Persistent cool extremities as an independent predictor of adverse clinical outcomes among critically ill patients: a single-center retrospective observational study

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Abstract

Cool extremities representing impaired skin perfusion are a classical sign of shock. We evaluated associations between the presence and persistence of subjective cool extremities observed by caring nurses and clinical outcomes. We conducted a retrospective observational study in an Intensive Care Unit (ICU) at a university hospital in Japan. Patients were divided into two groups based on the presence or absence of subjective cool extremities during the first 24 hours of their ICU stay. We compared their characteristics and outcomes. In total, 2956 patients were analyzed. Patients with cool extremities were older, had higher severity Acute Physiology and Chronic Health Evaluation (APACHE III) scores, had higher in-hospital mortality (4.1% *vs* 18%, $p<0.001$), and had a higher prevalence of acute kidney injury requiring renal replacement therapy (2.1% *vs* 10%, $p<0.001$) as compared to patients without nurse-reported cool extremities. Multivariable logistic regression showed cool extremities persisting for ≥12 hours were significantly associated with in-hospital death (adjusted Odds Ratio, OR, 1.64) and acute kidney injury requiring renal replacement therapy (adjusted OR 1.82). Patients with subjective cool extremities were more severely ill and had poorer outcomes. Subjective skin temperature assessment may be useful to detect high-risk patients.

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Introduction

Hemodynamic instability is common among critically ill patients and can lead to organ failure and poor outcomes. Hemodynamic monitoring is crucial to detect hemodynamic instability and start interventions to prevent organ damage. Although global hemodynamic measurements, such as blood pressure, heart rate, and cardiac output, are commonly used to assess hemodynamic status, these alone are insufficient for a comprehensive evaluation of a patient's circulatory status.[1] Recently, impaired microcirculation has been found to play a critical role in the development of organ dysfunction and adverse outcomes among critically ill patients.[2] Therefore, early detection of microcirculation impairment is essential in the management of these patients.

Signs of impaired skin perfusion, such as mottled skin, prolonged capillary refill time, and increased center-to-toe temperature gradient, are considered to indicate impaired microcirculation.[3] Several previous studies reported associations between signs of impaired skin perfusion and adverse outcomes.[4-7] Subjective skin temperature assessment is the simplest method of evaluating skin perfusion. Several studies reported associations between subjective cool extremities and higher lactate levels[4] and adverse outcomes.[6,8,9] However, most of these studies used small sample sizes and did not adjust for disease severity using multivariate analysis. Therefore, it remains unclear whether subjective cool extremities are indicative of severely ill patients or predictors of poor outcomes.

This study aimed to evaluate the associations between subjective cool extremities and patient characteristics, disease severity, and clinical outcomes among non-selected Intensive Care Unit (ICU) patients. We hypothesized that among these patients, i) subjective cool extremities could be associated with disease severity, and ii) subjective cool extremities and their persistence could be associated with adverse clinical outcomes.

Materials and Methods

Study design

This retrospective observational study was conducted in a 12-bed general ICU at a university hospital in Japan from April 2016 to December 2019. The Institutional Review Board waived the requirement for informed consent because of the observational and retrospective nature of this study (approval number R-43-12J).

Participants

All adult patients (aged ≥16 years) were included. For patients readmitted to the ICU during the same hospitalization, only the initial admission was included. We excluded patients without assessment of cool extremities during the first 24 hours from ICU admission.

Data collection

The information collected for all patients admitted to the ICU from their electrical medical records included: age, gender, height, weight, admission classification (elective surgery, emergency surgery, non-operative), admission type (elective or emergency), admission source (general ward, emergency room, operation room, others), hospitalization date, ICU admission date, chronic organ insufficiency (congestive heart failure, respiratory failure, liver cirrhosis, use of immunosuppressants, chronic hemodialysis, lymphoma, acute leukemia, cancer with metastases), diagnosis at ICU admission, and vital signs and laboratory data within 24 hours after ICU admission. We also recorded patients' severity scores, including the Acute Physiology and Chronic Health Evaluation (APACHE) II, APACHE III, and Simplified Acute Physiology Score (SAPS) II, along with the treatment received during their ICU stay (mechanical ventilation use, vasopressor use, and Renal Replacement Therapy, [RRT], use) and prognosis, including in-ICU death and in-hospital death.

