The impact of body temperature abnormalities on the disease severity and outcome in patients with severe sepsis: an analysis from a multicenter, prospective survey of severe sepsis

Shigeki Kushimoto1*, Satoshi Gando2, Daizoh Saitoh3, Toshihiko Mayumi4, Hiroshi Ogura5, Seitaro Fujishima6, Tsunetoshi Araki7, Hirotto Ikeda8, Joji Kotani9, Yasuo Miki10, Shin-ichiro Shiraishi11, Koichiro Suzuki12, Yasushi Suzuki13, Naoshi Takeyama14, Kiyotaka Takuma15, Ryosuke Tsuruta16, Yoshihiro Yamaguchi17, Norio Yamashita18, Naoki Aikawa6, JAAM Sepsis Registry (JAAMSR) Study Group

Abstract

Introduction: Abnormal body temperatures ($T_b$) are frequently seen in patients with severe sepsis. However, the relationship between $T_b$ abnormalities and the severity of disease is not clear. This study investigated the impact of $T_b$ on disease severity and outcomes in patients with severe sepsis.

Methods: We enrolled 624 patients with severe sepsis and grouped them into 6 categories according to their $T_b$ at the time of enrollment. The temperature categories ($\leq 35.5^\circ C$, $35.6^\circ C$–$36.5^\circ C$, $36.6^\circ C$–$37.5^\circ C$, $37.6^\circ C$–$38.5^\circ C$, $38.6^\circ C$–$39.5^\circ C$, $\geq 39.6^\circ C$) were based on the temperature data of the Acute Physiology and Chronic Health Evaluation II (APACHE II) scoring. We compared patient characteristics, physiological data, and mortality between groups.

Results: Patients with $T_b$ of $\leq 36.5^\circ C$ had significantly worse sequential organ failure assessment (SOFA) scores when compared with patients with $T_b > 37.5^\circ C$ on the day of enrollment. Scores for APACHE II were also higher in patients with $T_b \leq 35.5^\circ C$ when compared with patients with $T_b > 36.5^\circ C$. The 28-day and hospital mortality was significantly higher in patients with $T_b \leq 36.5^\circ C$. The difference in mortality rate was especially noticeable when patients with $T_b \leq 35.5^\circ C$ were compared with patients who had $T_b$ of $> 36.5^\circ C$. Although mortality did not relate to $T_b$ ranges of $\geq 37.6^\circ C$ as compared to reference range of $36.6^\circ C$–$37.5^\circ C$, relative risk for 28-day mortality was significantly greater in patients with $35.6^\circ C$–$36.5^\circ C$ and $\leq 35.5^\circ C$ (odds ratio: 2.032, 3.096, respectively). When patients were divided into groups based on the presence ($\leq 36.5^\circ C$, n = 160) or absence ($>36.5^\circ C$, n = 464) of hypothermia, disseminated intravascular coagulation (DIC) as well as SOFA and APACHE II scores were significantly higher in patients with hypothermia. Patients with hypothermia had significantly higher 28-day and hospital mortality rates than those without hypothermia (38.1% vs. 17.9% and 49.4% vs. 22.6%, respectively). The presence of hypothermia was an independent predictor of 28-day mortality, and the differences between patients with and without hypothermia were observed irrespective of the presence of septic shock.

Conclusions: In patients with severe sepsis, hypothermia ($T_b \leq 36.5^\circ C$) was associated with increased mortality and organ failure, irrespective of the presence of septic shock.

Trial registration: UMIN-CTR ID UMIN000008195
Introduction

Body temperature (Tb) abnormalities are amongst the most commonly noted symptoms of critically ill patients. Fever occurs in approximately half of patients admitted to the ICU and has been associated with adverse outcomes [1]. Fever is one of the most prominent symptoms of infection [2] and it is part of the host acute-phase response to infections as well as non-infectious inflammatory stimuli [3]. Fever is also believed to be harmful, especially in patients with life-threatening illness, because febrile responses are known to increase the metabolic rate and minutes ventilation and oxygen consumption, and it can have adverse effects on neurological outcomes [4-6]. Fever could also be beneficial because it is believed to reduce bacterial growth, and a higher Tb is believed to promote the synthesis of antibodies and cytokines, thereby activating immune cells and improving survival [7-9]. Several studies have suggested that suppression of the febrile response with antipyretic drugs could worsen patient outcomes [10,11].

