therapy (CRRT) is common in critically ill patients with acute kidney injury (AKI), especially those who are hemodynamically unstable, in the intensive care unit (ICU) [1]. Research in this field has mainly focused on the intensity, modality, use of anticoagulants, and timing of RRT initiation rather than on quality improvements in treat-

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ment, including prevention of hypothermia [2-5]. Hypothermia is a relatively common complication during continuous extracorporeal blood purification because blood is circulated continuously throughout this process, involving exposure to ambient temperature, resulting in heat removal from the blood over time. Moreover, CRRT-related hypothermia is probably more highly aggravated by either a higher dose or use of un-heated dialysate and replacement fluid [6,7]. Hypothermia has potential harmful effects, including cardiac arrhythmia, increased oxygen demand, hemodynamic instability, coagulopathy, and potential to mask ongoing fever or sepsis, which are typically associated with poor outcomes [7-9]. Such iatrogenic hypothermia might be avoided by identifying high-risk patients and implementing preventive strategies. A previous meta-analysis determined that hypothermia is independently associated with increased mortality [10]. Nonetheless, a lower blood temperature can improve hemodynamic stability without disturbing the hepatosplanchnic oxygen concentration or the energy balance [11,12]. Moreover, the standard guideline and current recommendations do not provide suggestions to mitigate this issue, allowing uncertainty to persist [1,13].

Accordingly, we carried out a cohort study to identify the incidence of hypothermia in critically patients with AKI requiring CRRT. We also evaluated the factors associated with hypothermia in such patients. Moreover, we examined the characteristics of temperature modulation during CRRT and their impact on patient outcomes.

KEY MESSAGES

- During continuous renal replacement therapy (CRRT), patients at high risk for hypothermia, which include older individuals and those with lower body weight, higher positive fluid balance, and/or higher CRRT dose, should be monitored for temperature intensively.

MATERIALS AND METHODS

Study Design

This was a single-center, retrospective cohort study of patients in five medical ICUs (3 general ICUs, 1 respiratory ICU, and 1 cardiac ICU) in a tertiary hospital. This study is compliant with the Declaration of Helsinki. The study was approved by the Siriraj Institutional Review Board (No. SI 189/2021). Written informed consent for participant in the study was waived.

Population

All critically ill patients with severe AKI receiving CRRT in the five medical ICUs between January 2020 and December 2021 were considered for eligibility in the study. Patients who died or withdrew from treatment within 24 hours of CRRT or who had incomplete electronic medical records were excluded. The criteria for RRT initiation, its intensity, and anticoagulant use depended on the treating physician and patient needs.

Continuous venovenous hemofiltration, continuous venovenous hemodialysis, or continuous venovenous hemodiafiltration was carried out using a CRRT machine (either Prismaflex [Baxter] or Aquarius [Nikkiso]). The heating system of the Prismaflex machine is known as the Prisma Flow system and heats the return limb of the extracorporeal circuit, while the Aquarius heating system heats the dialysate fluid. We used either an M100 filter for the Prismaflex or an HF12 hemofilter (Nikkiso) for the Aquarius system. Either commercial or customized replacements and dialysate fluids were used. The blood flow rate was set at 150–200 mL/min, and the replacement and dialysate fluid were started at a rate of 2,000–3,000 mL/hr according to patient requirements.

Data Collection

We collected data from the patients' electronic medical records, including demographic data, comorbidities, Acute Physiology and Chronic Health evaluation (APACHE) II score, ICU mortality, indication for RRT, and clinical information at baseline before CRRT initiation. Each patient's baseline temperature was recorded before starting CRRT and then measured every 2–4 hours thereafter. In our hospital, axilla and tympanic membrane thermometers are normally used for such measurements. The CRRT prescription details, including modalities, blood flow rate, CRRT dose, and ultrafiltration rate, were recorded.

Primary and Secondary Outcomes

The primary outcome of the present study was the incidence of hypothermia during the first 24 hours of CRRT. Hypothermia was defined as a time-weighted average temperature (TWA^{Temp}) during CRRT <36 °C. The secondary outcomes were the factors associated with hypothermia among patients who began receiving CRRT in the following 24 hours and the impact of TWA^{Temp} indices on ICU mortality. Other indices of the time-weighted average temperature were also calculated: (1) Maximum TWA^{Temp}: defined as the maximum TWA^{Temp}

(T-max^{Temp}) in the 24-hour period after a patient started CRRT; (2) Maximum time at the TWA^{Temp}, defined as the time spent at the maximum TWA^{Temp} in the 24-hour period after a patient started CRRT; (3) Minimum TWA^{Temp}, defined as the minimum TWA^{Temp} (T-min^{Temp}) in the 24-hour period after a patient started CRRT; (4) Minimum time at the TWA^{Temp}, defined as the time spent at the minimum TWA^{Temp} in the 24-hour period after a patient started CRRT; (5) Coefficient of variance of the TWA^{Temp} (CV^{Temp}), defined as the standard deviation of the TWA^{Temp} divided by the mean TWA^{Temp} in the 24-hour period after a patient started CRRT, expressed as a percentage; and (6) Amplitude of the TWA^{Temp} (Amplitude^{Temp}), defined as the difference between the maximum TWA^{Temp} and the mean TWA^{Temp} in the 24-hour period after a patient started CRRT.

