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ORIGINAL RESEARCH

Effect of hypothermia and hyperthermia on all-cause in-hospital mortality in emergencies: a comprehensive nationwide analysis from the Republic of Korea

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Abstract

Hypothermia has been shown to be a predictor of poor outcomes in various settings, but the association between elevated body temperature (BT) and patients' outcomes remains unclear. This study aimed to investigate the relationship between body temperature and mortality in general emergency departments. A nationwide cohort study was conducted to evaluate the effects of BT on all-cause in-hospital mortality in patients in the emergency departments of the Republic of Korea. Data from the National Emergency Department Information System, which stores regional and local emergency medical center data, were retrieved from 01 January 2014, to 31 December 2016. The patients were classified into a disease group (infection and cerebrovascular accident (CVA)) and an injury group (traumatic brain injury and non-traumatic brain injury), and the association between their mortality and body temperature were evaluated. The Mantel-Haenszel test was used to identify patterns in Odd-Ratio (OR). In all, 52.73% (837,506) of the study were male and the median age of the entire cohort was 59 (interquartile range, 44–73) years. In the Mantel-Haenszel test, adjusted ORs were negatively correlated with mortality in the disease group (χ^2 = 1087.28; $p < 0.001$, χ^2 = 1886.27; $p < 0.001$, <36.6 °C and >37.0 °C respectively). In the injured group, a negative correlation below the reference range (χ^2 = 447.21; $p < 0.001$) and a tendency for a positive correlation above the reference range (χ^2 = 5.62; p = 0.02) were detected. Among the disease group, BT was negatively correlated with in-hospital mortality (χ^2 = 493.90; $p < 0.001$, χ^2 = 1741.2; $p < 0.001$, <36.6 °C and >37.0 °C, respectively) in patients with infection, and negatively correlated in the lower BT range (χ^2 = 497.67; $p < 0.001$) but was not significant in the higher BT range (χ^2 = 5.97; p = 0.01) in patients with CVA. Lower BTs were associated with higher in-hospital mortality in patients from the disease or injury group in general emergency departments. Higher BTs were associated with lower in-hospital mortality in the disease group, especially in those with an infection, but not in patients with CVA or injury.

Keywords
Body temperature; Mortality; Hypothermia

1. Introduction

Human body temperature (BT) is normally maintained within a constant range (36.0–37.5 °C) by a homeostatic mechanism called thermoregulation, which is controlled by the hypothalamus [1, 2]. Out of the normal range BTs have been historically considered a bad treatment outcomes. A BT lower than the normal range (hypothermia) has almost always been associated with poor outcomes in various clinical settings [3–6], whereas a BT higher than the normal range (fever) has not been consistently associated with patient outcomes. Several experimental [7, 8] and human [9, 10] studies have suggested that fever is associated with favorable outcomes in infections, and numerous studies have shown that antipyretic therapy could be harmful in patients with infections [11–15]. The beneficial effects of fever include a boost in innate and adaptive immune systems, suppression of bacterial proliferation and viral replications, and enhanced antibiotic capacity [16, 17]. Contradictorily, other studies have demonstrated the harmful effects of fever, such as an association between a hypermetabolic state with higher oxygen needs [18], direct myocardial and neurologic injuries, and poor oxygen exchange in patients with lung injuries [19]. Even though fever alone can rarely lead to adverse consequences, it is considered a predictor of poor outcomes. In the Systemic Inflammatory Response Syndrome [20] and the National Early Warning Score [21], higher and lower BTs are thought to be an early sign of sepsis and a predictor of imminent compromise.

However, previous literature on this topic was accompanied by significant limitations. First, in all but one study [10], the limited population was confined to intensive care unit (ICU) patients, making the results hardly applicable to most patients who meet their physician in non-ICU settings, such as emergency departments (EDs), general ward, outpatient clinic, *etc*. Second, when patients admitted to the ICU inevitably undergo pre-ICU treatments, such as tepid massage and antipyretic or antibiotic treatment, in the ED or general ward, observation data from these patients could yield a certain amount of bias. Third, most published studies have focused on patients with bacterial infections.