A large epidemiological study that included patients with and without infection reported that the presence of fever per se could not be associated with increased ICU mortality. Nevertheless, fever with Tb ≥39.5°C was associated with a significant increase in mortality (20.3% versus 12.0% (P <0.001) for patients with Tb ≥39.5°C and <39.5°C, respectively). These very high fevers could be complicated with cardiac arrhythmias, tachycardia, increased oxygen demand, convulsions, and brain damage [1]. A recent study that used data from Australia, New Zealand, and the United Kingdom investigated the association between peak Tb in the first 24 h after admission to ICU and inhospital mortality [12]. This study showed that elevated peak Tb in the first 24 h in the ICU could be associated with decreased in-hospital mortality in patients with infection. The lowest mortality risk was among patients with Tb between 39.0°C and 39.4°C. However, mortality risk was increased among patients who did not have infection. Patients with fever in response to non-infective causes may well experience the harmful effects of fever without any fever-related benefits, such as protection against viruses or bacteria.

Hypothermia can be caused by a variety of factors including cold exposure, severe infection, endocrine abnormalities, and drug overdoses, and hypothermic patients require immediate medical intervention [13-15]. Although hypothermia may be an unintended consequence of critical illness and may be associated with an increased risk of mortality in patients with sepsis and non-infectious conditions, the influence of hypothermia on the physiological severity and outcome of critically ill patients, particularly patients with severe sepsis, is not well understood [12,16-22].

Although there are many reports of Tb abnormalities in patients with sepsis, there is a relative paucity of information on the influences of hyper- or hypothermia on disease severity and outcomes in patients with severe sepsis. The aim of present study was to investigate the association between Tb and disease severity and patient outcomes in patients with a definitive diagnosis of severe sepsis.

Materials and methods

This was a prospective study conducted as a part of a multicenter prospective evaluation of severe sepsis in Japan, undertaken by the Japanese Association for Acute Medicine Sepsis Registry (JAAMSR) Study Group [23]. Both the Japanese Association for Acute Medicine and the Ethics Committees of the hospitals that participated in this study approved the study protocol. Data collection was performed as part of the routine clinical examinations without any medical intervention. Data management and statistical analyses were processed anonymously. Based on these reasons, written informed consent was waived by both the Japanese Association for Acute Medicine and the Ethics Committees of the participating hospitals. The study was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR ID: UMIN000008195).

Patients

Between June 1, 2010, and May 31, 2011, we enrolled 624 patients in this study. All of the patients were diagnosed with severe sepsis and admitted to one of 15 critical care centers in the tertiary care hospitals in Japan. We did not have any exclusion criteria.

Definitions

Sepsis, severe sepsis, septic shock, and systemic inflammatory response syndrome (SIRS) were defined according to the American College of Chest Physicians/Society of Critical Care Medicine consensus conference and its revised version of 2003 [24,25]. The severity of illness was evaluated according to the acute physiology and chronic health evaluation (APACHE) II score at the time of enrollment [26]. Organ dysfunction was assessed according to the sequential organ failure assessment (SOFA) score [27]. Multiple organ dysfunction syndrome (MODS) was defined as a SOFA score ≥12 [27]. A diagnosis of disseminated intravascular coagulation (DIC) was made on the basis of the scoring system of the International Society on Thrombosis and Haemostasis (ISTH) [28]. The change in fibrin/fibrinogen degradation product (FDP) was used as the fibrin-related marker for the ISTH criteria. FDP values of <10, ≥10 but <25, and ≥25 mg/L, were defined as no increase, moderate increase, and strong increase, respectively. The outcome measure was the 28-day and hospital all-cause mortality.
Body temperature

T_b recorded within 24 h of a diagnosis of severe sepsis was used for the APACHE II score and the recorded temperature was used in this analysis. We recorded the value measured by the method most preferred by the American College of Critical Care Medicine and the Infectious Diseases Society of America [2]. Although the method used to measure core T_b was not standardized and the specific methods used for each individual measurement of core T_b was not recorded in this survey, all the institutions that participated in this study used standard methods for determining core T_b. The sites used for T_b measurement at the institutions were as follows: urinary bladder, ten institutions; urinary bladder or rectal, three institutions; rectal, one institution; and intravascular, one institution. To ascertain the effect of T_b aberrance on disease severity and outcome, patients were grouped into one of six categories based on their core T_b as recorded for the APACHE II scoring. The categories were ≤35.5°C, 35.6 to 36.5°C, 36.6 to 37.5°C, 37.6 to 38.5°C, 38.6 to 39.5°C, and ≥39.6°C, as previously reported. A core T_b of 35.5°C was taken as the lowest T_b value because previous studies have reported this temperature as the threshold of hypothermia with high mortality [16,29-34]. Although previous studies considered 35.5°C as the threshold for hypothermia [16,29-32], we opted to use 36.5°C as the threshold because we found significant differences in the mortality of patients with T_b ≤36.5°C compared with those with T_b >36.5°C based on the results of a temperature categorical analysis, as shown in Tables 1 and 2. We also compared the mortality of patients divided into two groups using 36.5°C as a cutoff value. This analysis demonstrated significant differences between groups in both the 28-day and hospital mortality (P <0.001). Based on these findings, we evaluated the effect of hypothermia defined as T_b ≤36.5°C on not only mortality but also disease severity, which may affect mortality. For analysis, patients were divided into two groups, namely, hypothermia (T_b ≤36.5°C, n = 160) and no-hypothermia (T_b >36.5°C, n = 464).

