Fever in the Emergency Department Predicts Survival of Patients With Severe Sepsis and Septic Shock Admitted to the ICU*

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Objectives: To study the prognostic value of fever in the emergency department in septic patients subsequently admitted to the ICU.

Design: Observational cohort study from the Swedish national quality register for sepsis.

Setting: Thirty ICU's in Sweden.

Patients: Two thousand two hundred twenty-five adults who were admitted to an ICU within 24 hours of hospital arrival with a diagnosis of severe sepsis or septic shock were included.

Interventions: None.

Measurements and Main Results: Body temperature was measured and classified according to four categories (< 37°C, 37–38.29°C, 38.3–39.5°C, ≥ 39.5°C). The main outcome was in-hospital mortality. Odds ratios for mortality according to body temperature were estimated using multivariable logistic regression. Subgroup analyses were conducted according to age, sex, underlying comorbidity, and time to given antibiotics. Overall mortality was 25%. More than half of patients had a body temperature below 38.3°C. Mortality was inversely correlated with temperature and decreased, on average, more than 5% points per °C increase, from 50% in those with the lowest temperatures to 9% in those with the highest. Increased body temperature in survivors was also associated with shorter hospital stays. Patients with fever received better quality of care, but the inverse association between body temperature and mortality was robust and remained consistent after adjustment for quality of care measures and other factors that could have confounded the association. Among vital signs, body temperature was best at predicting mortality.

Conclusions: Contrary to common perceptions and current guidelines for care of critically ill septic patients, increased body temperature in the emergency department was strongly associated with lower mortality and shorter hospital stays in patients with severe sepsis or septic shock subsequently admitted to the ICU. (*Crit Care Med* 2017; 45:591–599)

Key Words: fever; ICU; sepsis; survival, emergency department

*See also p. 747.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccmjournal).

The Swedish national quality register for severe sepsis and septic shock was originally funded by the Swedish Infectious disease society; current funding is from the Swedish Association of Local Authorities and Regions. This study was supported by grants from Swedish Government Research Grant (ALF) and the Royal Physiographic Society in Lund. The funders played no role in the design of the study, data collection or analysis, decision to publish, or preparation of the article.

Dr. Rylance's institution received funding from Department of Infectious Diseases Skane University Hospital, Lund, and she disclosed work for hire. Dr. Inghammar received funding from Swedish Government Research Grant (ALF) and the Royal Physiographic Society in Lund. The remaining authors have disclosed that they do not have any potential conflicts of interest.

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DOI: 10.1097/CCM.0000000000002249

Mortality from severe sepsis and septic shock is declining but remains high (1, 2). Prompt recognition and treatment is important for survival (3), but it remains a challenge to distinguish these conditions in a heterogeneous patient group and in the often chaotic context of an emergency department (ED). Body temperature (BT) is routinely measured on ED arrival. As fever rises, so does the suspicion of infection, contributing to faster recognition and treatment of infectious conditions. However, many critically ill, infected patients do not have fever (4), making identification more difficult.

Various beneficial effects of fever have been described, including negative feedback on the release of pyrogenic

cytokines (5), improved immune cell function (6) and antibiotic activity during fever (7). Furthermore, harmful effects of antipyresis have been found in experimental sepsis (8, 9). In infected patients in ICUs (10), increased BT during the first 24 hours has been associated with improved survival but the role of fever in critically ill patients in the ED has not been systematically studied.

In this large multicenter study, we assessed the prognostic significance of BT, as measured in the ED, in a population with severe sepsis or septic shock, who were admitted to ICUs within 24 hours of hospital arrival.

MATERIALS AND METHODS

Study Design

We conducted a cohort study using a prospectively compiled Swedish national quality sepsis register (NQSR), estimating in-hospital mortality according to BT at admission. The NQSR comprises adult patients, aged greater than 17 years, admitted to any of 30 ICU's throughout Sweden with a diagnosis of severe sepsis or septic shock within 24 hours of arrival to an ED. Registration started in 2007 and this report includes patients registered until February 2015. The study protocol was approved by the ethical review board in Stockholm (2013/956). Written informed consent was waived.

Data Collection and Quality Variables

The first recorded vital signs or lactate measurement in the ED, after hospital arrival, was used. As measure of quality of care, we used the achievement of sepsis bundles (or individual bundle components) similar to the 2015 revised sepsis bundle promoted by the Surviving Sepsis Campaign (SSC) (11) but, in line with Swedish guidelines, to be completed within one, rather than 3 hours as permitted in the SSC. For details on this, on data collection and definitions, see **supplemental data** (Supplemental Digital Content 1, http://links.lww.com/CCM/C311).