Exposure

The primary exposure in this study was subjective cool extremities within 24 hours after ICU admission and the duration of cool extremities. The presence of cool extremities was based on the ICU chart recorded by the nurse providing care. In the studied ICU, the caring nurse routinely assesses and documents the presence of subjective cool extremities. The timing of this assessment is not predefined and is based on the caring nurse's discretion. For this study, the duration of cool extremities was defined as follows. Among patients who exhibited at least one episode of cool extremities within 24 hours after ICU admission, the duration of the cool extremities episode was calculated as the time between the onset and resolution of cool extremities. If cool extremities appeared and disappeared more than once within 24 hours after ICU admission, the duration was calculated as the sum of these episodes. In cases where the resolution of cool extremities was not documented within 24 hours after ICU admission or by the time of ICU discharge, the cool extremities were considered to have persisted until 24 hours after ICU admission or ICU discharge (Figure 1). For patients that did not have cool extremities, the duration was defined as zero. The duration of cool extremities was categorized into two groups: "transient" if the duration was less than 12 hours and "persistent" if the duration was ≥12 hours. This threshold was based on a previous study.[10]

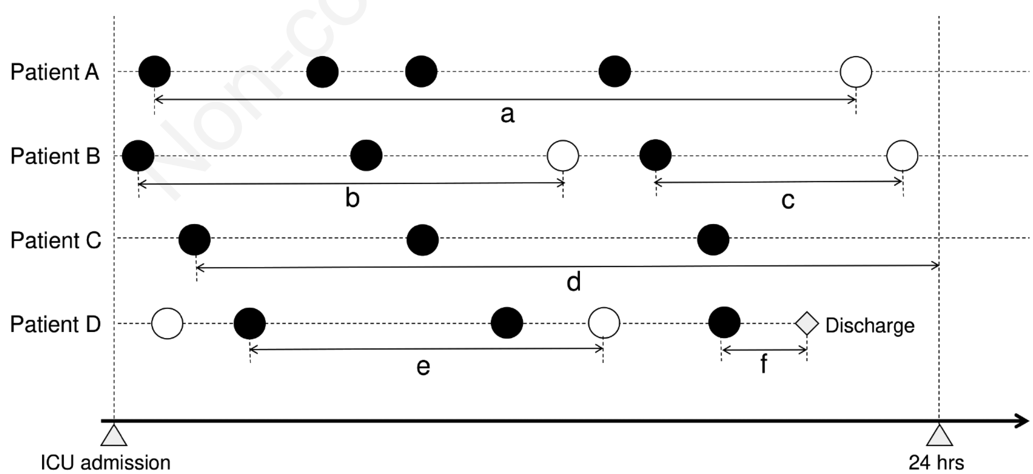

Figure 1. Examples of the duration of cool extremities. Black circles represent cool extremities and white circles represent no cool extremities at that time point. Patient A: Cool extremities appeared and disappeared within first 24 hours. The duration was defined as interval between this sign appearing and disappearing (**a**). Patient B: Cool extremities appeared and disappeared multiple times within 24 hours. The duration was defined as the sum of intervals between each episode (**b** + **c**). Patient C: Cool extremities appeared but did not disappear within first 24 hours. The duration was defined as interval of time point when this sign appeared and 24 hours after ICU admission (**d**). Patient D: Cool extremities appeared multiple times within 24 hours but disappeared and were not observed until discharge for a second episode. The duration of the second episode was defined as the interval between when the sign appeared and discharge (**f**), and the total duration was defined as sum of these periods (**e** + **f**).

Outcomes

The primary outcome was in-hospital mortality. The secondary outcome was Acute Kidney Injury (AKI) that required RRT, which was defined as RRT use during the ICU stay for patients not on chronic dialysis.