Assessments

Blood was collected at the time of admission to ICU and then daily thereafter as part of the routine clinical and laboratory tests using established standard laboratory techniques. Platelet counts and coagulation variables necessary to diagnose DIC were collected and APACHE II, SOFA, and DIC scores were assessed.

Statistical analysis

Data are expressed as medians and interquartile ranges. All statistical analyses were performed using SPSS 19.0 for Windows (SPSS, Chicago, IL, USA). Comparisons between the 2 groups were performed using the Mann-Whitney’s U test, and categorical variables were summarized using proportions and compared between groups using either the Pearson’s chi-square or Fisher’s exact test, where appropriate. Kruskal-Wallis one-way analysis of variance and multiple chi-square tests were used for comparisons between multiple groups, and P-values were adjusted with the Bonferroni correction for multiple testing.

Odds ratios (OR) are reported relative to a reference range of T_b, as previously reported [33]. We defined the reference range here as the T_b category of 36.6 to 37.5°C. Additionally, survival curves were derived by the Kaplan-Meier method and compared by the log-rank test for each range. We used a multivariate logistic model to assess the relationships between 28-day mortality and independent variables in patients with severe sepsis. Outcome (dead, 1; survived, 0) was used as the criterion variable, and age, gender (male or female), admission category of underlying medical condition (medical or other cause), SOFA score, APACHE II score, positive blood culture (yes or no), the

### Table 1 Baseline characteristics and outcome of the enrolled patients (n = 624)

| Characteristic                  | Value         |
|--------------------------------|---------------|
| Age, years                     | 72 (61–81)    |
| Gender, male/female            | 391/233       |
| APACHE II score                | 23 (17–29)    |
| SOFA score                     | 8 (6–11)      |
| MODS, n (%)                    | 144 (23.1)    |
| Septic shock, n (%)            | 282 (45.2)    |
| Admission category             |               |
| Medical                        | 519 (83.2%)   |
| Trauma                         | 27 (4.3%)     |
| Surgery                        | 19 (3.0%)     |
| Burns                          | 19 (3.0%)     |
| Other                          | 40 (6.4%)     |
| Site of Infection              |               |
| Pulmonary                      | 261 (41.8%)   |
| Intra-abdominal                | 133 (21.3%)   |
| Urinary                        | 78 (12.5%)    |
| Skin/soft tissue               | 78 (12.5%)    |
| Meningitis                     | 15 (2.4%)     |
| Catheter-related               | 11 (1.8%)     |
| Bone/joint                     | 10 (1.6%)     |
| Infective endocarditis         | 3 (0.5%)      |
| Other                          | 25 (4.0%)     |
| 28-day mortality, n (%)        | 144 (23.1%)   |
| Hospital mortality, n (%)      | 184 (29.5%)   |

Values are presented as median (IQR) or number (%). APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment; MODS, multiple organ dysfunction syndrome.
Table 2 Body temperature and severity of coagulation abnormality/organ failure scores

| Body temperature, °C | ≤35.5 (n = 99) | 35.6 to 36.5 (n = 61) | 36.6 to 37.5 (n = 112) | 37.6 to 38.5 (n = 155) | 38.6 to 39.5 (n = 133) | ≥39.6 (n = 64) |
|----------------------|----------------|----------------------|-----------------------|----------------------|-----------------------|----------------|
| Age, years           | 76 (65 to 82) | 78 (62.5 to 83.5)    | 75 (66 to 84)        | 72 (61 to 82)       | 67 (58 to 76)        | 65 (45.25 to 78.75) |
| Septic shock, n (%)  | 62 (62.6%)    | 33 (54.1%)           | 46 (41.1%)           | 63 (40.6%)          | 54 (40.6%)           | 24 (37.5%)       |
| SIRS criteria        | 4 (3 to 4)    | 15 (24.6%)           | 22 (19.6%)           | 20 (12.9%)          | 21 (15.8%)           | 7 (10.9%)        |
| DIC score            | 5 (2 to 6)    | 10 (7 to 12)         | 8 (5 to 11)          | 8 (5 to 11)        | 7 (5 to 10.75)       | 7 (6 to 10)      |
| SOFA score           | 28 (23 to 33) | 15 (24.1%)           | 27 (24.1%)           | 32 (20.6%)         | 23 (17.3%)           | 10 (15.6%)       |
| MODS, n (%)          | 35 (35.4%)    | 23 (37.8%)           | 27 (24.1%)           | 32 (20.6%)         | 23 (17.3%)           | 10 (15.6%)       |
| APACHE II            | 28 (23 to 33) | 24 (20 to 29)        | 21 (16.25 to 27)     | 21 (16 to 27)      | 22 (17 to 26)        | 22 (17.25 to 30)  |