Thus, this study aimed to assess the association between initial BT at ED presentation and all-cause in-hospital mortality in patients not previously treated before arrival in the ED using nationwide data collected from about 145 hospitals over 3 years. We also aimed to demonstrate differences between disease (infection and cerebrovascular accident (CVA)) and injury (with and without traumatic brain injury (TBI)) subgroups.

2. Methods

2.1 Study design and setting

The present study was an observational cohort study from a nationwide assessment of patients treated at the EDs in the Republic of Korea. Data were retrieved from the National Emergency Department Information System (NEDIS) (N20180320328).

Officially registered EDs in the Republic of Korea are obliged to send their treated patients' data to NEDIS, a government-run system established in 2003. In 2012, when the National Statistical Office (Republic of Korea) designated NEDIS as a nationally approved system, the NEDIS Quality Management System was introduced and implemented under the supervision of the Ministry of Health and Welfare (Republic of Korea) [22].

2.2 Data collection and participants

Officially, there were 424, 420 and 413 registered EDs in the Republic of Korea in 2014, 2015 and 2016, respectively. Of them, 94.4% had sent data to NEDIS [22]. We conducted this study using data from consecutive patients treated at regional and local emergency medical centers (n = 141, 144, and 151 in 2014, 2015, and 2016, respectively) from 01 January 2014, to 31 December 2016. Extracted data included demographics (age and sex), time of visit and discharge from the treated hospital, route of visit (direct or referred), patient category (disease or injury), vital signs at presentation (systolic blood pressure (SBP), heart rate (HR), respiratory rate (RR), and BT), results of hospital admission (discharged, transferred, left the hospital against medical advice, or death), and diagnosis at admission and discharge, based on the International Classification of Diseases-10 (ICD-10). The included patients were aged $\geq$ 18 years, presented directly to the ED (not transferred from another medical facility), and admitted after ED management. Their BTs were 20–45 °C. Cases were excluded if their SBP, HR, or RR were missing or out of survival ranges (SBP = 0 or > 300 mmHg; HR = 0 or > 300 bpm; RR = 0 or > 99), transferred or left the hospital against medical advice after hospital admission, and diagnosed with accidental hypothermia, had frost injury, drowned or submersion, heat-related illness, burns and poisoning. The enrolled patients were categorized into a disease or injury group. Each group was then subcategorized into subgroups based on the following: the disease group was further classified into an infection and cerebrovascular accident group, while the injured group was divided into patients with and without traumatic brain injury. The ICD-10 diagnostic codes used in the exclusion criteria and the subgroup categorization are shown in **Supplementary Table 1**.

2.3 Study outcome

The primary outcome of the study was all-cause in-hospital mortality.

2.4 Data analysis

SBP, HR, RR, BT and age were categorized into 7 to 14 strata (**Supplementary Table 2**). In the preliminary analysis, multivariate linear logistic regression could not be performed because of the U-shape distribution of the odds ratios (ORs) for the categorized SBP, HR, RR and BT on in-hospital mortality (**Supplementary Fig. 3**). Therefore, logistic regression analysis was performed, assuming the variables were categorical. Unadjusted ORs of each BT category on in-hospital mortality and ORs of each BT category adjusted for each SBP, HR, RR, age and sex category were calculated using the logistic regression. A BT range of 36.6–37.0 °C was chosen as a reference for the analysis. The same analysis was performed in groups according to patient category (disease and injury), and the same analysis was performed for each subgroup of the disease group (infection and CVA) and injury (TBI and non-TBI) groups. The Mantel-Haenszel test was used to investigate the trend in the ORs for each analysis. The trend test was performed for lower and higher BT ranges.

All p-values were two-sided, and a p-value < 0.01 was considered statistically significant to minimize type 1 error. Additionally, because multiple comparisons were performed in this study in 14 categorized BT ranges in the multivariate analysis, we chose an adjusted $p < 0.0001$ (0.01 divided by 13) using Bonferroni's adjustment to assess the significance of the ORs. Analyses were performed using the Stata version 13 software (StataCorp, LP, College Station, TX, USA).

