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Body Temperature at the Emergency Department as a Predictor of Mortality in Patients With Bacterial Infection

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Abstract: Hypothermia is a risk factor for death in intensive care unit (ICU) patients with severe sepsis and septic shock. In the present study, we investigated the association between body temperature (BT) on arrival at the emergency department (ED) and mortality in patients with bacterial infection.

We conducted a retrospective cohort study in consecutive ED patients over 15 years of age with bacterial infection who were admitted to an urban teaching hospital in Japan between 2010 and 2012. The main outcome measure was 30-day in-hospital mortality. Each patient was assigned to 1 of 6 categories based on BT at ED admission. We conducted multivariable logistic regression analysis to adjust for predictors of death.

A total of 913 patients were enrolled in the study. The BT categories were <36, 36 to 36.9, 37 to 37.9, 38 to 38.9, 39 to 39.9, and ≥40 °C, with respective mortalities of 32.5%, 14.1%, 8.7%, 8.2%, 5.7%, and 5.3%. Multivariable analysis showed that the risk of death was significantly low in patients with BT 37 to 37.9 °C (adjusted odds ratio [AOR]: 0.2; 95% confidence interval [CI] 0.1–0.6, $P = 0.003$), 38–38.9 °C (AOR: 0.2; 95% CI 0.1–0.6, $P = 0.002$), 39–39.9 °C (AOR: 0.2; 95% CI 0.1–0.5, $P = 0.001$), and ≥40 °C (AOR: 0.1; 95% CI 0.02–0.4, $P = 0.001$), compared with hypothermic patients (BT <36 °C).

The higher BT on arrival at ED, the better the outcomes observed in patients with bacterial infection were.

Abbreviations: AOR = adjusted odds ratio, BT = body temperature, CI = confidence interval, ED = emergency department, RR = respiratory rate.

Key Point

- The higher the BT on arrival at the ED, the better the outcomes observed in patients with bacterial infection were. An ED clinician should be aware that patients without fever may be more worrisome than those with fever.

INTRODUCTION

Fever is a common feature of infection, and the febrile response exerts a number of beneficial effects by fighting sepsis and enhancing chemotaxis, neutrophil migration, phagocytosis, antibody production, and T-cell proliferation.[1–4] A recent observational study reported that elevated peak temperature during the 1st 24 hours in an ICU is associated with decreased mortality in critically ill patients with infection.[5] Several reports have also shown an association between hypothermia and increased mortality in ICU patients with infection.[6–10] However, fever can also harm the host, as an increase of 1 °F (0.56 °C) leads to an increase in pulse rate of 10 beats/minute, and the increased metabolic rates caused by fever may exacerbate cardiopulmonary function.[1] Additionally, extreme hyperthermia can damage the central nervous system.[1] Fever in patients with noninfectious diseases is associated with worse outcomes.[5,11]

Body temperature (BT) at emergency department (ED) admission is more relevant to clinicians in the ED than is BT at admission to an ICU. To our knowledge, no studies have investigated the relationship between BT at presentation to the ED and prognosis in patients with bacterial infection.

In this study, to facilitate the assessment of a patient's severity of condition on admission to the ED, we investigated the association between BT on arrival at the ED and mortality in patients with bacterial infection.

MATERIALS AND METHODS

Study Design, Setting, and Population

This retrospective cohort study used data from patients suspected to have sepsis in our previous study.[12] The cohort was

designed to evaluate the clinical usefulness of serum C-reactive protein in patients with suspected sepsis. First, SY extracted the consecutive ED patients over 15 years of age admitted to the Kyoto City Hospital, an urban Japanese teaching hospital with 548 beds, after having a blood culture drawn in the ED between January, 2010 and December, 2012. Then, SY, TS, KT, YT, and KS extracted the following data anonymously from electronic medical records for each patient with suspected sepsis: age, gender, underlying disease, diagnosis for admission, vital signs, laboratory findings, and outcome in our previous study. That cohort included 1310 patients.[12] Of these patients, 926 were ultimately diagnosed with bacterial infection and deemed eligible for the present study. Classification of bacterial infection was determined based on the agreement between the diagnosis of the treating physician at the time of discharge from the hospital and the investigators' assessment. To promote data independence, only the index admission was included for patients with multiple admissions during the study period. Patients transferred from another hospital or who had cardiopulmonary arrest on arrival at the hospital were excluded.