| Outcome              |                 |                     |                      |                     |                      |                 |
|----------------------|----------------|----------------------|----------------------|----------------------|----------------------|----------------|
| 28-day mortality, n (%) | 40 (40.4%)     | 21 (34.4%)           | 23 (20.5%)           | 28 (18.1%)          | 21 (15.8%)           | 11 (17.2%)       |
| Hospital mortality, n (%) | 52 (52.5%)    | 27 (44.3%)           | 27 (24.1%)           | 39 (25.2%)         | 26 (19.5%)           | 13 (20.3%)       |

SIRS, systemic inflammatory response syndrome; DIC, disseminated intravascular coagulation; SOFA, sequential organ failure assessment; MODS, multiple organ dysfunction syndrome; APACHE, acute physiology and chronic health evaluation. \( P \leq 0.0033 \) (after Bonferroni correction) versus 35.6 to 36.5°C; \( P \leq 0.047 \) versus 36.6 to 37.5°C; \( P \leq 0.062 \) versus 38.6 to 39.5°C; \( P \geq 0.062 \) versus ≥39.6°C.

The presence of comorbidity (yes or no), and hypothermia (T_b ≤36.5°C or >36.5°C) were used as explanatory variables. Results are reported as OR, \( P \)-values, and 95% CI. Differences with a \( P \)-value <0.05 were considered to be statistically significant. Furthermore, \( P <0.0033 \) (after Bonferroni correction) was used for comparisons between groups in multiple testing (Table 2).

Results

Baseline characteristics and patient outcome

During the 1-year study period, a total of 14,417 patients were admitted to the 15 critical care centers, and 624 (4.3%) of these patients were diagnosed with severe sepsis and enrolled in this study. The characteristics at enrollment and outcomes of patients are shown in Table 1. The mean age was 69 years, and the mean initial APA-CHIE II score and SOFA scores were 23.4 and 8.6, respectively. The major sites of infection were pulmonary, intra-abdominal, urinary, and skin/soft tissue. More than half of the patients had dysfunction of three or more organ systems. The 28-day mortality was 23.1% and the overall hospital mortality was 29.5%. Sepsis-related hospital mortality was 25.6% (160/624 patients).

Relationships between body temperature and severity scores

Patients with T_b >38.5°C were significantly younger than patients with T_b ≤38.5°C. The prevalence of septic shock was significantly higher among patients with T_b ≤35.5°C when compared with the incidence of septic shock among patients in the other T_b categories (Table 2). MODS and SOFA on the day of enrollment were significantly higher in patients with T_b 35.6 to 36.5°C and ≤35.5°C when compared with patients who had T_b >37.5°C. The APACHEII scores in patients with T_b ≤35.5°C were significantly higher when compared with patients who had T_b >36.5°C.

For mortality rates, patients who had T_b ≤36.5°C had significantly higher 28-day and hospital mortality rates when compared with patients who had T_b >36.5°C. The mortality rate among patients who had T_b ≤35.5°C was especially high at 40.4% and 52.5% for 28-day and hospital mortality rates, respectively. The lowest 28-day and hospital mortality were noted in patients with T_b between 38.6 and 39.5°C (15.8% and 19.5%, for 28-day and hospital mortality, respectively) (Table 2).

Body temperature and mortality

Table 3 shows 28-day mortality and OR for each T_b (taken on day 1) relative to the reference range of 36.6 to 37.5°C. We found no relationships between mortality and T_b in patients in the following categories: 37.6 to 38.5°C, 38.6 to 39.5°C, and ≥39.6°C. The relationship between mortality and T_b was significant in patients in the T_b categories of 35.6 to 36.5°C (OR 2.032, \( P = 0.047 \)) and ≤35.5°C (OR 3.096, \( P = 0.001 \)). Kaplan-Meier estimates for the probability of survival at 28 days were lower in patients

Table 3 Day-1 body temperature and 28-day mortality

| Range of body temperature (°C) | 28-day mortality | Unadjusted odds ratio | 95% CI | \( P \)-value |
|--------------------------------|------------------|----------------------|-------|-------------|
| ≤35.5                         | 40.4%            | 3.096                | 1.611, 5.947 | 0.001       |
| 35.6 to 36.5                  | 34.4%            | 2.032                | 1.009, 4.088 | 0.047       |
| 36.6 to 37.5                  | 20.5%            | 1.000                | (reference) |             |
| 37.6 to 38.5                  | 18.1%            | 0.853                | 0.461, 1.577 | 0.621       |
| 38.6 to 39.5                  | 15.8%            | 0.726                | 0.377, 1.395 | 0.404       |
| ≥39.6                         | 17.2%            | 0.803                | 0.363, 1.778 | 0.693       |
with \( T_b \) between 35.6°C and 36.5°C and \( \leq 35.5°C \) compared to patients who had \( T_b \geq 36.6°C \) (Figure 1).