3. Results

3.1 Baseline characteristics

From a total of 1,859,300 cases, 1,588,412 were eligible for final analysis (Fig. 1). The median age of the study cohort was 59 (interquartile range (IQR), 44–73) years, and 52.73% (837,506) of the patients were male. The median SBP, HR, RR, and BT were 130 (IQR, 114–150) mmHg, 84 (IQR, 74–98) beats/min, 20 (IQR, 18–20) times/min, and 36.6 °C (IQR, 36.3–37.0 °C), respectively. Among all patients, 1,273,539

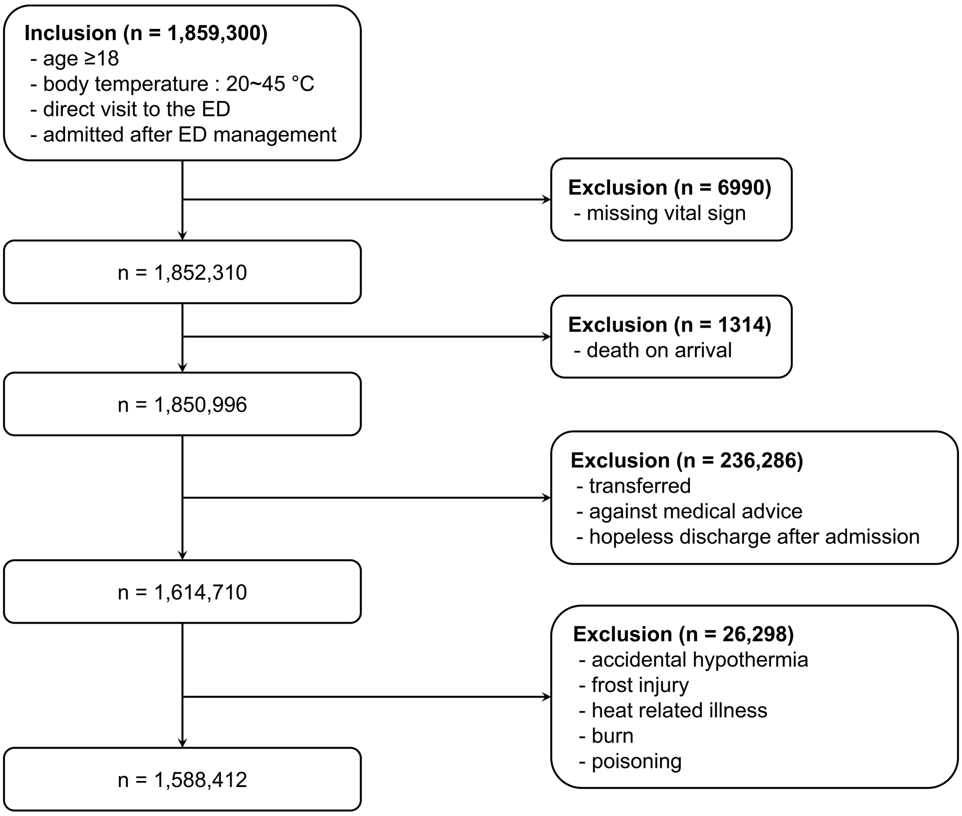


FIGURE 1. Flow chart of the study patient selection. ED, Emergency Department.

(80.18%) and 311,721 (19.62%) were categorized into the disease and injury groups. The rate of all-cause in-hospital mortality was 4.89% (n = 77,679) (Table 1).

3.2 The association between BT and all-cause in-hospital mortality

Unadjusted ORs of BT below the reference range (<36.6 °C) were negatively correlated with in-hospital mortality (χ^2 = 10502.91; $p < 0.001$), whereas BT and in-hospital mortality were positively associated above the reference ranges (>37.0 °C) (χ^2 = 679.50; $p < 0.001$). ORs adjusted for age, sex, SBP, HR and RR were negatively correlated in the range below and above the reference (χ^2 = 1486.53 and 1579.16, respectively; both $p < 0.001$) (Fig. 2A).