Statistical Analysis

Categorical variables are presented as number and percentage, and continuous variables are presented as mean±standard deviation or median and interquartile range as appropriate. Student t-test and the Mann-Whitney U-test were used for comparisons among continuous variables, and the chi-square test or Fisher's exact test was used for comparisons among categorical variables. Because the temperature during CRRT can vary dynamically, the time-weighted average temperature was calculated as the area under the temperature-versus-time plot (see the equation in Supplementary Material 1). Univariate analysis was performed, and all significant variables were considered for multivariate logistic regression analysis to identify the predictive factors associated with hypothermia. The impacts of the TWA^{Temp} indices on ICU mortality were estimated using a generalized linear model and considering the significant factors identified from the multivariate analysis as covariates. As multicollinearity was considered among the TWA^{Temp} indices, each index was used only once, resulting in a total of six models. Furthermore, we used hazard ratios and 95% CIs derived from Cox proportional hazards models, adjusted for the previously mentioned covariates, to evaluate the time to 30-day mortality and compare it between hypothermia and non-hypothermia cases. Patients were censored at 30 days, with those discharged before this period classified as alive at day 30. A two-sided P-value <0.05 was considered significant. All data analyses were performed using SPSS statistics version 18 (IBM Corp.) and R software version 4.2.1 (R Foundation).

RESULTS

Study Population

From January 2020 to December 2021, 300 critically ill patients were diagnosed with severe AKI, received CRRT, and were included in this study (Figure 1). Among the total study cohort, in the first 24 hours of CRRT initiation, 23.7% (71/300) had a time-weighted average temperature <36 °C and a time-to-hypothermia onset of approximately 3 hours, as shown in Figure 2. Patient baseline characteristics stratified by hypothermia are shown in Table 1. Baseline comorbidities, sex, sepsis, use of a mechanical ventilator, use of vasopressors, use of an external warmer, and baseline temperature before CRRT were similar between groups. However, the hypothermic patients were older (74.1 vs. 66.0 years, P=0.02) and had lower body weight (58.0 vs. 61.8 kg, P=0.03), higher APACHE II score (26.0 vs. 24.0 points, P=0.01), higher 30-day mortality rate (64.8% vs. 44.1%,

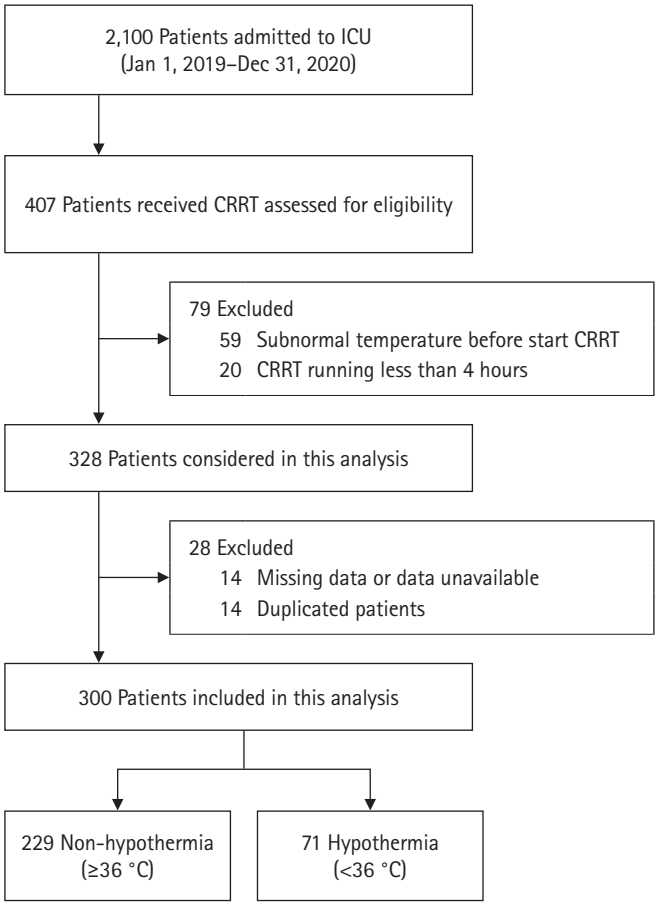

Figure 1. A study flow diagram. Hypothermia was defined as a time-weighted average temperature <36 °C. ICU: intensive care unit; CRRT: continuous renal replacement therapy.