**Severity scores and outcome in hypothermic and non-hypothermic patients**

After analyzing the data for the different \( T_b \) categories, we defined 36.5°C as the threshold temperature for hypothermia and compared variables and outcomes between patients with hypothermia (\( \leq 36.5°C, n = 160 \)) and those without hypothermia (\( >36.5°C, n = 464 \)).

The incidence of septic shock was significantly higher in patients with hypothermia compared to patients without hypothermia. DIC, SOFA, and APACHE II scores and the incidence of MODS were significantly increased among hypothermic patients (Table 4). In hypothermic patients, 28-day and hospital mortality were higher (more than double) than the mortality rates of patients without hypothermia (38.1% versus 17.9%, 49.4% versus 22.6%, for 28-day and for hospital mortality, respectively) (Table 4).

**Comparisons of severity scores and outcome between hypothermic and non-hypothermic patients with and without septic shock**

The incidence of septic shock was significantly higher in patients with hypothermia. We separately evaluated the influence of hypothermia on variables and outcomes in patients with septic shock, because mortality and severity scores in patients with septic shock were significantly higher when compared with other patients [23]. Patients with septic shock had higher DIC, SOFA, and APACHE II scores if they were hypothermic at the time of diagnosis. In these hypothermic patients, both 28-day and hospital mortality were nearly twice those of patients with septic shock and no hypothermia (Table 5). In patients without septic shock, hypothermic patients had a significantly higher incidence of MODS and they also had significantly higher SOFA and APACHE II scores when compared with patients who did not have hypothermia. Although the 28-day mortality was not significantly different between hypothermic and non-hypothermic patients, hospital mortality in hypothermic patients was nearly twice that of non-hypothermic patients (30.8% versus 17.0%) (Table 6). The 28-day and hospital mortality rates in hypothermic patients without

![Figure 1 Body temperature within 24 h of ICU admission and survival of patients with severe sepsis.](image)

The Kaplan-Meier estimates for the probability of survival, which at 28 days was lower in patients with body temperature of \( \leq 35.5°C \) and 35.6 to 36.5°C, as compared to patients with body temperatures of 36.6 to 37.5°C, 37.6 to 38.5°C, 38.6 to 39.5°C, and \( \geq 39.6°C \) (\( P < 0.001 \)). Body temperature was recorded as the highest score on the acute physiology and chronic health evaluation (APACHE) II scoring system and as the farthest value from 36.5 to 37.0°C within 24 h from the time of enrollment, which was divided into categorical variables with 1°C increments. Thus, body temperature was analyzed in six range categories: \( \leq 35.5°C, 35.6 \) to 36.5°C, 36.6 to 37.5°C, 37.6 to 38.5°C, 38.6 to 39.5°C, and \( \geq 39.6°C \).

**Table 4 Characteristics, physiology on day 1 and outcome in hypothermic (body temperature \( \leq 36.5°C \)) and non-hypothermic severe sepsis patients**

| Hypothermia (n = 160) | Non-hypothermia (n = 464) | \( P \)-value |
|-----------------------|--------------------------|--------------|
| Age, years            | 76 (64.25 to 83)         | 71 (60 to 80) | 0.001 |
| Septic shock          | 59.4% (n = 95)           | 40.3% (n = 187) | <0.001 |
| DIC score             | 4 (2 to 6)               | 3 (2 to 5)   | 0.009 |
| SOFA score            | 10 (7 to 13)             | 8 (5 to 11)  | <0.001 |
| APACHE II score       | 26 (21 to 32)            | 21 (16.25 to 27) | <0.001 |
| Outcome               |                          |              |         |
| 28-day mortality      | 38.1% (n = 61)           | 17.9% (n = 83) | <0.001 |
| Hospital mortality    | 49.4% (n = 79)           | 22.6% (n = 105) | <0.001 |

Results are presented as median (IQR) or % (number). DIC, disseminated intravascular coagulation; SOFA, sequential organ failure assessment; APACHE, acute physiology and chronic health evaluation.