Statistical Methods

Chi square, Wilcoxon signed rank, and Kruskal-Wallis tests were used to assess the distribution of risk factors for in-hospital mortality between different categories of BT and between survivors and nonsurvivors. Mortality was calculated for different categories of studied exposures. Using logistic regression, we estimated the odds ratios (ORs) for in-hospital mortality according to categories of temperature. We used generalized estimating equations (GEEs) to account for the possibility of dependency between individuals hospitalized in the same ICU. The aim of the study was to explore the effect of BT on mortality and not to predict mortality per se. We therefore selected potential confounders to the temperature-mortality association a priori from factors known or suspected to be associated with fever and death in septic shock (12). The covariates were first examined separately in univariable models, then in different models including age, sex, comorbidities, preliminary focus of infection and vital signs with admission temperature as the main explanatory variables, and then the main model, which included treatment in the form of sepsis bundles. Finally, we added definite diagnoses, incorrect antibiotics, and treatment limitation orders at 48 hours, that is, information that was not available in the ED, but later during hospital stay. Area under the receiver operating characteristic (ROC) curve was used to assess the capacity of individual clinical signs (BT, blood pressure, pulse rate, saturation, respiratory rate, and Reaction Level Scale [RLS]) (13) to predict death.

ORs were also estimated in subgroups of participants classified according to age, sex, underlying comorbidity, and whether antibiotics were given within 1 hour. Homogeneity of estimates across subgroups was assessed using likelihood ratio tests.

Lactate levels were missing for around 30% of patients. Addition of lactate resulted in fewer complete cases and was therefore excluded from the main analyses. We performed a sensitivity analysis including lactate in the final fully adjusted model, and we also imputed missing values on lactate level and time to antibiotics using chained equations with 20 imputation sets; the imputation model is described in detail in **supplements** (Supplemental Digital Content 1, http://links.lww.com/CCM/C311) (14, 15). In some of the additional analyses, temperature was additionally modeled as a continuous predictor. Analyses were performed using STATA/SE version 13.1 (StataCorp, College Station, TX).

RESULTS

Cohort

Two thousand six hundred ten patients were recorded in the NQSR by February 2015. One hundred fifty-four were excluded: 112 patients lacked data on hospital survival, 17 were never treated in an ICU, 15 were less than 18 years old, five lacked fundamental data, three were taken to the ICU after 24 hours, one had no infection, and one was registered twice. Also, 231 were excluded from the main analyses since BT was not recorded—their data are presented for clarity (**Table 1**). This left 2,225 patients in the main analyses. Missing values are specified in Table 1 and varied from 3% to 15% for individual risk factors, up to 21% for the 1-hour sepsis bundle, which is a composite factor.

Patients were from 30 ICU's, whereof 750 in seven tertiary (university) hospitals and 1,475 patients in 23 secondary (county) hospitals. Fifty-six percent were male and median age was 68 (interquartile range [IQR], 57–77). In-hospital mortality was 24.7% and median length of stay (LOS) of survivors was 13 days (IQR, 7–23). Distribution of risk factors between survivors and nonsurvivors are presented in **Table S1** (Supplemental Digital Content 1, http://links.lww.com/CCM/C311).

Admission Temperature and Mortality

Fifty-five percent of patients had a BT less than 38.3°C (100.9°F) and 23% had less than 37°C (96.8°F). On average, crude in-hospital mortality decreased more than 5% points per increase of °C from less than 35°C (95.0°F) up to greater than 41°C (105.8°F) (**Fig. 1**). OR per °C increase was 0.76 (0.71–0.81; $p < 0.001$). Of clinical signs, BT had the highest area under the ROC curve: BT, 0.62; RLS, 0.56; respiratory rate,