Covariates

Covariates for adjustment were selected based on previously reported outcome predictors among critically ill patients or clinical importance, and included: age, gender, comorbidities, days before ICU admission after hospitalization,[11] cardiopulmonary resuscitation before ICU admission, reason for ICU admission,[12,13] diagnosis for ICU admission (cardiovascular disease *vs* sepsis *vs* others), APACHE III score, hyperlactatemia (more than 2 mmol/L) within 24 hours after ICU admission, mechanical ventilation within 24 hours after ICU admission, and use of vasoactive agents within 24 hours after ICU admission.

Statistical analyses

Patients were first divided into those who had cool extremities within 24 hours after ICU admission and those who did not. Patient characteristics, severity of illness, treatment during ICU stay, and outcomes were compared between the two groups. Categorical variables were reported as counts and percentages, and comparisons between the two groups were made using Fisher's exact tests and chi-square tests as appropriate. Continuous variables were reported as median and Interquartile Range (IQR) and compared using a Mann–Whitney U-test. Locally Estimated Scatterplot Smoothing (LOESS) curves with 95% Confidence Intervals (CI) were used to illustrate the relationships between the duration of cool extremities and in-hospital mortality and prevalence of AKI requiring RRT. Multivariable logistic regression analyses were used to analyze associations between cool extremities and outcomes, adjusted for potential confounding factors, and the OR and 95% CI were calculated. In the multivariable logistic regression models, we treated cool extremities as a categorical value with three levels: i) no cool extremities, ii) transient cool extremities (duration <12 hours), and iii) persistent cool extremities (duration ≥12 hours). A sensitivity analysis was also conducted in which the duration of cool extremities was entered into the model as a continuous variable. All statistical tests were two-tailed, with p-values <0.05 considered statistically significant. All analyses were performed using R version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patients' characteristics and outcomes by the presence of subjective cool extremities

During the study period, 3278 cases were admitted to the ICU and 2956 patients were analyzed (Figure 2). Twenty-two patients were excluded because of no assessment of cool extremities within 24 hours after ICU admission. Of these patients, 14 patients had died within 6 hours after ICU admission.

Among the analyzed patients, there was a median of six assessments of cool extremities within 24 hours after ICU admission. Patients' characteristics, severity of illness, treatment during their ICU stay, and clinical outcomes are reported in Table 1. The median age was 70 years (IQR: 61-76 years), 35% of patients were female, the median APACHE III score was 58 (IQR: 44-74), 52% required mechanical ventilation, 43% received vasoactive agents, and 9.2% required RRT. The rate of in-hospital mortality was 8.8%, and that of AKI requiring RRT was 4.8%.