**Table 5 Characteristics, physiology on day 1, and outcome in hypothermic (body temperature \( \leq 36.5°C \)) and non-hypothermic patients with septic shock**

| Hypothermia (n = 95) | Non-hypothermia (n = 187) | \( P \)-value |
|----------------------|--------------------------|--------------|
| Age, years           | 75 (62 to 83)            | 72 (61 to 79) | 0.069 |
| DIC score            | 4.0 (2.0 to 5.0)         | 3.0 (2.0 to 5.0) | 0.047 |
| SOFA score           | 11.0 (9.0 to 13.0)       | 10.0 (8.0 to 13.0) | 0.039 |
| APACHE II score      | 29.0 (23.0 to 35.0)      | 25.0 (19.0 to 31.0) | 0.001 |
| Outcome              |                          |              |         |
| 28-day mortality     | 49.5% (n = 47)           | 24.6% (n = 46) | <0.001 |
| Hospital mortality   | 62.1% (n = 59)           | 31.0% (n = 58) | <0.001 |

Results are presented as median (IQR) or % (number). DIC, disseminated intravascular coagulation; SOFA, sequential organ failure assessment; APACHE, acute physiology and chronic health evaluation.
septic shock and non-hypothermic patients with septic shock were both double those in patients who were non-hypothermic and did not have septic shock. In addition, the 28-day and hospital mortality rates in hypothermic patients with septic shock were almost four times higher than those in non-hypothermic patients without septic shock. The mortality rate amongst patients with severe sepsis is significantly higher among those who have a Tb of ≤36.5°C, was an independent predictor of 28-day mortality in patients with severe sepsis, especially in the presence of septic shock.

Discussion

The results of this study clearly indicate that the mortality rate amongst patients with severe sepsis is significantly higher among those who have a Tb of ≤36.5°C compared to those who have a Tb of >36.5°C measured within 24 h of diagnosis. In this study, the mortality rate was more than two times higher among patients with severe sepsis who were hypothermic compared to patients with severe sepsis who had no hypothermia. Furthermore, the higher mortality rate was associated with a deterioration of organ function and DIC. The effect of hypothermia on mortality rate was consistently observed in patients with and without septic shock.

In our study, elevated Tb was not associated with an increase in disease severity or risk of mortality. Moreover, elevated Tb was not associated with a progressive increase in disease severity or mortality when compared with the reference Tb range of 36.6 to 37.5°C. Our results suggest that higher Tb is not harmful in patients with severe sepsis. Studies investigating the effect of fever control by means of antipyretic treatment or external cooling and the risk of mortality have reported contrasting results, and it is clear that the role of fever and its control in patients with severe sepsis still needs to be elucidated [34,35].

It has been suggested that hypothermia is associated with an increased risk of mortality in critically ill patients [12,33]. Moreover, the effect of hypothermia on increased mortality has been shown in patients with and without infection [12,17,18]. In the Methylprednisolone Severe Sepsis Study database, the Veterans Administration Systemic Sepsis Cooperative Study of Glucocorticoid Therapy, and the Ibuprofen Sepsis Study, the threshold Tb for hypothermia was set at 35.5°C and patients with severe sepsis were included. The incidence of hypothermia (<35.5°C), 28- or 30-day mortality in patients with hypothermia versus patients without hypothermia in these studies were 9%, 62% versus 26%; 10%, 57% versus 28%; and 9.6%, 70% versus 35%, respectively. The NORA-SEPT II study included only patients with septic shock and the incidence of hypothermia among these patients was 21%. The mortality in patients with hypothermia and in those without hypothermia was 59% and 34%, respectively. In the present study, the incidence of mortality among patients with Tb ≤35.5°C was 15.9% (99/624 patients), and the 28-day and hospital mortality rates were also significantly higher when compared with other patients (Tb >35.5°C; 40.4% versus 19.8%, 52.5% versus 34.0%, respectively). Although the underlying mechanism of sepsis-related

| Hypothermia (n = 65) | Non-hypothermia (n = 277) | P-value |
|----------------------|--------------------------|---------|
| Age, years 78 (70 to 82.5) | 71 (58 to 81) | 0.004 |
| DIC score 3 (2 to 5) | 3 (2 to 5) | 0.133 |
| SOFA score 7.5 (5 to 11) | 6 (4 to 8) | 0.004 |
| APACHE II score 24 (18 to 27) | 19 (15 to 24) | <0.001 |

| Hypothermia (body temperature <36.5°C) | 21.5% (n = 14) | 13.4% (n = 37) | 0.096 |

| Hospital mortality 30.8% (n = 20) | 17.0% (n = 47) | 0.012 |

Table 7 shows that hypothermia, defined as a core Tb of ≤36.5°C, was an independent predictor of 28-day mortality in patients with severe sepsis, especially in the presence of septic shock.