TABLE 1. Distribution of Risk Factors by Temperature Strata

Characteristic	< 37°C (98.6°F)	37–38.29°C (98.6–100.92°F)	38.3–39.49°C (100.9–103.1°F)	≥ 39.5°C (103.1°F)	p[a]	Missing Temperature
No. of patients	507	673	684	361		231
Patient outcomes						
Mortality, %	36.3	25.3	20.3	15.5	< 0.001	31.6
Hospital length of stay, survivors, median (IQR)	17 (8–34)	13 (7–23)	11 (7–19)	11 (6–21)	0.0001	17 (9–26)
Demography						
Age, median (IQR)	68 (57–77)	68 (57–76)	69 (57–78)	67 (57–77)	0.17	69 (60–78)
Sex, % female	45.0	45.0	43.3	42.7	0.83	47.6
Underlying comorbidity, %						
Diabetes[b]	23.3	23.6	21. 1	23.0	0.68	21.6
Chronic liver failure[b]	3.9	3.3	2.6	1.1	0.09	3.9
Malignancy[b]	12.4	13.1	15.9	12.5	0.23	13.8
Congestive heart failure[b]	17.0	16.5	16.7	16.6	0.99	16.4
Immunosuppression[b]	10.7	13.4	15.6	12.7	0.09	14.7
Chronic obstructive pulmonary disease[b]	12.6	13.2	9.4	10.5	0.11	8.7
Chronic kidney failure[b]	10.5	9.2	6.6	7.5	0.08	7.4
Other disease[b]	51.5	48.7	53.8	52.9	0.29	55.4
Preliminary (and definite) focus of infection, %						
Pneumonia	32.9 (33.1)	42.9 (41.9)	36.7 (35.8)	32.1 (30.2)	< 0.001	28.1 (31.6))
Urinary tract	14.2 (15.2)	15.3 (16.6)	22.9 (26.3)	23.0 (25.2)	< 0.001	16.4 (17.3)
Abdominal infection	15.2 (14.4)	12.6 (11.4)	9.1 (8.8)	8.0 (9.4)	0.001	14.3 (15.1)
Other focus	16.6 (22.7)	15.4 (19.6)	16.8 (20.3)	21.0 (22.7)	0.14	18.6 (22.1)
Unknown focus or missing (1.2%)	21.1 (14.6)	13.7 (10.4)	14.5 (8.8)	15.8 (12.5)	0.003	22.5 (13.9) (missing 7.8%)
Etiology, % of patients						
Gram-positive	38.1	38.0	34.9	39.3	0.47	35.1
Gram-negative	26.2	31.6	36.5	34.1	0.002	32.9
Other	3.2	3.0	5.4	3.9	0.09	5.6
Unknown or missing (0.9%)	32.5	27.3	23.1	22.7	0.001	26.4
Vital parameters % of patients and lactate (missing values, %)						
Systolic blood pressure < 90 mm Hg	30.1 (1.2)	22.8 (1.0)	21.4 (1.0)	14.0 (1.4)	< 0.001	32.0 (14.7)
Respiratory rate > 20	66.3 (11.0)	80.0 (10.0)	82.4 (5.4)	88.8 (6.1)	< 0.001	72.2 (23.8)
Reaction Level Scale > 1 (disturbed mentation)	26.8 (18.9)	23.7 (14.3)	22.9 (13.3)	31.4 (10.8)	0.03	41.8 (42.0)
Pulse > 90 beats/min	60.1 (1.6)	76.1 (2.2)	82.9 (0.9)	89.6 (1.7)	< 0.001	68.0 (16.0)
Saturation < 90%	25.4 (4.5)	31.0 (2.2)	27.2 (2.2)	23.2 (0.6)	0.035	40.9 (18.6)
Lactate mmol/L, median (IQR)	4.0 (2.2–6.7) (35)	3.3 (1.9–5.3) (33)	3.4 (2–5.3) (29)	3.2 (2.2–5.4) (24)	0.003	4.6 (2.6–6.6) (39)

(Continued)

TABLE 1. *(Continued)*. Distribution of Risk Factors by Temperature Strata

Characteristic	< 37°C (98.6°F)	37–38.29°C (98.6–100.92°F)	38.3–39.49°C (100.9–103.1°F)	≥ 39.5°C (103.1°F)	*p*[a]	Missing Temperature
Quality of care % achieved (missing values, %)						
Time to antibiotics (median, IQR)	1 hr 44 min, 43 min to 3 hr 20 min (13)	1 hr 14 min, 35 min to 2 hr 35 min (10)	1 hr 0 min, 26 min to 2 hr 0 min (10)	49 min, 22 min to 1 hr 47 min (9)	0.0001	1 hr 27 min, 40 min to 3 hr 35 min (29)
AB within 1 hr	35 (13)	42 (10)	50 (9)	59 (9)	< 0.001	41 (29)
AB within 3 hr	70 (13)	80 (10)	87 (9)	87 (9)	< 0.001	73 (29)
BC before AB[c]	90 (11)	95 (9)	96 (9)	96 (8)	< 0.001	93 (27)
IV fluids within 1 hr[c]	81 (6)	77 (7)	84 (6)	87 (8)	0.008	78 (22)
Lactate or base excess in 1h measured	72	78	77	81	0.02	66
Lactate within 1 hr	65	67	71	76	0.003	61
Bundle 1 hr—optimal score[c]	25 (24)	32 (20)	39 (19)	43 (19)	< 0.001	33 (45)
Incorrect AB	7 (14)	8 (11)	8 (10)	7 (9)	0.84	10 (14)
Treatment limitations % of patients (missing values, %)						
At 48 hr	18 (5)	14 (5)	12 (5)	10 (5)	0.004	20 (10)