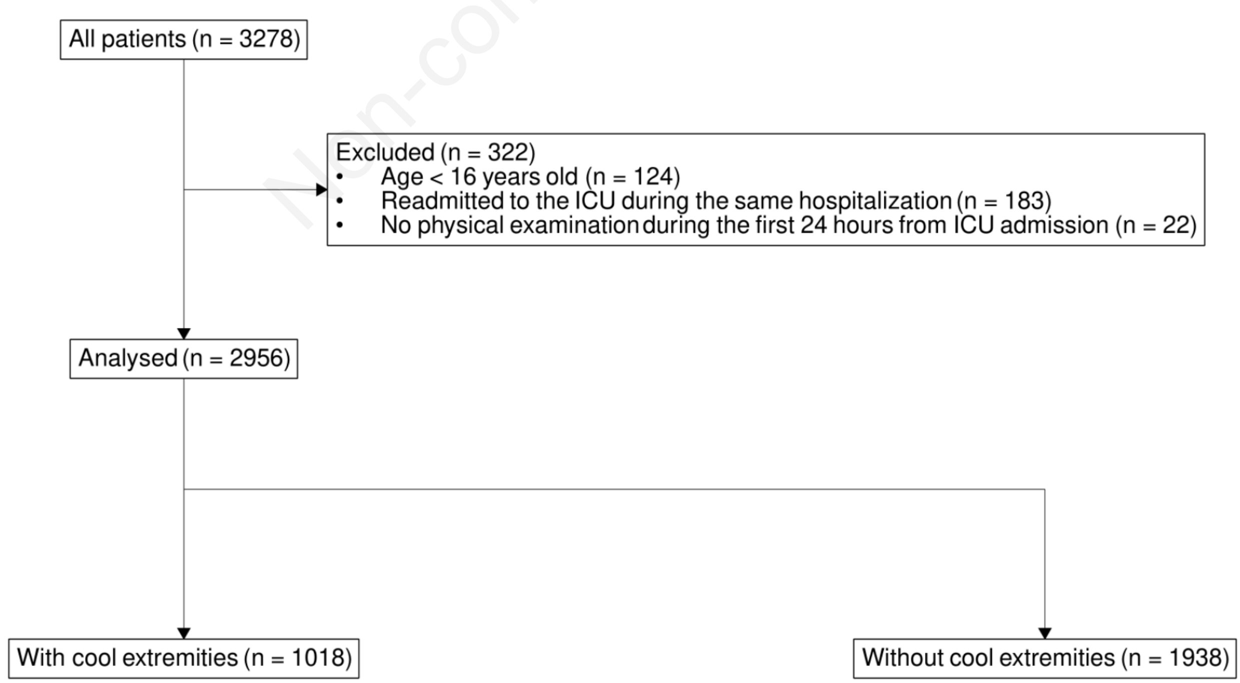

Figure 2. Patient flow diagram.

In total, 1018 patients had cool extremities within 24 hours after ICU admission. Patients with cool extremities were older (69 [61-75] years *vs* 71 [63-77] years, p<0.001) and more likely to be on chronic dialysis (3.9% *vs* 11%, p<0.001) than those without cool extremities. Cardiovascular disease (33% *vs* 57%, p<0.001) and infection (7.0% vs. 18%, p<0.001) were more common diagnoses at ICU admission among patients with cool extremities than among those without cool extremities. These patients also had higher severity scores on admission (APACHE III score: 52 [41-65] *vs* 71 [55-89], p<0.001; SAPS II score: 28 [21-36] *vs* 41 [31-55], p<0.001), more frequently required mechanical ventilation (41% *vs* 72%, p<0.001), vasopressors (32% *vs* 65%, p<0.001), and RRT (4.6% *vs* 18%, p<0.002), and had higher in-hospital mortality (4.1% *vs* 18%, p<0.001) and prevalence of AKI requiring RRT (2.1% *vs* 10%, p<0.001).

Clinical outcomes by the duration of subjective cool extremities

The LOESS curve showed positive relationships between the duration of cool extremities and the proportions of AKI requiring RRT and in-hospital mortality (Figure 3). Multivariable logistic regression analysis revealed that persistent cool extremities were significantly associated with in-hospital death (adjusted OR 1.64, 95% CI 1.08-2.47, p=0.018) and AKI requiring RRT (adjusted OR 1.82, 95% CI 1.11-3.01, p=0.018) (Table 2). The sensitivity analysis showed that the duration of cool extremities was significantly associated with in-hospital mortality and AKI requiring RRT, with the odds of in-hospital death increasing by 2% and that for AKI requiring RRT by 4% for each hour increase in duration (Table 3).

Table 1. Patients' characteristics and outcomes (N=2956).