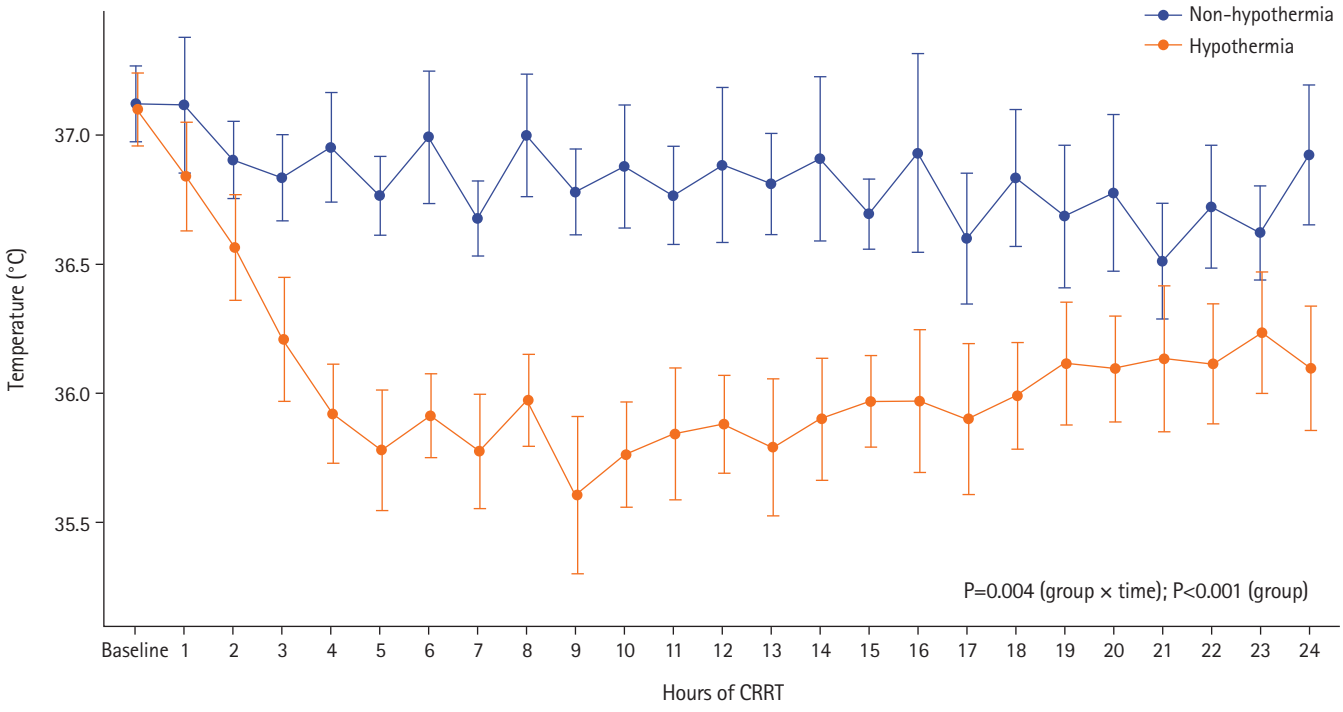

Figure 2. Hourly temperature in degrees (°C) in the first 24 hours of continuous renal replacement therapy (CRRT) stratified by time-weighted average temperature. Temperature is expressed as mean, error bars represent 95% CI. Hypothermia was defined as a time-weighted average temperature <36 °C.

P=0.004), and higher ICU mortality rate (59.2% vs. 44.1%, P=0.04). Also, metabolic acidosis was a more common indication for CRRT in these patients (63.4% vs. 44.1%, P=0.01). The fluid balance values and the results of laboratory and CRRT analyses are shown in Table 2. Baseline blood urea nitrogen, creatinine, hemoglobin level, CRRT modality, initial blood flow rate, and median ultrafiltration were similar between the groups. The fluid balance was higher in the hypothermic group on both the day before and the day of CRRT. The CRRT dose was also greater in the hypothermia group than in the non-hypothermia group (33.4 vs. 30.9 ml/kg/hr, P=0.01), together with a higher initial CRRT temperature setting (37.5 °C vs. 37.0 °C, P=0.04).

Univariate and Multivariate Analyses

In univariate analysis, patient age, body weight, metabolic acidosis, fluid balance on both the day before and the day of CRRT, and the CRRT dose were all significantly associated with TWA^{Temp} <36 °C. However, in the multivariate logistic regression analysis, the factors predicting hypothermia were age >70 years (OR, 2.59; 95% CI, 1.38–4.98; P=0.004), fluid balance on the day before CRRT (OR, 1.11; 95% CI, 1.02–1.22; P=0.02), and CRRT dose (OR, 1.003; 95% CI, 1.00–1.01; P=0.04). Moreover, an increase in body weight was independently associated with decreased risk of hypothermia (OR, 0.89; 95% CI, 0.81–0.97; P=0.01) (Table 3).