A negative correlation was observed in patients categorized into the disease group (n = 1,273,539) in both the lower and higher BT ranges (χ^2 = 1087.28; $p < 0.001$, χ^2 = 1886.27; $p < 0.001$, <36.6 °C and >37.0 °C, respectively). For patients of the injury group (n = 311,721), adjusted ORs were negatively correlated with mortality below the reference range (χ^2 = 447.21; $p < 0.001$), but a tendency for a positive correlation was detected above the reference range (χ^2 = 5.62; $p = 0.02$) (Fig. 2B). For patients of the infection group (n = 456,955), BT was negatively correlated with in-hospital mortality (χ^2 = 493.90; $p < 0.001$, χ^2 = 1741.2; $p < 0.001$, <36.6 °C and >37.0 °C, respectively). For patients of the CVA subgroup (n = 125,556), BT was negatively correlated in the lower BT range (χ^2 = 497.67; $p < 0.001$) but not significantly in the higher BT range (χ^2 = 5.97; $p = 0.01$). For patients of the TBI subgroup (n = 81,815), BT was negatively correlated in the lower BT range (χ^2 = 562.87; $p < 0.001$) and positively correlated in the higher BT range (χ^2 = 23.93; $p < 0.001$). For patients in the injured but without TBI (n = 229,906), BT was negatively correlated in the lower BT range (χ^2 = 142.38; $p < 0.001$), but the result was not significant in the higher BT range (χ^2 = 8.17; $p = 0.004$) (Fig. 3).

4. Discussion

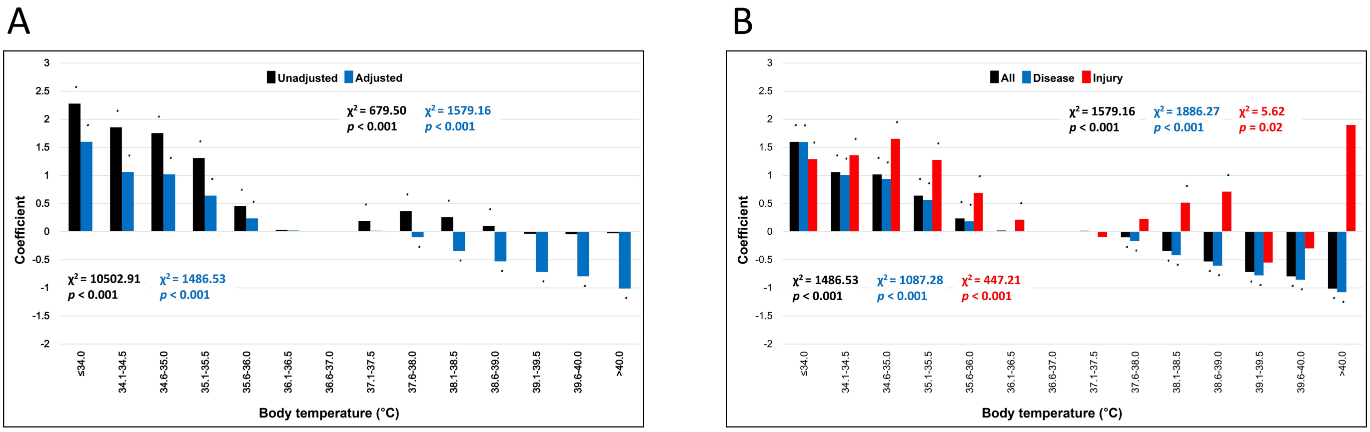
In this observational study based on a large nationwide database, an increase in BT was found to be significantly associated with lower in-hospital mortality among unselected patients who visited ED and were admitted to the hospital. In particular, this negative correlation (higher BT associated with a greater number of patients survived) was robust in patients with infection from the disease group, as the adjusted ORs of all categorized BT ranges were significant ($p < 0.01$) despite a conservative null hypothesis (99% confidence interval), and not confined to the hypothermic range, but was consistent in the higher BT range above 37.0 °C. A significant negative correlation was detected in the lower BT range in injured patients, but it was not significant in the higher BT range.