| Factors | Odds ratio | P value | 95% CI |
|---------|------------|---------|--------|
| Severe sepsis (n = 602) | | | |
| Age | 1.026 | 0.001 | 1.010–1.042 |
| Gender (male) | 1.476 | 0.091 | 0.940–2.317 |
| Admission category (medical conditions) | 1.098 | 0.778 | 0.572–2.109 |
| SOFA score | 1.111 | 0.002 | 1.041–1.186 |
| APACHE II score | 1.062 | 0.000 | 1.029–1.095 |
| Positive blood culture | 1.471 | 0.073 | 0.965–2.242 |
| Presence of comorbidity | 0.880 | 0.569 | 0.566–1.367 |

| Hypothermia (body temperature <36.5°C) | 1.952 | 0.003 | 1.253–3.040 |

Severe sepsis with septic shock (n = 273)

| Factors | Odds ratio | P value | 95% CI |
|---------|------------|---------|--------|
| Age | 1.036 | 0.001 | 1.014–1.059 |
| Gender (male) | 1.676 | 0.095 | 0.914–3.074 |
| Admission category (medical conditions) | 1.110 | 0.829 | 0.431–2.860 |
| SOFA score | 1.078 | 0.119 | 0.981–1.186 |
| APACHE II score | 1.050 | 0.019 | 1.008–1.094 |
| Positive blood culture | 1.761 | 0.052 | 0.996–3.114 |
| Presence of comorbidity | 0.722 | 0.290 | 0.395–1.319 |
| Hypothermia (body temperature <36.5°C) | 2.778 | 0.001 | 1.555–4.965 |

CI, confidence interval; SOFA, Sequential Organ Failure Assessment; APACHE, Acute Physiology and Chronic Health Evaluation; Comorbidity, at least one comorbidity.
hypothermia is still unclear, our results are consistent with previous studies [16,29-32].

We defined 36.5°C as the threshold of hypothermia based on the results of our evaluation of the outcomes for the different Tb categories. We also generated the receiver operating characteristic curves using Tb on the day of enrollment for the 28-day and hospital mortality evaluation. The analysis revealed that the cutoff values for predicting the 28-day and hospital mortality were 36.9°C and 36.3°C, respectively, for maximizing both sensitivity and specificity (data not shown), and these suggest a Tb of 36.5°C as an acceptable cutoff value to define hypothermia in this study.

Although the impact of hypothermia, defined as a threshold temperature of 35.5°C, on mortality has been demonstrated in previous studies [16,29-32], the effect of hypothermia on disease severity has not been fully evaluated. Therefore, we evaluated the effects of Tb ≤36.5°C on both mortality and disease severity by comparing patients with and without hypothermia. The incidence of organ failure, DIC and outcomes were significantly different in patients with Tb of ≤36.5°C compared to those with Tb of >36.5°C, and there was no significant difference between patients who had Tb of ≤35.5°C compared to those with a Tb of >35.5°C. Therefore, 36.5°C was considered the threshold for hypothermia in patients with severe sepsis, irrespective of the presence of septic shock.

It is important to note that the inclusion of Tb abnormalities as a measure of the severity of illness varies between different scoring systems. APACHE II assigns points for patients with either high or low Tb, SAPS II only assigns points for high Tb, and SAPS III only assigns points for low Tb [26,36,37]. Although it is widely accepted that fever has an adverse effect on patients with neurologic injury [38], little is known about the impact of temperature abnormalities on the outcome of other ICU patients, especially patients with sepsis [1,18]. The results of this study add valuable knowledge with regard to the influence of Tb abnormalities on the outcome of patients with severe sepsis. From our results, it is clear that hypothermia has a greater impact on organ dysfunction and outcomes. Thus far, the mechanism underlying the harmful effects of hypothermia is not yet known, but it is evident that hypothermia is more important than elevated temperature for the severity of illness scores in patients with severe sepsis.

Limitations
There are some limitations to our study. Tb was recorded within 24 h of a diagnosis of severe sepsis as the highest core Tb value of the APACHE II score. However, we did not standardize the method by which core Tb was measured, and we did not attempt to differentiate between patients who had an elevated Tb as a result of hyperthermia syndrome or because of fever. Although some patients might have been categorized differently if we employed a systematic protocol for measuring Tb, our recorded core Tb data were not merely arbitrary values obtained within the 24-h period after a diagnosis of severe sepsis, but these measurements were assessed objectively. In addition, the outcome and influence of treatment may vary significantly on that basis.

We did not specifically control for therapeutic modalities that may have influenced Tb, such as antipyretic drugs or active external temperature control strategies. Although it is widely accepted that temperature control improves outcome in patients with neurologic injury, the effect of acetaminophen, ibuprofen, or external control on the outcome of other critically ill patients is not well understood.