When we considered the influences of the TWA^{Temp} indices on ICU mortality (Table 4 and Figure 3), the survivors had higher TWA^{Temp}, lower minimum TWA^{Temp}, longer T-MaxTemp, and lower CV^{Temp} and $Amplitude^{Temp}$ values compared to the non-survivors. However, following adjustment for age, body weight, CRRT dose, and fluid balance before CRRT, a higher CV^{Temp} during CRRT treatment in the first 24 hours was associated with greater ICU mortality (OR, 1.41; 95% CI, 1.13–1.78; P=0.003) (Table 5). When sepsis and mechanical ventilation were included as adjusted covariates, there were no changes in either the factors predicting hypothermia or in the relationship between CV^{Temp} and ICU mortality (Supplementary Tables 1 and 2).

Hypothermia, defined as TWA^{Temp} <36 °C, was associated with an increased 30-day mortality rate. The adjusted hazard ratio for the hypothermia group was 1.47 (95% CI, 1.01–2.13; P=0.04) in comparison to the non-hypothermia group (Figure 4).

Table 1. Baseline characteristics and outcome of patients stratified by time-weighted average temperature in the first 24 hours of CRRT

Variable	Non-hypothermia[a] (n=229, 76.3%)	Hypothermia[b] (n=71, 23.7%)	P-value
Age (yr)	66 (53–79)	74 (61–81)	0.02
Female	95 (41.5)	29 (40.8)	0.99
Body weight (kg)	61.8 (54.0–70.9)	58.0 (50.0–65.0)	0.03
APACHE II score	24.0 (20.0–29.0)	26.0 (22.0–31.5)	0.01
Comorbidity			
Diabetes	98 (42.8)	31 43.7)	0.99
Hypertension	144 (62.9)	42 (59.2)	0.67
Chronic kidney disease	133 (58.1)	37 (52.1)	0.45
Stage 3	44 (19.2)	14 (19.7)	
Stage 4	29 (12.7)	7 (9.9)	
Stage 5	59 (25.8)	16 (22.5)	
Coronary artery disease	87 (38.0)	26 (36.6)	0.95
Congestive heart failure	41 (17.9)	11 (15.5)	0.77
Liver disease	39 (17.0)	7 (9.9)	0.20
Malignancy	47 (20.5)	15 (21.1)	0.99
Indication for RRT			
Metabolic acidosis	101 (44.1)	45 (63.4)	0.01
Fluid overload	92 (40.2)	27 (38.0)	0.85
Hyperkalemia	25 (10.9)	7 (9.9)	0.97
Sepsis	129 (56.3)	49 (69.0)	0.08
Vasopressor	184 (80.3)	60 (84.5)	0.54
Norepinephrine equivalent dose[c] (μg/kg/min)	0.2 (0.1–0.5)	0.3 (0.2–0.5)	0.20
Mechanical ventilator	201 (87.8)	68 (95.8)	0.09
Baseline temperature before CRRT (°C)	36.9 (36.5–37.6)	36.8 (36.4–37.5)	0.34
External warmer	21 (9.2)	3 (4.2)	0.28
ICU mortality	101 (44.1)	42 (59.2)	0.04
Hospital mortality	134 (58.5)	51 (71.8)	0.06
Renal outcome: MAKE30	154 (67.2)	54 (76.1)	0.21
Mortality at day 30	101 (44.1)	46 (64.8)	0.004
Doubling serum creatinine	8 (10.7)	3 (15.8)	0.82
RRT dependence	45 (37.2)	5 (20.8)	0.19

Values are presented as median (interquartile range) or number (%).
CRRT: continuous renal replacement therapy; APACHE: Acute Physiology and Chronic Health Evaluation; RRT: renal replacement therapy; ICU: intensive care unit; MAKE30: Major Adverse Kidney Event at day 30.
a) Defined by time-weighted average temperature more than or equal 36 °C; b) Defined by time-weighted average temperature less than 36 °C;
c) Norepinephrine equivalent dose = dose of norepinephrine (μg/kg/min) + dose of adrenaline (μg/kg/min) + (dopamine (μg/kg/min) / 150.

DISCUSSION

This retrospective cohort study investigated the incidence of CRRT-related hypothermia and the factors associated with developing hypothermia in the first 24 hours of CRRT, and hypothermia developed in 23.7% of cases. The significant predisposing factors associated with hypothermia were age >70 years, a higher positive fluid balance on the day before CRRT, and a greater CRRT dose. Greater body weight was independently associated with reduced risk of hypothermia. We also found that greater temperature variability was associated with increased ICU mortality and identified hypothermia as a significant risk factor for 30-day mortality.