Variables	Overall, N=2956[1]	Cool extremities, n=1018[1]	No cool extremities, n=1938[1]	p-value[2]
Age (years), median (IQR)	70 (61, 76)	71 (63, 77)	69 (61, 75)	<0.001
Gender, n (%)				0.4
Female	1048 (35)	351 (34)	697 (36)	
Male	1908 (65)	667 (66)	1241 (64)	
Height (cm), median (IQR)	161 (153, 168)	160 (153, 168)	162 (154, 168)	0.4
Weight (kg), median (IQR)	58 (50, 67)	56 (49, 65)	59 (51, 67)	<0.001
Comorbidities, n (%)				
Chronic heart failure	8 (0.3)	2 (0.2)	6 (0.3)	0.7
Chronic respiratory failure	24 (0.8)	11 (1.1)	13 (0.7)	0.2
Liver cirrhosis	48 (1.6)	10 (1.0)	38 (2.0)	0.045
Use of immunosuppressants	266 (9.0)	88 (8.6)	178 (9.2)	0.6
On chronic hemodialysis	189 (6.4)	114 (11)	75 (3.9)	<0.001
Lymphoma	30 (1.0)	12 (1.2)	18 (0.9)	0.5
Acute leukemia	7 (0.2)	2 (0.2)	5 (0.3)	>0.9
Cancer with metastases	174 (5.9)	39 (3.8)	135 (7.0)	<0.001
Days before ICU admission after hospitalization, median (IQR)	4 (2, 7)	4 (0, 8)	4 (2, 7)	<0.001
Cardiopulmonary resuscitation before ICU admission, n (%)	89 (3.0)	78 (7.7)	11 (0.6)	<0.001
Reason for ICU admission, n (%)				<0.001
Transfer from ward	368 (12)	232 (23)	136 (7.0)	
Transfer from emergency room	285 (9.6)	150 (15)	135 (7.0)	
Elective surgery	1867 (63)	430 (42)	1437 (74)	
Urgent surgery	330 (11)	144 (14)	186 (9.6)	
Other	106 (3.6)	62 (6.1)	44 (2.3)	
Diagnosis at ICU admission, n (%)				
Cardiovascular diseases	1220 (41)	577 (57)	643 (33)	<0.001
Infectious diseases	316 (11)	180 (18)	136 (7.0)	<0.001
Others	1472 (50)	293 (29)	1179 (61)	<0.001
APACHE III score, median (IQR)	58 (44, 74)	71 (55, 89)	52 (41, 65)	<0.001
SAPS II score, median (IQR)	32 (23, 43)	41 (31, 55)	28 (21, 36)	<0.001
Hyperlactatemia[3], n (%) (N=2920)	1638 (56)	641 (64)	997 (52)	<0.001
Mechanical ventilator use, n (%)	1531 (52)	729 (72)	802 (41)	<0.001
Vasoactive agents use, n (%)	1278 (43)	663 (65)	615 (32)	<0.001
RRT use, n (%)	271 (9.2)	181 (18)	90 (4.6)	<0.001
AKI requiring RRT[4], n (%) (N=2767)	134 (4.8)	94 (10)	40 (2.1)	<0.001
In-hospital death, n (%) (N=2955)	261 (8.8)	181 (18)	80 (4.1)	<0.001

ICU, Intensive Care Unit; IQR, Interquartile Range; AKI, Acute Kidney Injury; RRT, Renal Replacement Therapy. [1]Data presented as median (IQR) or n (%). [2]Wilcoxon rank sum test; Pearson's chi-squared test; Fisher's exact test. [3]Lactate more than 2 mmol/L within 24 hours after ICU admission. [4]RRT use during the ICU stay for patients not on chronic dialysis.

Discussion

Key findings

This retrospective observational study evaluated the clinical significance of subjective skin temperature assessment. Subjective cool extremities were recorded for 34.4% of critically ill patients admitted in the studied ICU. Patients who had cool extremities were older, had higher severity scores, required more invasive treatment, and more frequently had adverse clinical outcomes than those without cool extremities. The proportion of adverse clinical outcomes increased with the duration of cool extremities. Persistent cool extremities with 12 or more hours duration was associated with in-hospital mortality and AKI requiring RRT, independent of potential confounders.