AB = antibiotic, BC = blood culture, IQR = interquartile range.

[a]For difference between temperature categories.

[b]Missing values were treated as negative for this variable.

[c]Years 2009–2015 (excluding 2007–2008).

Bundle 1 hr optimal score: percentage of patients for whom all the following have been achieved within 1 hr: BC (before AB) taken, lactate or base excess measured, 1 L IV fluids and AB administered.

0.55; heart rate, 0.54; saturation, 0.54; systolic blood pressure, 0.52 ($p < 0.0001$).

Table 1 shows outcome and risk factor distribution by BT strata. Mortality fell significantly with increasing temperature, as did LOS of survivors. Age, sex, and underlying comorbidities were equally distributed, but focus, etiology, and vital signs were not.

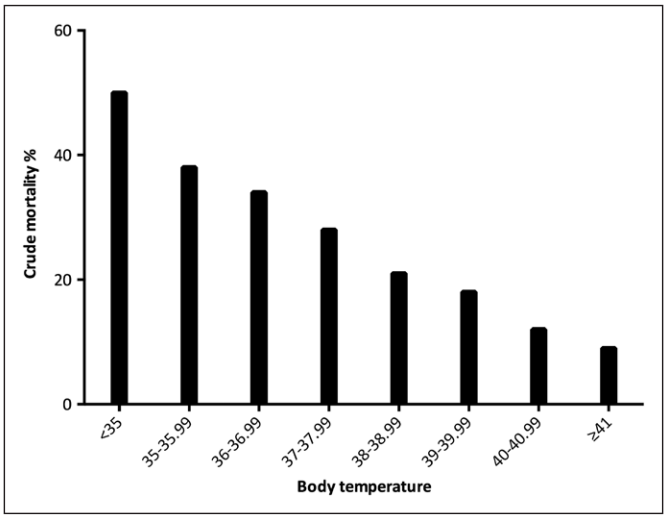


Figure 1. Temperature and crude mortality all patients, 35°C = 95°F, 36°C = 96.8°F, 37°C = 98.6°F, 38°C = 100.4°F, 39°C = 102.2°F, 40°C = 104°F, 41°C = 105.8°F.

Lactate was higher in those with a temperature below 37°C but did not differ in other strata. Quality of care as measured by optimal bundle achievement improved markedly with rising temperatures. Treatment limitations were almost twice as common in the lowest compared with the highest temperature category.

Table 2 (main model) and **Table S2** (Supplemental Digital Content 1, http://links.lww.com/CCM/C311) (alternative models) show the univariate ORs for individual risk factors and the ORs from multivariable analyses for in-hospital mortality comparing the different temperature strata. The association between BT and mortality was robust when adjusting for age, sex, underlying comorbidity, vital signs, preliminary focus of infection, and bundle achievement.

Subgroup Analyses

Figure 2 shows how the relationship between BT and survival remained unchanged whether stratified by age, lactate level, bacterial etiology, or bundle achievement. We observed no statistically significant differences in the ORs of in-hospital mortality by BT according to different subgroups of age ($p = 0.33$), sex ($p = 0.61$), underlying comorbidity ($p = 0.94$), full 1-hour bundle achievement ($p = 0.52$), or antibiotic administered within an hour ($p = 0.54$), in models adjusted for age, sex, underlying comorbidity, vital signs, and optimal bundle achievement, the stratum specific ORs are shown in **Table S3** (Supplemental Digital Content 1, http://links.lww.com/CCM/C311).