Comparison between Current and Previous Findings

The relationship between body temperature and mortality in critically ill patients showed a U-shaped curve [14]. The rate of CRRT-related hypothermia has been reported at 30%–50%

Table 2. Fluid balance, laboratory and CRRT prescription of patients stratified by time-weighted average temperature in the first 24 hours of CRRT

Variable	Non-hypothermia[a] (n=229, 76.3%)	Hypothermia[b] (n=71, 23.7%)	P-value
Hemoglobin (g/dl)	8.8 (7.9–10.1)	9.4 (8.2–10.6)	0.12
BUN (mg/dl)	66.0 (41.0–90.0)	59.0 (38.0–83.5)	0.16
Creatinine (mg/dl)	3.6 (2.4–5.4)	4.0 (2.7–5.5)	0.26
Fluid balance day before CRRT (mL)	1,421 (67–3,216)	1,943 (1,254–4,390)	0.01
Fluid balance on the day of CRRT (mL)	744 (–1,926 to 2,767)	1,850 (–1,071 to 4,758)	0.04
CRRT modality			0.25
CVVH	210 (91.7)	66 (93.0)	
CVVHDF	4 (1.7)	3 (4.2)	
SCUF	15 (6.6)	2 (2.8)	
Blood flow rate (ml/min)	200 (150–200)	200 (150–200)	0.08
Duration of CRRT (hr)	19.5 (10.5–24.0)	21.1 (11.3–24.0)	0.52
Dose of CRRT (ml/kg/hr)	30.9 (24.9–35.9)	33.4 (29.0–38.7)	0.01
CRRT dose >30 ml/kg/hr	120 (52.4)	50 (70.4)	0.01
Ultrafiltration (ml/day)	420 (0–1,790)	475 (0–1,401)	0.69
Ultrafiltration (ml/kg/hr)	0.4 (0.0–1.6)	0.5 (0.0–1.5)	0.92
Temperature setting of CRRT (°C)	37.0 (37.0–38.0)	37.5 (37.0–38.0)	0.04
Number of temperature observations	7.0 (5.0–11.0)	8.0 (5.0–11.0)	0.42

Values are presented as median (interquartile range) or number (%).
CRRT: continuous renal replacement therapy; BUN: blood urea nitrogen; CVVH: continuous venovenous hemofiltration; CVVHDF: continuous venovenous hemodiafiltration; SCUF: sustain continuous ultrafiltration.
a) Defined by time-weighted average temperature more than or equal 36 °C; b) Defined by time-weighted average temperature less than 36 °C.

Table 3. Univariable and multivariable models for the time-weight average temperatures less than 36 °C

Variable	Univariable model		Multivariable model[a]	
	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
Age (yr)	1.02 (1.00–1.03)	0.005	1.02 (1.00–1.04)	0.05
Age >70 yr	2.04 (1.19–3.54)	0.01	2.59 (1.38–4.98)	0.004
Body weight (kg)	0.97 (0.95–0.99)	0.01	0.89 (0.81–0.97)	0.01
Metabolic acidosis[b]	2.19 (1.28–3.84)	0.005	1.56 (0.80–3.08)	0.20
Fluid balance on the day before CRRT (L)	1.12 (1.03–1.23)	0.01	1.11 (1.02–1.22)	0.02
Fluid balance on the day of CRRT (L)	1.10 (1.03–1.17)	0.007	1.10 (1.00–1.21)	0.05
Dose of CRRT (ml/kg/hr)	1.04 (1.01–1.06)	0.01	1.003 (1.00–1.01)	0.04
Temperature of CRRT (°C)	1.12 (0.91–1.37)	0.27	-	-

CRRT: continuous renal replacement therapy.
a) Multivariable models were performed by significant factors on univariable models; b) Defined as blood pH less than 7.3.

depending on the definition of hypothermia [15-17]. Although there is no standard definition of hypothermia, two common cutoff points of 35 °C and 36 °C are generally accepted [14,16,17]. Our study defined hypothermia using the latter cutoff point because a previous meta-analysis reported that hypothermia defined as <36 °C is associated with an approximately twofold increase in mortality, while a threefold increase was observed when using a cutoff point <35 °C [10], which indicates a dose–response relationship between hypothermia and patient outcomes. Moreover, longer exposure to hypothermia is also associated with worse outcomes [18]. Therefore, we believe that early detection of CRRT-induced hypothermia could prevent additional and more severe detrimental effects of hypothermia [6,10]. Moreover, the temperature during CRRT can vary dynamically, and the duration of CRRT exposure may be a major influencing factor in this variation. Thus, we considered the time-weighted average for developing hypothermia rather than the development of hypothermia at a single time point.

Table 4. Temperature indices according to ICU survivors and non-survivors

Variable	Survivor (n=157)	Non-survivor (n=143)	Absolute differenc (95% CI)	P-value
TWA^{Temp} (°C)	36.42±0.56	36.27±0.76	0.16 (0.003 to 0.31)	0.04
$Maximum^{Temp}$ (°C)	37.36±0.72	37.46±0.94	−0.10 (−0.29 to 0.09)	0.30
$Minimum^{Temp}$ (°C)	35.68±0.82	35.34±1.10	0.34 (0.12 to 0.56)	0.002
CV^{Temp} (°C)	1.56±0.90	2.09±1.47	−0.53 (−0.81 to -0.25)	<0.001
$T\text{-}max^{Temp}$ (°C)	6.43±7.57	4.32±6.75	2.11 (0.48 to 3.74)	0.01
$T\text{-}min^{Temp}$ (°C)	10.35±6.36	10.33±6.48	0.02 (−1.44 to 1.48)	0.98
$Amplitude^{Temp}$ (°C)	0.90±0.65	1.11±0.83	−0.22 (−0.39 to −0.05)	0.01

Values are presented as mean±standard deviation.