Study Protocol

The following data were extracted from electronic medical records for each patient: age, gender (male/female), use of corticosteroids (yes/no), malignancy (present/absent), bacteremia (present/absent), vital sign values (blood pressure, respiratory rate [RR], mental confusion, and BT), blood urea nitrogen value, and outcome. The following predictors were defined based on previous studies: mental confusion (present/absent), blood urea nitrogen >7 mmol/L (20 mg/dL), RR $\geq$30/minute, and systolic blood pressure <90 mm Hg or diastolic blood pressure $\leq$60 mm Hg (either alone or in combination).[12–16] Mental confusion was defined as disorientation in person, place, or time or the presence of a stupor or coma, in accordance with a previous study.[13] For vital signs and laboratory data, initial values for the hospital visit were recorded. Each patient was assigned to 1 of 6 categories based on BT at admission to the ED: <36, 36 to 36.9, 37 to 37.9, 38 to 38.9, 39 to 39.9, and $\geq$40 °C. BT was mainly measured via electronic thermometer at the axilla, except in patients with extremely low BT (<35 °C), in which case the core BT was measured using a bladder or rectal probe.

Outcomes

The main outcome measure was 30-day in-hospital mortality. Patients who were discharged or transferred from the hospital within 30 days of admission or who remained in the hospital for more than 30 days were considered alive in this analysis.[17]

Data Analysis

We conducted multivariable logistic regression analysis to adjust for the predictors of death by introducing prespecified variables (age, gender, condition severity, steroid use, malignancy, and bacteremia) based on the findings of previous studies and clinical relevance.[12,14–16,18–21] We used prespecified variables to adjust for the predictors because the present study was not an exploratory analysis to select statistically significant variables among many other candidate variables. To adjust for condition severity, we used the CURB-65 score, which was originally developed as a severity score for community-acquired pneumonia and later validated in patients with suspected sepsis, regardless of source, and patients admitted for

nonsurgical illness.[12,14–16] To evaluate which of the parameters were more closely associated with mortality, we treated each component of the CURB-65 score, as a separate explanatory variable. As normal BT varies with age, the age component was used as a continuous variable.[22] We calculated both unadjusted and adjusted odds ratios (aORs) and 95% confidence intervals (CIs) and considered a 2-sided *P* value <0.05 statistically significant. We assessed the calibration of the model using the Hosmer–Lemeshow goodness-of-fit test. A *P* value <0.05 indicates a lack of good fit for the model. Regarding the model discrimination, we also computed the area under the receiver operating characteristic curve with a 95% CI using 500 bootstrap resampling.[23] We did not conduct formal sample size calculations, and all available data were used to maximize the power. Previous studies have suggested that at least 8 to 10 events per variable are needed for reliable multiple logistic regression analysis.[24,25] As for missing values, we planned to conduct a complete case analysis if the missing values were below 5%, as such an analysis might have been feasible in that case.[26] If the missing values were at or above 5%, we planned to perform the appropriate imputation. All data were analyzed using Stata software, version 13 (StataCorp, College Station, TX).

Ethical Approval

The Ethics Committees of the Kyoto University Graduate School and Faculty of Medicine approved this protocol. As the study was observational and data were collected anonymously, the institutional review board waived the need for patient consent. Instead, we gave the participants the opportunity to disclaim their participation.