In the Republic of Korea, emergency personnel begin initial triage based on vital signs and presenting complaints, then use the Korean Triage and Acuity Scale to calculate a final score [23]. Every registered ED in the country has to send their initial patient data to the NEDIS system. As this obligation is essential for qualification to run an ED, almost all EDs involved in the NEDIS system maintain an approximate 95% completion rate of data [22]. We believe that the guarantee of annual assessments by the NEDIS Quality Management System to

TABLE 1. Baseline characteristics of study patients.

Variable	Total	Survived	Died
No. of patients (%)	1,588,412	1,510,733 (95.11)	77,679 (4.89)
Age (years (range))	59 (44–73)	58 (44–73)	72 (60–80)
Sex (n (%))			
Men	837,506 (52.73)	790,106 (94.34)	47,400 (5.66)
Women	750,906 (47.27)	720,627 (95.97)	30,279 (4.03)
Systolic blood pressure (mmHg (range))	130 (114–150)	130 (116–150)	120 (100–141)
Heart rate (beats/min (range))	84 (74–98)	84 (74–97)	96 (80–114)
Respiratory rate (times/min (range))	20 (18–20)	20 (18–20)	20 (20–24)
Body temperature (°C (range))	36.6 (36.3–37.0)	36.6 (36.3–37.0)	36.6 (36.2–37.1)
Patient grouping (n (%))			
Disease	1,273,539 (80.18)	1,201,496 (94.34)	72,043 (5.66)
Injury	311,721 (19.62)	306,232 (98.24)	5489 (1.76)
Unknown	325 (0.02)	259 (79.69)	66 (20.31)
Missing	2827 (0.18)	2746 (97.13)	81 (2.87)

Values are presented as median and interquartile range, unless stated otherwise.



(A) Number of patients / Odds ratios (99% CI)

Variable	≤34.0	34.1-34.5	34.6-35.0	35.1-35.5	35.6-36.0	36.1-36.5	36.6-37.0	37.1-37.5	37.6-38.0	38.1-38.5	38.6-39.0	39.1-39.5	39.6-40.0	>40.0
Unadjusted	2028	2747	9470	15,048	264,976	746,026	711,093	255,928	127,720	85,273	55,615	32,832	15,290	7012
	9.76 (8.39-11.37)	6.40 (5.55-7.37)	5.77 (5.33-6.24)	3.07 (3.44-3.98)	1.57 (1.53-1.62)	1.03 (1.01-1.06)	-	1.21 (1.16-1.25)	1.44 (1.38-1.50)	1.29 (1.23-1.36)	1.11 (1.04-1.18)	0.96 (0.89-1.05)	0.96 (0.85-1.07)	0.97 (0.82-1.15)
Adjusted	2028	2747	9470	15,048	264,976	746,026	711,093	255,928	127,720	85,273	55,615	32,832	15,290	7012
	5.77 (5.04-6.06)	3.88 (3.43-4.38)	3.12 (2.90-3.35)	2.09 (1.96-2.23)	1.31 (1.28-1.34)	1.03 (1.01-1.05)	-	1.03 (1.00-1.06)	0.93 (0.9-0.97)	0.74 (0.70-0.77)	0.61 (0.57-0.64)	0.49 (0.46-0.53)	0.47 (0.42-0.52)	0.41 (0.35-0.47)

(B) Number of patients / Odds ratios (99% CI)