ICU: intensive care unit; TWA: time-weighted average; TWA^{Temp}: TWA temperature was calculated as the area under the temperature-versus-time plot; $Maximum^{Temp}$: maximum temperature in the period of 24 hours of CRRT; $Minimum^{Temp}$: minimum temperature in the period of 24 hours of CRRT; CV: coefficient of variation; CV^{Temp}: standard deviation of the temperature divided by the mean temperature in the period of 24 hours of CRRT; $T\text{-}max^{Temp}$: time spent on the maximum temperature in the period of 24 hours of CRRT; $T\text{-}min^{Temp}$: time spent on the minimum temperature in the period of 24 hours of CRRT; $Amplitude^{Temp}$: difference between the maximum and the mean temperature in the period of 24 hours of CRRT; CRRT: continuous renal replacement therapy.

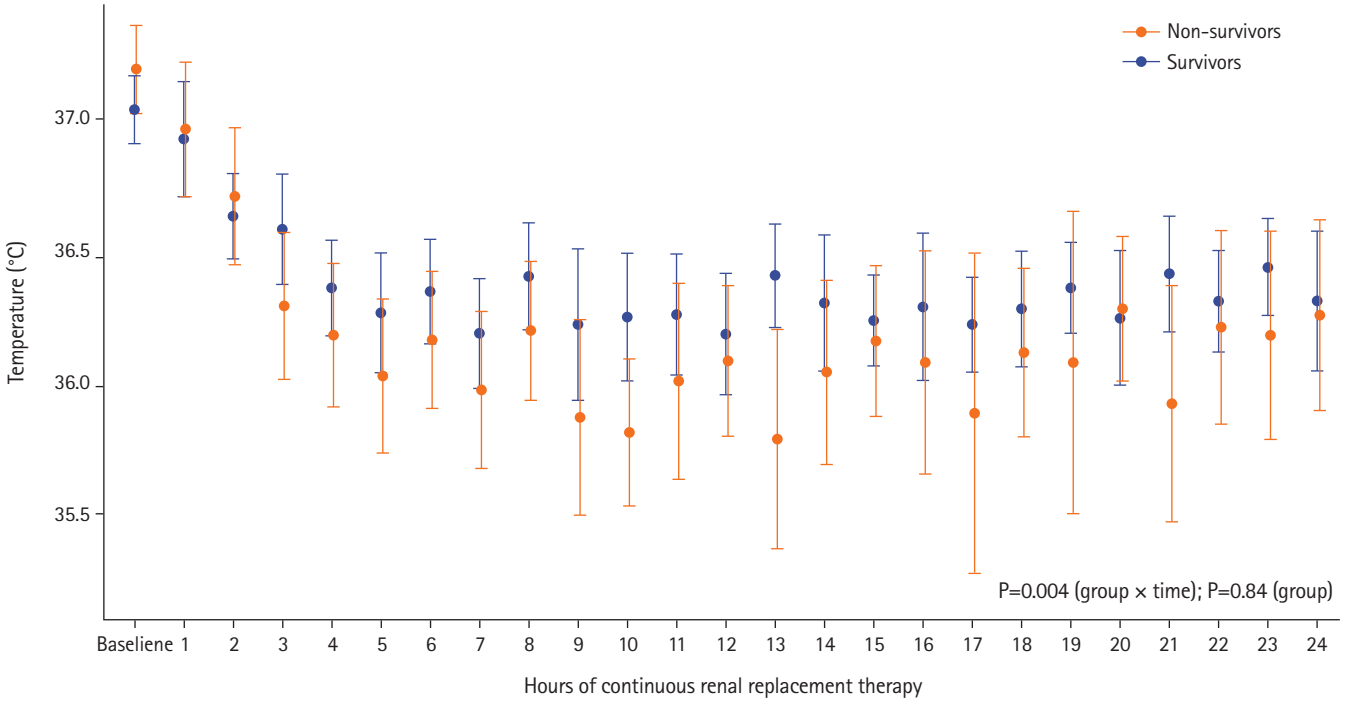

Figure 3. Hourly temperature in degrees Celsius in the first 24 hours of continuous renal replacement therapy stratified by intensive care unit mortality. Temperature is expressed as the mean and error bars represent the 95% CI.