RESULTS

Of the 926 participants with bacterial infection, only RR data were missing for 13 patients (1.4%). We therefore conducted a complete case analysis, leaving 913 patients for further evaluation. The 30-day in-hospital mortality was 9.6% (88 deaths). Demographics, underlying illnesses, vital signs, laboratory findings, and diagnoses are presented in Table 1. The most common diagnosis was pneumonia, followed by urinary tract infection, skin and soft tissue infection, acute cholangitis, and acute cholecystitis. Mortality ranged from 32.5% among patients with BT <36 °C to 5.3% among patients with BT $\geq$40 °C (Table 1), and mortality decreased as BT increased.

The unadjusted ORs for the mortality of each BT category relative to the reference range of <36 °C are presented in Table 2. Multivariable analysis showed that the risk of death was significantly low in patients with BT 37 to 37.9 °C (AOR: 0.2; 95% CI 0.1–0.6, *P* = 0.003), 38 to 38.9 °C (AOR: 0.2; 95% CI 0.1–0.6, *P* = 0.002), 39 to 39.9 °C (AOR: 0.2; 95% CI 0.1–0.5, *P* = 0.001), and $\geq$40 °C (AOR: 0.1; 95% CI 0.02–0.4, *P* = 0.001), compared with hypothermic patients (BT <36 °C) (Table 2). The multivariable model showed good calibration for mortality, with a Hosmer–Lemeshow test of 7.05 (df = 8, *P* = 0.53), indicating good fit. The area under the receiver operating characteristic curve of the model was 0.84 (95% CI: 0.80–0.87).

DISCUSSION

In the present study, we found that the risk of mortality decreased as the BT on arrival at the ED increased in patients with bacterial infection. Our findings are consistent with those of previous observational studies, which reported that a low BT

TABLE 1. Patients' Characteristics, Underlying Illnesses, Diagnoses, and Outcomes

	Body Temperature, °C						
	<36 (n = 40)	36–36.9 n = 149)	37–37.9 (n = 195)	38–38.9 (n = 279)	39–39.9 (n = 175)	40≤ (n = 75)	Total (n = 913)
Demographics, n, %							
Age, years, median (IQR)	78 (69–86)	76 (68–84)	77 (67–84)	77 (64–84)	77 (57–83)	74 (65–83)	77 (65–83)
Female	16 (40%)	63 (41%)	75 (38%)	135 (48%)	86 (49%)	33 (44%)	408 (45%)
Steroid use	1 (3%)	6 (4%)	6 (3%)	16 (6%)	8 (5%)	3 (4%)	40 (4%)
Malignancy	8 (20%)	28 (19%)	33 (17%)	54 (19%)	23 (13%)	12 (16%)	158 (17%)
Diagnosis, n, %							
Pneumonia	21 (53%)	60 (40%)	110 (56%)	119 (43%)	65 (37%)	22 (29%)	397 (43%)
UTI	5 (13%)	28 (19%)	20 (10%)	66 (24%)	51 (29%)	23 (31%)	193 (21%)
SSTI	5 (13%)	12 (8%)	10 (5%)	15 (5%)	17 (10%)	6 (8%)	65 (7%)
Acute cholangitis	1 (3%)	4 (3%)	10 (5%)	15 (5%)	9 (5%)	8 (11%)	47 (5%)
Acute cholecystitis	1 (3%)	11 (7%)	10 (5%)	5 (2%)	3 (2%)	4 (5%)	34 (4%)
Other bacterial infections	7 (18%)	34 (23%)	35 (18%)	59 (21%)	30 (17%)	12 (16%)	177 (19%)
Severity							
Mental confusion, n, %	13 (33%)	20 (13%)	34 (17%)	44 (16%)	23 (13%)	17 (23%)	151 (17%)
BUN >7 mmol/L, n, %	28 (70%)	89 (60%)	93 (48%)	127 (46%)	82 (47%)	31 (41%)	450 (49%)
Tachypnea, n, %	6 (15%)	26 (17%)	25 (13%)	35 (13%)	23 (13%)	25 (33%)	140 (15%)
Hypotension, n, %	18 (45%)	56 (38%)	49 (25%)	80 (29%)	47 (27%)	25 (33%)	275 (30%)
Bacteremia, n, %	9 (23%)	29 (19%)	29 (15%)	66 (24%)	46 (26%)	33 (44%)	212 (23%)
30-day in-hospital mortality, n, %	13 (32.5%)	21 (14.1%)	17 (8.7%)	23 (8.2%)	10 (5.7%)	4 (5.3%)	88 (9.6%)