Relationship to previous studies

Peripheral hypoperfusion is the clinical manifestation of circulatory failure, and several skin hypoperfusion signs have been examined in relation to laboratory values and clinical outcomes. Skin mottling refers to a purpuric discoloration of the skin caused by hypoperfusion of the skin.[14] It was previously reported that skin mottling was associated with lower skin microcirculatory saturation,[15] higher lactate level,[5] and mortality.[7,16] In terms of capillary refill time, the time required to recolor the tip of a finger was reported to be associated with postoperative complications,[17] higher lactate,[18] and mortality.[18] Both the presence and persistence of these skin hypoperfusion signs have been associated with mortality.[16] These skin hypoperfusion signs can be observed noninvasively, but this has the disadvantages of requiring training for evaluation and having capillary refill time cutoff values that vary from study to study.[17,18]

Although subjective assessment of cool extremities is highly examiner-dependent and can be found in conditions that differ from peripheral hypoperfusion, such as hypothermia and peripheral artery diseases, several previous studies reported similar results to our study. Kaplan *et al.* investigated associations between subjective extremity skin temperature and hypoperfusion among surgical ICU patients.[4] That study found patients who had cool extremities had higher serum lactate and lower cardiac output than those without cool extremities. Lima *et al*. investigated the relationships between subjective abnormal peripheral perfusion (increase in capillary refill time or subjective cool extremities) and hyperlactatemia and Sequential Organ Failure Assessment (SOFA) score improvement among initial resuscitated ICU patients.[6] They reported that patients with subjective abnormal peripheral perfusion were more likely to have hyperlactatemia and had lower SOFA score improvements than those without abnormal peripheral perfusion. Wiersema *et al.* reported that subjective cool extremities within 24 hours after ICU admission was associated with AKI during the ICU stay among patients who were acutely admitted to the ICU.[8] Lin *et al.* reported that post-resuscitated patients with severe sepsis and septic shock who had cool extremities had higher APACHE II scores and higher mortality than other patients.[9] These findings suggested that despite assessment being subjective, cool extremities had clinical significance for the assessment of peripheral hypoperfusion and patient illness severity.

The duration and adverse clinical outcomes have been reported for other peripheral hypoperfusion signs.[1,19,20] Therefore, we investigated the relationship between the duration of cool extremities and outcomes and found a dose-dependent association between the duration of cool extremities and adverse clinical outcomes. Furthermore, cool extremities that persisted for 12 hours or more were associated with adverse clinical outcomes, even after adjusting for potential confounders. There are various possible reasons for this finding. Previous studies showed that persistent peripheral hypoperfusion was associated with poor outcomes despite normalization of global hemodynamic measurements (*e.g.*, blood pressure, cardiac output) as a result of initial resuscitation.[1] In the modern ICU context, it is assumed that many patients with shock could have been initially resuscitated within 6 hours because of the influence of early goal-directed therapy[21] and surviving sepsis cam-

Table 2. Multivariable logistic regression analysis for the associations between cool extremities and clinical outcomes.

Variables	In-hospital death				AKI requiring RRT			
	N	Adjusted OR	95% CI	p-value	N	Adjusted OR	95% CI	p-value
Cool extremities	2,919				2,735			
No cool extremities		—	—			—	—	
Transient cool extremities[1]		1	0.65, 1.53	>0.9		0.9	0.51, 1.56	0.7
Persistent cool extremities[2]		1.64	1.08, 2.47	0.018		1.82	1.11, 3.01	0.018

AKI, Acute Kidney Injury; RRT, Renal Replacement Therapy; OR, Odds Ratio; CI, Confidence Interval; ICU, Intensive Care Unit. [1]Cool extremities duration less than 12 hours. [2]Cool extremities duration 12 hours or more. Multivariable logistic regression model adjusted for age, gender, chronic heart failure, chronic respiratory failure, liver cirrhosis, use of immunosuppressants, on chronic hemodialysis, lymphoma, acute leukemia, cancer with metastases, days before ICU admission after hospitalization, cardiopulmonary resuscitation before ICU admission, reason for ICU admission, diagnosis for ICU admission (cardiovascular disease vs. sepsis vs. others), APACHE III score, hyperlactatemia (more than 2 mmol/L) within 24 hours after ICU admission, mechanical ventilation within 24 hours after ICU admission, and vasoactive agents use within 24 hours after ICU admission.

Table 3. Multivariable logistic regression analysis for the associations between cool extremities duration as a continuous variable and clinical outcomes.