Previous studies have reported that factors associated with CRRT-related hypothermia include low body weight, continuous venovenous hemodiafiltration, sedation, immobility, and sepsis [15,19]. In the present study, older age, a more positive cumulative fluid balance, and a higher CRRT dose were independently associated with hypothermia, while a greater body weight was associated with a lower risk of hypothermia. Possible mechanistic explanations for these results include impairment of thermoregulation in elderly individuals and greater exposure to ambient temperature for fluid administration and dialysate or replacement fluid. Consequently, a relatively high fluid administration rate and CRRT dose should be reduced according to patient body weight. We could not explore the impact of the CRRT modality on hypothermia because most of the patients in the present study underwent continuous venovenous hemofiltration.

Table 5. Univariable and multivariable models for ICU mortality

Temperature indices	Univariable models		Multivariable models[a]	
	Odds ratio[b] (95% CI)	P-value	Odds ratio[b] (95% CI)	P-value
TWA^{Temp}	0.70 (0.47–0.99)	0.05	0.85 (0.57–1.25)	0.41
$Maximum^{Temp}$	1.16 (0.88–1.53)	0.30	1.18 (0.88–1.58)	0.27
$Minimum^{Temp}$	0.69 (0.53–0.88)	0.003	0.76 (0.57–1.00)	0.05
CV^{Temp}	1.46 (1.19–1.82)	< 0.001	1.41 (1.13–1.78)	0.003
$T\text{-}max^{Temp}$	0.96 (0.93–0.99)	0.01	0.97 (0.93–1.00)	0.05
$T\text{-}min^{Temp}$	1.00 (0.97–1.04)	0.98	1.00 (0.96–1.04)	0.99
$Amplitude^{Temp}$	1.49 (1.09–2.06)	0.01	1.32 (0.94–1.88)	0.12

Values are presented mean±standard deviation. Temperature was expressed as degree Celsius. Each model was adjusted with factors including age, body weight, fluid balance before continuous renal replacement therapy, dose of continuous renal replacement therapy.
ICU: intensive care unit; TWA: time-weighted average; TWA^{Temp}: TWA temperature was calculated as the area under the temperature-versus-time plot; $Maximum^{Temp}$: maximum temperature in the period of 24 hours of CRRT; $Minimum^{Temp}$: minimum temperature in the period of 24 hours of CRRT; CV: coefficient of variation; CV^{Temp}: standard deviation of the temperature divided by the mean temperature in the period of 24 hours of CRRT; $T\text{-}max^{Temp}$: time spent on the maximum temperature in the period of 24 hours of CRRT; $T\text{-}min^{Temp}$: time spent on the minimum temperature in the period of 24 hours of CRRT; $Amplitude^{Temp}$: difference between the maximum and the mean temperature in the period of 24 hours of CRRT; CRRT: continuous renal replacement therapy.
a) Since multicollinearity is expected among the indices of TWA^{Temp}, each one was included alone and one at a time in the models, resulting in a total of six models; b) Odds ratio calculated per 1-hour increase.