Variable	≤34.0	34.1-34.5	34.6-35.0	35.1-35.5	35.6-36.0	36.1-36.5	36.6-37.0	37.1-37.5	37.6-38.0	38.1-38.5	38.6-39.0	39.1-39.5	39.6-40.0	>40.0
All	1389	1980	7067	11,260	196,087	513,069	468,557	154,936	82,303	62,157	43,559	26,996	12,933	6119
	4.95 (4.18-5.87)	2.89 (2.47-3.37)	2.77 (2.54-3.02)	1.90 (1.76-2.06)	1.27 (1.23-1.31)	1.02 (0.99-1.05)	-	1.02 (0.98-1.06)	0.90 (0.86-0.95)	0.71 (0.67-0.75)	0.59 (0.55-0.63)	0.49 (0.45-0.53)	0.45 (0.40-0.51)	0.36 (0.31-0.43)
Disease	1183	1787	6133	9792	153,521	389,856	356,463	128,043	76,943	60,993	43,105	26,774	12,852	6094
	4.93 (4.12-5.89)	2.73 (2.33-3.21)	2.55 (2.33-2.80)	1.76 (1.62-1.91)	1.20 (1.16-1.24)	1.00 (0.98-1.03)	-	1.00 (0.96-1.03)	0.85 (0.81-0.89)	0.66 (0.63-0.69)	0.55 (0.51-0.58)	0.46 (0.42-0.50)	0.43 (0.38-0.48)	0.34 (0.29-0.41)
Injury	15	57	183	381	1086	5230	26,601	111,210	122,034	42,171	1452	920	184	197
	3.63 (1.98-6.66)	3.89 (2.14-7.06)	5.22 (3.95-6.90)	3.58 (2.76-4.64)	1.99 (1.79-2.22)	1.24 (1.12-1.36)	-	0.91 (0.77-1.07)	1.26 (0.97-1.63)	1.68 (1.15-2.44)	2.04 (1.20-3.48)	0.58 (0.19-1.77)	0.74 (0.14-3.87)	6.68 (1.08-41.27)

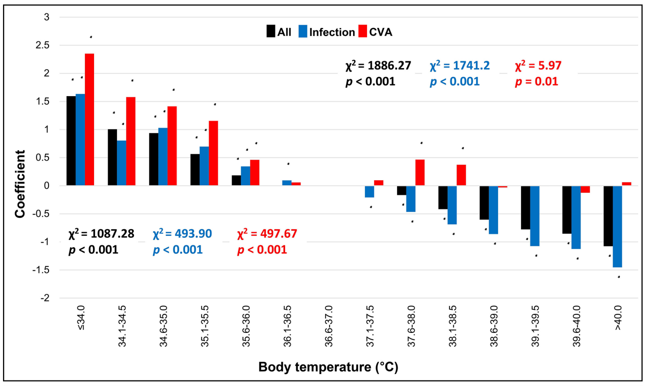
FIGURE 2. Coefficients of logistic regression analysis on all-cause in-hospital mortality. χ^2 and p values were obtained from the Mantel-Haenszel test. Values in the lower are below the reference range (<36.6 °C), while those in the upper right are above the reference range (>37.0 °C). Asterix (*) means that the coefficient is statistically different from the reference range (36.6–37.0 °C) (Bonferroni corrected $p < 0.0001$). (A) The black bars represent the coefficients of univariate analysis, and the blue bars represent those from multivariate analysis adjusted for systolic blood pressure, heart rate, respiratory rate, age, and sex. (B) Coefficients of multivariate analysis adjusted for systolic blood pressure, heart rate, respiratory rate, age, and sex.

maintain the quality of the ED recorded data strengthens our study.

The association between hypothermia and poor outcomes in various clinical settings, especially in patients with sepsis or trauma, has been frequently reported in the literature [24–27]. A recent meta-analysis of 42 clinical trials revealed a negative correlation between clinical outcomes and sepsis [24]. In a study by Perlman *et al*. [28], the authors found that hypothermia was an independent risk factor for mortality in trauma victims and that rewarming therapy should begin during the prehospital phase to improve outcomes. Although therapeutic hypothermia (TH) or normothermia have been recommended by the American Heart Association (AHA) Guidelines for cardiopulmonary resuscitation [29], a recent randomized clinical trial and an observational cohort study reported that TH was not associated with better clinical outcomes in cases of in-hospital cardiac arrest [30, 31]. This conflicting evidence in the resuscitation field suggests that hypothermia may not always be beneficial, even in patients suffering from a cardiac arrest.