Tachypnea is defined as a respiratory rate ≥30/minute, and hypotension is defined as a systolic blood pressure <90 mm Hg or diastolic blood pressure ≤60 mm Hg (either alone or in combination). BUN = blood urea nitrogen, IQR = interquartile range, SSTI = skin and soft tissue infection, UTI = urinary tract infection.

in critically ill patients with infection in ICUs is associated with increased mortality.[5–10] Moreover, the results are consistent with those of studies reported that hypothermia in patients with bacteremia, including noncritically ill patients, was associated with a worse survival outcome than in patients with a normal or high BT.[27–30] In our study, BT at admission to an ED was associated with mortality in patients with infection, including mildly to moderately ill nonbacteremic patients. These findings should help raise awareness among ED doctors that a patient without fever may have a severe bacterial infection.

TABLE 2. Unadjusted and Adjusted ORs with 95% CIs for Mortality

Variables	Unadjusted OR (95% CI), *P*-Value	Adjusted OR (95% CI), *P*-Value[*]
Body temperature, °C		
<36	1 [Reference]	1 [Reference]
36–36.9	0.3 (0.2–0.8), P = 0.009	0.4 (0.2–1.0), P = 0.052
37–37.9	0.2 (0.1–0.5), P < 0.001	0.2 (0.1–0.6), P = 0.003
38–38.9	0.2 (0.1–0.4), P < 0.001	0.2 (0.1–0.6), P = 0.002
39–39.9	0.1 (0.1–0.3), P < 0.001	0.2 (0.1–0.5), P = 0.001
40≤	0.1 (0.04–0.4), P < 0.001	0.1 (0.02–0.4), P = 0.001
Age, year	1.04 (1.02–1.06), P < 0.001	1.03 (1.01–1.06), P = 0.004
Female	0.6 (0.4–0.9), P = 0.02	0.6 (0.3–0.99), P = 0.048
Severity		
Mental confusion	3.4 (2.11–5.5), P < 0.001	2.4 (1.4–4.2), P = 0.002
BUN >7 mmol/L	4.6 (2.7–7.8), P < 0.001	2.2 (1.2–4.0), P = 0.008
Tachypnea	3.0 (1.8–4.9), P < 0.001	2.4 (1.4–4.3), P = 0.003
Hypotension	2.9 (1.8–4.4), P < 0.001	1.7 (1.0–2.8), P = 0.04
Steroid use	1.7 (0.7–4.2), P = 0.2	2.4 (0.9–6.7), P = 0.1
Malignancy	3.4 (2.1–5.4), P < 0.001	3.5 (2.1–6.1), P < 0.001
Bacteremia	2.0 (1.3–3.3), P = 0.003	1.8 (1.1–3.1), P = 0.03

BUN = blood urea nitrogen, CI = confidence interval, OR = odds ratio.
[*]Adjusted for age, gender, mental confusion, BUN >7 mmol/L, tachypnea, hypotension, steroid use, malignancy, and bacteremia.

The association between high fever and low risk of mortality in patients with infection may have several explanations. First, patients with hypothermia may simply have been dying of severe bacterial infection and may have been beyond the point of treatment.