Variables	In-hospital death				AKI requiring RRT			
	N	Adjusted OR	95% CI	p-value	N	Adjusted OR	95% CI	p-value
Cool extremities duration (hours)	2,919	1.02	1.00, 1.04	0.026	2,735	1.04	1.02, 1.07	0.001

AKI, Acute Kidney Injury; RRT, Renal Replacement Therapy; OR, Odds Ratio; CI, Confidence Interval; ICU, Intensive Care Unit. Multivariable logistic regression model adjusted for age, gender, chronic heart failure, chronic respiratory failure, liver cirrhosis, use of immunosuppressants, on chronic hemodialysis, lymphoma, acute leukemia, cancer with metastases, days before ICU admission after hospitalization, cardiopulmonary resuscitation before ICU admission, the reason for ICU admission, diagnosis for ICU admission (cardiovascular disease vs. sepsis vs. others), APACHE III score, hyperlactatemia (more than 2 mmol/L) within 24 hours after ICU admission, mechanical ventilation within 24 hours after ICU admission, and vasoactive agents use within 24 hours after ICU admission.

paign guidelines.[22] Therefore, many patients who had cool extremities for more than 12 hours may have had persistent peripheral hypoperfusion after initial resuscitation.

In contrast, cool extremities that persisted for less than 12 hours were not associated with poor outcomes. These patients may have had circulatory failure but were resuscitated adequately or had another reason for cool extremities that was not peripheral hypoperfusion, such as transient hypothermia. Cool extremities due to peripheral hypoperfusion may be distinguished from other "low-risk" cool extremities by focusing on the duration. Moreover, the relationships between cool extremities and adverse outcomes did not change when we adjusted for hyperlactatemia, which is a well-known sign of peripheral hypoperfusion. This finding may be attributed to the fact that not all hyperlactatemia is due to tissue hypoperfusion.[22] This result suggested that regardless of lactate measurement, assessing skin perfusion is important for understanding a patient's circulatory status.

Significance and implications

In this study, we revealed that subjective cool extremities were associated with patient illness severity, and persistent cool extremities were an independent predictor of adverse clinical outcomes. These results suggested that physical examination findings play an important role in assessing patient illness severity and determining the need for additional treatment. However, physical examination findings are subjective and cannot be used to make decisions on their own. An individual's physical examination findings may lead to more objective examinations, such as a multi-person evaluation, bedside ultrasonography, and blood tests, which may provide a more accurate picture of the patient's condition. In recent years, point-of-care testing and the development of new testing equipment have made it possible to obtain objective data immediately. Therefore, subjective information (*e.g.*, physical examination) tends to be overlooked. A previous survey found that half of the participating physicians reported physical examinations had limited value for ICU patients, and more than half of attending physicians and fellows reported that they only saw patients occasionally.[24] We believe physical examinations provide clues to determine whether a patient should receive more invasive and expensive procedures.

Strengths and limitations

To our knowledge, this is the largest study that evaluated subjective skin temperature assessment and clinical outcomes among ICU patients. However, our study had several limitations. First, the presence or absence of cool extremities in this study was based on subjective assessment, and the objective accuracy was not evaluated. Although the examiner might have rated more severely ill patients as having cool extremities, persistent cool extremities were associated with adverse outcomes after adjusting for severity score, serum lactate level, mechanical ventilation use, and vasoactive agents use. Therefore, the results considered any bias resulting from vital signs, laboratory data, and treatment received. Moreover, subjective assessment of skin temperature has been reported to be correlated with objective peripheral hypoperfusion signs.[6] Although the lowest body temperature in the cool extremities group was significantly lower than that in the group without cool extremities, the effect of body temperature on in-hospital mortality was adjusted for in the APACHE III score. Therefore, this did not affect our finding that subjective cool extremities were an independent predictor of poor prognosis independent of severity score. The fact that even a subjective, untrained assessment may be an independent prognostic factor is of great clinical value in that routine clinical records may be useful to predict patients' outcomes. Second, we only focused on the first 24 hours after ICU admission. Therefore, cool extremities that appeared after 24 hours