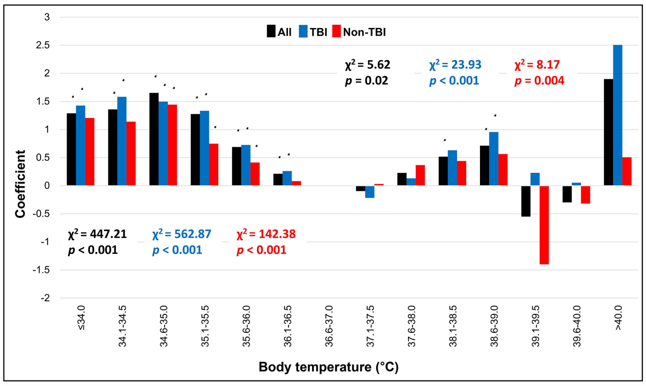
Conflicting results have also been reported for the associ-

A



Variable	Number of patients Odds ratios (99% CI)												
All	1389	1980	7067	11,260	196,087	513,069	468,557	154,936	82,303	62,157	43,559	26,996	12,933	6119
	4.95 (4.18-5.87)	2.89 (2.47-3.37)	2.77 (2.54-3.02)	1.90 (1.76-2.06)	1.27 (1.23-1.31)	1.02 (0.99-1.05)	-	1.02 (0.98-1.06)	0.90 (0.86-0.95)	0.71 (0.67-0.75)	0.59 (0.55-0.63)	0.49 (0.45-0.53)	0.45 (0.40-0.51)	0.36 (0.31-0.43)
Infection	319	391	1451	2176	36,009	98,802	106,278	58,595	47,670	41,466	30,607	19,459	9302	4430
	5.12 (3.67-7.15)	2.23 (1.61-3.10)	2.80 (2.36-3.32)	2.01 (1.72-2.34)	1.41 (1.33-1.50)	1.10 (1.05-1.15)	-	0.81 (0.76-0.86)	0.63 (0.59-0.67)	0.50 (0.47-0.54)	0.42 (0.39-0.46)	0.34 (0.31-0.38)	0.32 (0.28-0.38)	0.23 (0.19-0.29)
CVA	117	210	719	1239	19,911	48,298	39,330	8648	2975	1807	1171	636	318	177
	10.50 (6.26-17.60)	4.85 (3.20-7.33)	4.11 (3.23-5.22)	3.17 (2.60-3.87)	1.58 (1.46-1.72)	1.06 (0.99-1.14)	-	1.10 (0.98-1.24)	1.59 (1.37-1.85)	1.45 (1.20-1.75)	0.97 (0.75-1.25)	0.99 (0.71-1.38)	0.88 (0.56-1.38)	1.06 (0.62-1.81)

B



Variable	Number of patients Odds ratios (99% CI)												
All	197	184	920	1452	42,171	122,034	111,210	26,601	5230	1086	381	183	57	15
	3.63 (1.98-6.66)	3.89 (2.14-7.06)	5.22 (3.95-6.90)	3.58 0(2.76-4.64)	1.99 (1.79-2.22)	1.24 (1.12-1.36)	-	0.91 (0.77-1.07)	1.26 (0.97-1.63)	1.68 (1.15-2.44)	2.04 (1.20-3.48)	0.58 (0.19-1.77)	0.74 (0.14-3.87)	6.68 (1.08-41.27)
TBI	74	64	426	625	12,922	32,513	27,479	6197	1142	232	82	43	11	5
	4.17 (1.76-9.86)	4.87 (2.12-11.20)	4.47 0(3.09-6.47)	3.80 (2.74-5.26)	2.07 (1.79-2.39)	1.30 (1.14-1.48)	-	0.81 (0.62-1.04)	1.14 (0.73-1.79)	1.88 (1.01-3.48)	2.60 (1.14-5.93)	1.26 (0.31-5.16)	1.06 (0.05-21.15)	12.26 (0.71-211.41)
Non-TBI	123	120	494	827	29,249	89,521	83,731	20,404	4088	854	299	140	46	10
	3.34 (1.39-8.01)	3.13 (1.34-7.33)	4.24 (2.71-6.61)	2.11 (1.34-3.34)	1.51 (1.28-1.79)	1.09 (0.94-1.25)	-	1.03 (0.83-1.29)	1.44 (1.05-1.99)	1.55 (0.95-2.53)	1.76 (0.84-3.66)	0.25 (0.03-1.99)	0.73 (0.09-5.65)	1.66 (0.04-70.84)