TABLE 2 Odds Ratios for Death According to Categories of Admission Temperature[a]

	Univariate Analysis ($n = 2,225$)			Multivariate Analysis[b] ($n = 1,282$)		
Characteristic	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***
Demography						
Age (per year increase)	**1.05**	**1.04–1.05**	**< 0.001**	**1.05**	**1.04–1.06**	**< 0.001**
Sex (female)	1.08	0.88–1.33	0.46	1.15	0.87–1.53	0.32
Body temperature			**< 0.0001**			**< 0.0001**
< 37	**1.69**	**1.31–2.17**		**2.08**	**1.39–3.11**	
37.0–38.29	**1.00**	**Reference**		**1.00**	**Reference**	
38.3–39.49	**0.75**	**0.59–0.96**		**0.71**	**0.53–0.96**	
≥ 39.5	**0.54**	**0.41–0.72**		**0.54**	**0.34–0.86**	
Underlying comorbidity						
Diabetes	1.17	0.89–1.53	0.25	1.18	0.81–1.73	0.39
Chronic liver failure	**2.45**	**1.66–3.61**	**< 0.001**	**3.29**	**1.64–6.60**	**0.001**
Malignancy	**1.75**	**1.29–2.36**	**< 0.001**	**1.46**	**1.00–2.12**	**0.05**
Congestive heart failure	**1.96**	**1.56–2.47**	**< 0.001**	**1.47**	**1.02–2.11**	**0.04**
Immunosuppression	1.12	0.88–1.44	0.35	1.05	0.58–1.92	0.86
Chronic obstructive pulmonary disease	1.15	0.91–1.45	0.24	**0.53**	**0.34–0.81**	**0.003**
Chronic kidney failure	**1.46**	**1.10–1.92**	**0.008**	1.34	0.91–1.97	0.14
Other disease	1.06	0.80–1.39	0.70	0.92	0.64–1.31	0.65
Preliminary diagnosis			**< 0.0001**			**0.001**
Pneumonia	**1.00**	**Reference**		**1.00**	**Reference**	
Urinary tract	**0.62**	**0.50–0.77**		**0.55**	**0.36–0.84**	
Abdominal	**1.55**	**1.07–1.94**		**1.14**	**0.73–1.78**	
Other focus	**0.92**	**0.70–1.21**		**1.16**	**0.73–1.87**	
Unknown focus	**1.79**	**1.45–2.21**		**1.55**	**1.00–2.41**	
Vital signs and lactate						
Systolic blood pressure < 90	1.10	0.90–1.34	0.37	1.03	0.79–1.34	0.81
Respiratory rate > 20	1.17	0.85–1.61	0.33	**1.95**	**1.15–3.29**	**0.01**
Saturation < 90	**1.50**	**1.24–1.82**	**< 0.001**	**1.36**	**1.09–1.70**	**0.006**
Pulse > 90	**0.76**	**0.61–0.94**	**0.01**	1.11	0.88–1.39	0.39
Reaction Level Scale > 1 (disturbed mentation)	**1.86**	**1.27–1.58**	**< 0.001**	**1.47**	**1.16–1.87**	**0.001**
Lactate (per 1 mmol/L increase)	**1.13**	**1.07–1.19**	**< 0.001**			
Quality of care						
Bundle1hr			0.58			0.14
B0[c]	0.84	0.33–2.13		1.80	0.71–4.79	
B1[c]	1.21	0.94–1.56		1.68	1.05–2.69	
B2[c]	1.14	0.85–1.53		1.33	0.90–1.94	
B3[c]	1.08	0.88–1.33		1.08	0.80–1.45	
B4[c]	1.00	Reference		1.00	Reference	

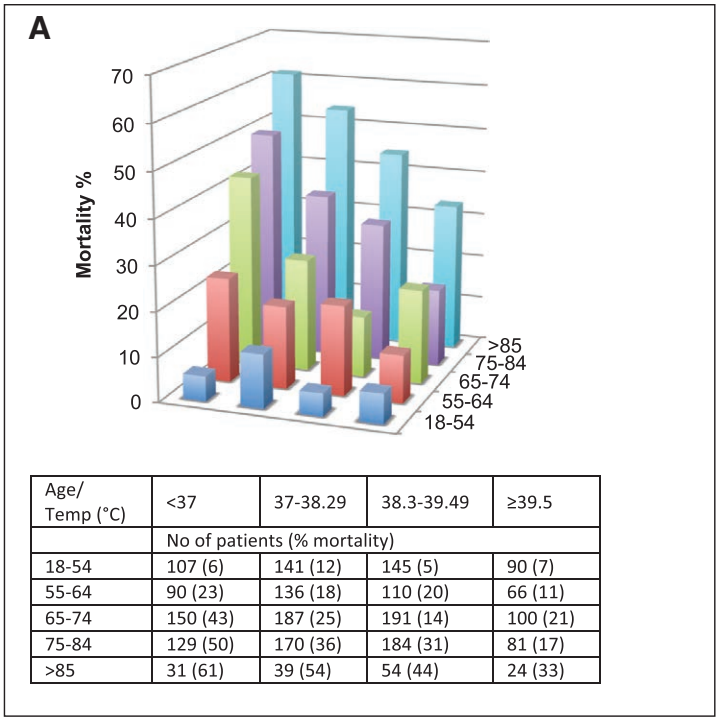
OR = odds ratio.