Second, patients with poor febrile response may have been vulnerable to infectious disease because fever per se is an important host defensive mechanism against infection, with a number of beneficial effects. Fever enhances the phagocytosis of extracellular organisms, intracellular killing of ingested intracellular bacteria, chemotaxis, neutrophil migration, production and activity of antibodies, T-cell proliferation, and complement activation.[1–4] Additionally, fever also directly exerts adverse effects on many pathogens, because elevated BT suppresses the replication of a number of pathogenic organisms. Levels of serum iron, an important virulence factor in pathogenic bacteria, are decreased under hyperthermic conditions, resulting in decreased microbial virulence. Fever also induces lysis of many bacteria if BT is sufficiently elevated.[1,3,31,32]

Third, the association between BT and mortality risk may be less direct, as low BT/absence of fever may merely delay the diagnosis of a bacterial infection. Given that fever is a common feature of infection,[33] if a patient presents a high fever, a physician typically considers the possibility of infection. However, if a patient does not have a fever, a physician may not consider infection, thereby delaying the accurate diagnosis of patients who actually have a bacterial infection, thereby leading to increased mortality.[34] As such, physicians should be alert to the possibility of bacterial infection even in patients without a fever. Considering the possibility of bacterial infection then allows for the application of clinical prediction rules, such as CURB-65, which may help evaluate condition severity in patients suspected of any source of sepsis.[12,14–16]

Limitations

Several limitations to the present study warrant mention. First, the method of measuring BT was not standardized, and BT was measured mainly at the axilla using a digital thermometer. The axilla is not an optimal site for measuring BT, because axillary temperature is susceptible to error and can be misleading.[35] A recent systematic review reported that peripheral (tympanic membrane, temporal artery, axillary, or oral) thermometers did not have clinically acceptable accuracy.[36] However, measuring BT with central (pulmonary artery catheter, urinary bladder, esophageal, or rectal) thermometers in all ambulatory patients in EDs would not be realistic. Previous studies in Japanese populations have shown that axillary temperature is only 0.1 to 0.2 °C lower than oral temperature.[37,38] In critically ill Japanese patients, mean difference for axillary temperature compared with bladder temperature was -0.33 ± 0.55 °C.[39] Therefore, the axilla is considered an acceptable site for measuring BT among Japanese.[22] Second, we were unable to determine the difference between BT at admission to the ED and each patient's normal temperature, preventing us from identifying which was more relevant to the patient's outcome: the absolute value of BT or the change in BT from normal. Third, we were unable to determine the usage of antipyretics before patients came to the ED because the precise data as to whether or not patients took antipyretics, including over-the-counter drugs, were unavailable from the medical record. The benefits of antipyretics in treating fever have not been confirmed; in fact, some antipyretic agents have been shown to cause coronary vasoconstriction in patients with coronary artery disease.[33,40] Additionally, the administration of nonsteroidal antiinflammatory drugs or acetaminophen has been associated with increased mortality in septic patients.[41,42] Taking antipyretic drugs before visiting the ED might have thus contributed to a poor prognosis in patients without a fever. In contrast, a recent randomized controlled trial showed that the early administration of acetaminophen for fever in critically ill patients with probable infection did not affect the number of ICU-free days and mortality.[43] Given that antipyretics do not affect mortality in infection, a misclassification of patients taking antipyretics prior to coming the ED into a lower BT group than their true BT would attenuate the relationship between BT on admission at the ED and mortality. Fourth, bacterial infections may cause abrupt changes in BT, especially in cases of bacteremia. Thus, a patient who arrived at the ED afebrile or with mild fever would have been classified as such, even though 1 hour before or after that recording, this patient could have had a high fever. Therefore, these recordings may have been influenced by chance and may not be representative of the true BT. Even so, the dose–response relationship between BT on admission at the ED and mortality would be helpful in screening high risk patients in the ED. Finally, this study was conducted retrospectively, and the data were collected from electric medical records, which may be incomplete and inaccurate. However, the number of missing values was relatively small (less than 5%), and we used mortality as an outcome due to its robust nature. This was a single center study, and further prospective studies on different patients are warranted before conclusions can be drawn on the true impact of BT on patient outcomes.

CONCLUSIONS

In conclusion, the higher the BT on arrival at the ED, the better the outcomes observed in patients with bacterial infection were. An ED clinician should be aware that patients without fever may be more worrisome than those with fever.

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