FIGURE 3. Coefficients of logistic regression analysis on all-cause in-hospital mortality. χ^2 and p values were obtained from the Mantel-Haenszel test. Values in the lower are below the reference range (<36.6 °C), while those in the upper right are above the reference range (>37.0 °C). Asterix (*) means that the coefficient is statistically different from the reference range (36.6–37.0 °C) (Bonferroni corrected $p < 0.0001$). (A) Patients from the disease group. CVA, cerebrovascular accident. (B) Patients from the injury group. TBI, traumatic brain injury.

ation between fever and clinical outcomes. Several previous studies have demonstrated an association between fever and poor outcomes in patients with brain trauma or stroke [32, 33], while others have suggested that fever might be beneficial or harmful depending on the presence of an infection. A cohort study of multinational databases (n = 636,051) found that an elevated BT was associated with decreased in-hospital mortality in critically ill patients with an infection but with increased mortality in patients without an infection [9]. A prospective observational study (n = 1429) reported similar results, which suggested that high BT (≥ 39.5 °C) was not associated with increased mortality in critically ill patients with sepsis, but was associated in patients without sepsis [6]. Another study showed that high fever, even in patients with infection in the central nervous system, was not associated with increased mortality [34]. These results suggest that the presence of fever in patients with an infection could be possibly beneficial, but not in patients without infection. In our study, the beneficial effects of fever were strengthened based on the presence of infection but weakened by CVA. These findings are in agreement with previous studies.

Most of the collected data were demographics and time variables and did not include information that represented the patients' clinical condition, except for initial vital signs. The available data were not suitable for imputing missing variables, despite the relatively high number of patients; therefore, we decided to conduct the present study as a complete case analysis. The data-missing mechanism could be omitted during data input or mechanical problems in the data server, or uncheckable vital signs due to cardiac arrest or severe shock. We did not include patients who were not admitted to the hospital after ED management due to the lack of data on patients' outcomes. It should be noted that the NEDIS system did not contain follow-up data of these patients after discharge from the ED.

The main strength of our study was that we evaluated the association between initial BT at first presentation and in-hospital mortality in consecutive patients treated at EDs with qualified nationwide big data over a 3-year period. The entire analysis was performed after adjusting for age, sex, SBP, HR and RR. We also assessed the impact of initial BT on in-hospital mortality in patients categorized based on whether they were treated in ED for a disease or injury, based on their diagnosis. We can only know that the included patients who directly arrived at the ED, to remove the effects of previous medical treatment on vital signs. We provide scientific evidence relating to a classic question in medicine concerning the issue of whether fever is beneficial or harmful.

Our approach had some limitations. First, important information about patients, such as comorbidities, hospital management, laboratory findings and an accurate diagnosis, that could have seriously affected the study outcomes were unavailable. Second, the recording of vital signs could have been altered by several unpredictable factors, including methods for taking vital signs, over-the-counter drugs, prehospital medications, and the external environment. Third, as we did not include patients with severe shock or cardiac arrest, our results cannot be applied to such patients. Fourth, a certain amount of selection bias could have been present, which is unavoidable in an observational study.

5. Conclusions

Lower BTs were associated with higher in-hospital mortality in patients with disease or injury. Higher BTs were associated with lower in-hospital mortality in patients presenting with a disease, especially in those with an infection, but not in patients presenting with CVA or injury.

AUTHOR CONTRIBUTIONS

HS, DHK, AJS designed the research study. AJS performed the research. JHJ, SBL and DSL analyzed the data. HS and AJS wrote the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The Institutional Review Board of Gyeongsang National University Hospital (GNUH 2018-02-018)-Republic of Korea approved the study protocol, and this study was exempted from informed consent.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.signavitae.com/mre-signavitae/article/1550049928933195776/attachment/Supplementary%20materials.docx.

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