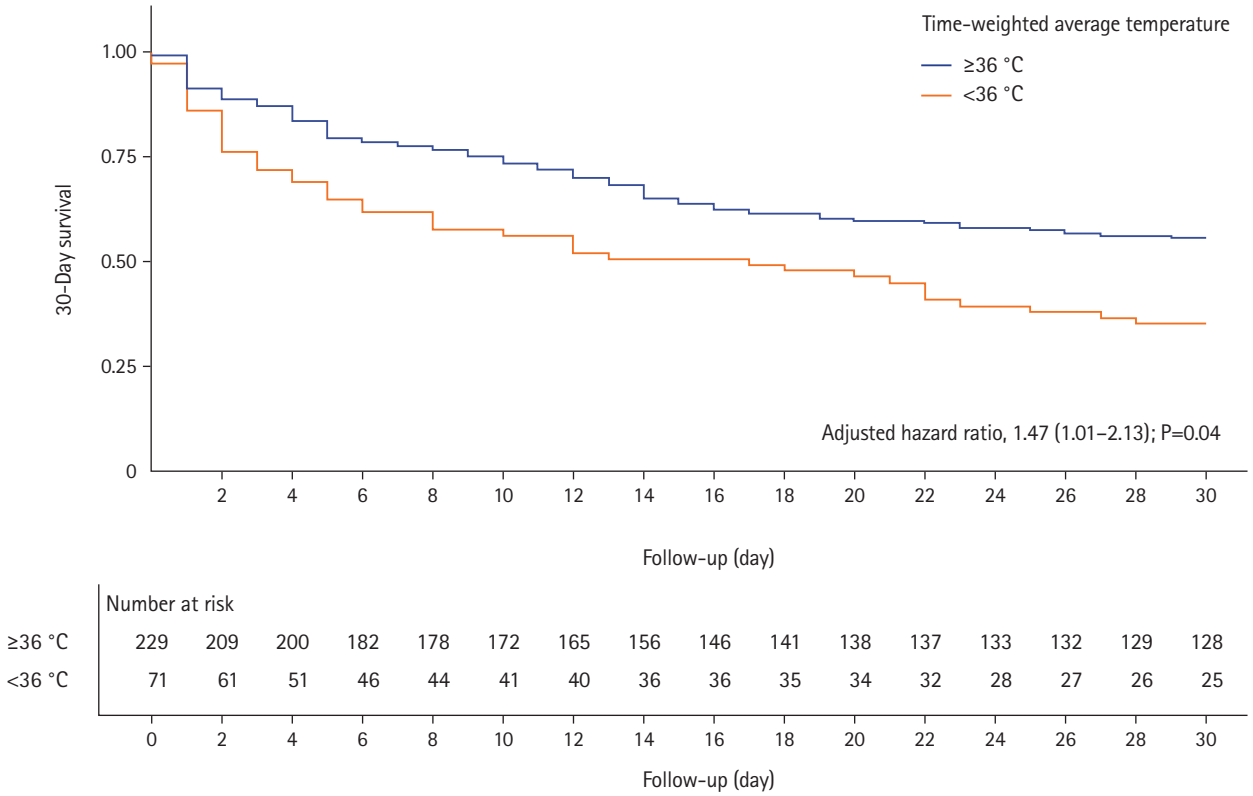

Figure 4. The Kaplan–Meier 30-day survival curves for continuous renal replacement therapy (CRRT) patients stratified by time-weighted average temperature. The figure depicts the 30-day survival rates following initiation of CRRT for both non-hypothermia and hypothermia groups, with hypothermia defined as a time-weighted average temperature <36 °C.

The Kidney Disease Improving Global Outcomes (KDIGO) guideline recommends a delivery dose of CRRT of 20–25 mL/kg/hr [1]. In our study, the initial CRRT dose was greater than the suggested dose. This might be because most of the included patients had sepsis, while metabolic acidosis was the most common indication for CRRT. Moreover, in such patients, aggressive fluid resuscitation is commonly prescribed, resulting in a greater potential for hypothermia onset.

Currently, the heating system in commercial CRRT machines performs either blood warming or replacement fluid warming. Blood-warming systems can perform either direct warming using a heating machine or indirect warming using a sleeve on the blood return line. Bell et al. [20] showed that a direct blood warmer better reduces the risk of hypothermia compared to a heating sleeve. However, neither the current standard guideline for prevention of hypothermia nor that for optimal target temperature management in patients undergoing CRRT includes such a recommendation [13].

Temperature variability was a predictor of poor outcomes in brain-injured patients in a previous study [21]. In the present study, greater temperature variability during the 24-hour period after CRRT initiation also was associated with increased ICU mortality. However, whether there is a causal relationship between temperature fluctuations and poor ICU outcomes in either non-neurological patients or during RRT requires further research.

Various physiological mechanisms may explain the relationship between hypothermia and mortality, such as detrimental consequences of increased susceptibility to infection due to compromised immune function, cardiac arrhythmias resulting from severe electrolyte imbalances, coagulopathy, and reduced responsiveness to catecholamines [22,23].

This study implies that CRRT-induced hypothermia is a relatively common complication in the early phase of CRRT. The high-risk group of patients in this study was older, had low baseline body weight, and/or had higher positive fluid accumulation balance. We suggest that patients with these characteristics should undergo more frequent temperature monitoring. Our findings also suggest that the CRRT dose should be adjusted according to the patient's body weight; this is a modifiable risk factor that can prevent iatrogenic prescription of a higher CRRT dose. Preemptive or early intervention to prevent hypothermia in such patients should be considered.

We used the time-weighted average temperature to determine hypothermia, which considered both temperature and time on CRRT, as this was considered a better approach than using a single cutoff point value. We also found some signs of relationships between TWA^{Temp} indices during CRRT and patient outcomes. However, there are several limitations in our study. First, we routinely recorded the tympanic membrane and axillary temperature rather than the core temperature, and we normally documented the temperature every 2–4 hours. Thus, there could be some erroneous and missing values. Second, some patients received passive external rewarming or active external rewarming, and these might be confounding factors. However, in our study, the percentage use of such interventions was quite low. Moreover, therapeutic intervention to prevent hypothermia requires further investigation. Third, this was a retrospective study that involved unmeasured confounders due to the nature of the study design. Fourth, the TWA^{Temp} indices during CRRT did not demonstrate a causal relationship with patient outcomes, and such association was examined only during the first 24 hours after CRRT initiation. Nevertheless, this suggests that a considerable number of patients may experience prolonged hypothermia during CRRT, highlighting the potential for quality-improvement efforts in this area. Moreover, the present study did not provide the optimal temperature target during CRRT. However, this study identifies a knowledge gap for future clinical trials to confirm or refute these findings.

In conclusion, in a cohort of critically ill patients with AKI requiring CRRT, hypothermia was common and developed rapidly. Older age, lower body weight, higher positive fluid balance on the day before CRRT, and higher CRRT dose were independently associated with hypothermia. Increased temperature variability and hypothermia during CRRT were linked to ICU mortality and 30-day mortality, respectively. These findings require validation by additional investigation.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.4266/acc.2024.00038.

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