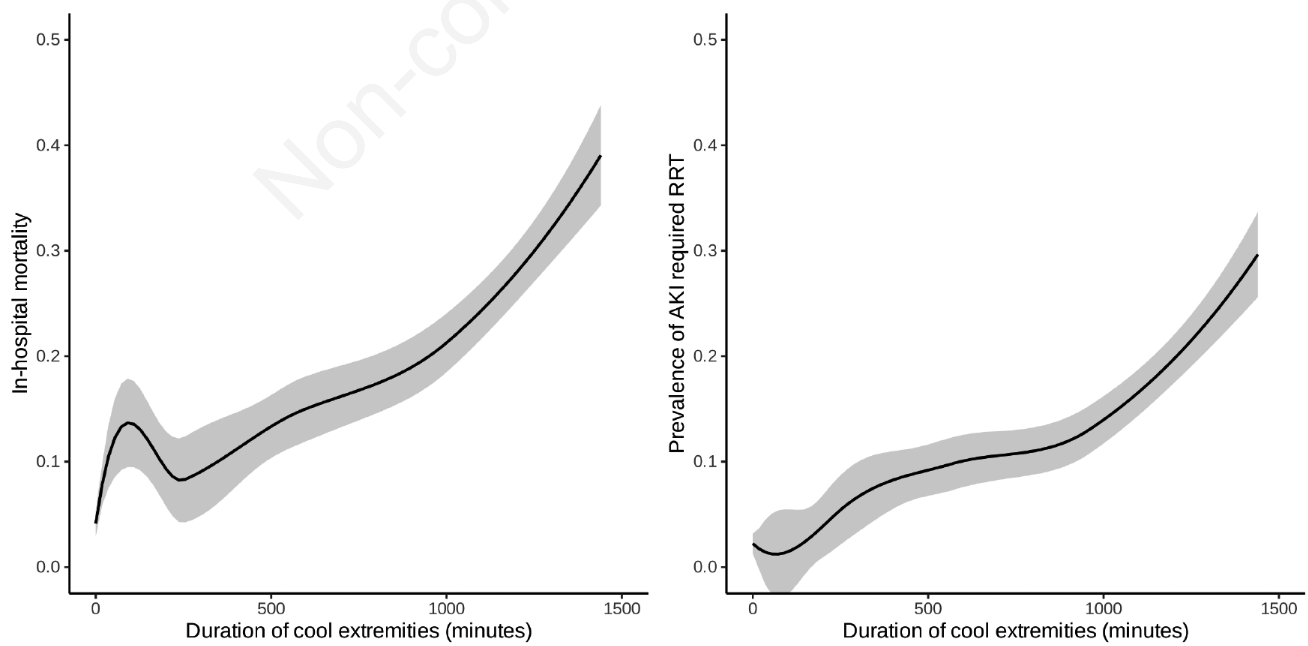

Figure 3. Association between duration of cool extremities and in-hospital mortality and prevalence of Acute Kidney Injury (AKI) requiring Renal Replacement Therapy (RRT). The gray bands represent the 95% confidence interval.

were not evaluated. As most critically ill patients are most severely ill immediately after the start of ICU treatment, we believed that assessing the significance of physical findings at that time had great clinical value. Third, the duration of cool extremities was not precise because the assessment of cool extremities was intermittent. To address this issue, the duration was divided into two groups for our multivariable analysis. Most of the analyzed patients had at least five physical examinations within 24 hours of admission to the ICU. Therefore, this classification had acceptable accuracy in assessing the duration of cool extremities. Fourth, because this was a single-center study, the findings might not apply to other centers because of differences in patient backgrounds and examiners' examination skills. The reproducibility of our results should be confirmed in a multicenter study.

Conclusions

Patients with subjective cool extremities had higher severity scores, required more invasive treatment, and had more frequent adverse clinical outcomes than those without cool extremities. Cool extremities that persisted for 12 or more hours were associated with in-hospital mortality and AKI requiring RRT. Subjective skin temperature assessment may be useful as a quick, no-cost, and noninvasive tool to help predict high-risk patients and could be used as a "trigger" for additional, time-consuming, and expensive invasive testing.

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