Conclusions
Tb of patients with severe sepsis, as measured at the time of diagnosis, significantly affected patient outcome. In our study, hypothermia (≤36.5°C) was associated with a significantly higher risk of mortality. The risk of mortality was almost double among hypothermic patients compared to patients without hypothermia. Hypothermia was also associated with a significant physiological decline in these patients, irrespective of whether they experienced septic shock or not. Elevated Tb was not associated with an increased disease severity and risk of mortality.

Key messages
- In patients with severe sepsis, the impact of elevated body temperature and hypothermia on mortality and severity of physiologic decline is different.
- Hypothermia, defined as body temperature of ≤36.5°C, is significantly associated with an increased mortality risk of more than double that of non-hypothermic patients; moreover, it is associated with a physiological decline in severe sepsis, irrespective of the presence of septic shock.
- Elevated body temperature was not associated with increased disease severity or risk of mortality.

Abbreviations
APACHE: Acute physiology and chronic health evaluation; DIC: Disseminated intravascular coagulation; FDP: Fibrin/fibrinogen degradation product; ISTH: International Society on Thrombosis and Haemostasis; JAAM: Japanese Association for Acute Medicine; JAAMSR: Japanese Association for Acute Medicine Sepsis Registry; MODS: Multiple organ dysfunction syndrome; OR: Odds ratio; SAPS: Simplified acute physiology score; SIRS: Systemic inflammatory response syndrome; SOFA: Sequential organ failure assessment; Tb: Body temperature.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
SK participated in study design and data collection and interpretation, performed the statistical analysis, and drafted the manuscript. SG, DS, HO,
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Author details
1Division of Emergency Medicine, Tohoku University Graduate School of Medicine, Sendai-ku, Miyagi 980-8574, Japan.
2Division of Acute and Critical Care Medicine, Department of Anesthesiology and Critical Care Medicine, Hokkaido University Graduate School of Medicine, Kita-2 Jou Nishi-5, Kitaku, Sapporo-shi, Hokkaido 060-8638, Japan.
3Division of Traumatology, Research Institute, National Defense Medical College, 3-2 Namiki, Tokorozawa-shi, Saitama 359-8513, Japan. Emergency Center, Department of Emergency and Critical Care Medicine, Ichinomiya Municipal Hospital, Bunryu 2-2-2, Ichinomiya-shi, Aichi 491-8558, Japan.
4Department of Traumatology and Acute Critical Medicine, Osaka University Graduate School of Medicine, 2-15 Yamadaoka, Suita-shi, Osaka 565-0871, Japan.
5Department of Emergency & Critical Care Medicine, School of Medicine, Keio University, Shinanomachi 35, Shinjuku-ku, Tokyo 160-8582, Japan.
6Department of Emergency Medicine, Trauma and Resuscitation Center, Teikyo University School of Medicine, Kaga 2-11-1, Itabashi-ku, Tokyo 173-8606, Japan. Department of Emergency, Critical Care and Disaster Medicine, Hyogo College of Medicine, Mookagawa-cho 1-1, Nishinomiya-shi, Hyogo 663-8501, Japan. Advanced Critical Care Center Aichi University Medical Hospital, Yazakokuramata 1-1, Nagakute-shi, Aichi 480-1195, Japan.
7Department of Emergency and Critical Care Medicine, Nippon Medical School, Sendagi 1-1-5, Bunkyou-ku, Tokyo 113-8603, Japan. Department of Acute Critical Care Medicine, Kawasaki Medical School, Matsushita 577, Kurashiki, Okayama 701-0114, Japan. Department of Critical Care Medicine, Iwate Medical University, Uchimaru 19-1, Morioka-shi, Iwate 020-8505, Japan.
8Department of Emergency and Acute Intensive Care Medicine, Fujita Health University, Dengakugakubo 1-9-1, Kutsukake-cho, Toyoake-shi, Aichi 470-1192, Japan. Emergency & Critical Care Center, Kawasaki Municipal Hospital, Shinkawadori 12-1, Kawasaki-shi, Kanagawa 210-0013, Japan.
9Advanced Medical Emergency & Critical Care Center, Yamaguchi University Hospital, Minamikokugushi 1-1-1, Ube-shi, Yamaguchi 755-8505, Japan. Department of Trauma & Critical Care Medicine, Kyorin University, School of Medicine, Shinkawa 6-20-2, Mitaka-shi, Tokyo 181-8611, Japan.
10Department of Emergency & Critical Care Medicine, School of Medicine, Kurume University, Asahimachi 67, Kurume-shi, Fukuoka 830-0011, Japan.

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