[a]Estimated by generalized estimating equation logistic regression.

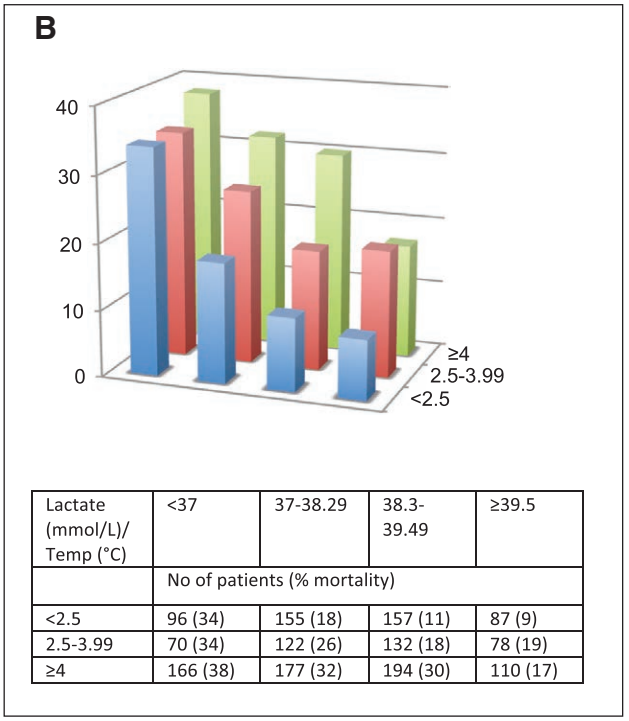
[b]Adjusted for all variables in the column.

[c]Number of sepsis bundle components achieved.

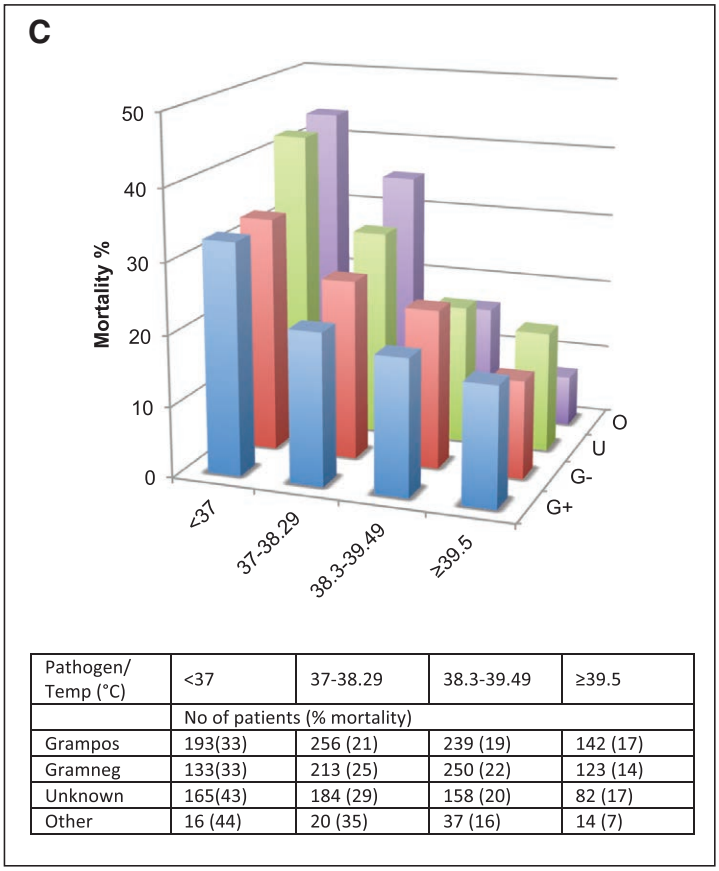
Bundle 1 hr optimal score: percentage of patients for whom all the following have been achieved within 1 hr: blood culture (before antibiotics) taken, lactate or base excess measured, 1 L IV fluids and antibiotics administered. Significant risk factors are listed in boldface font.



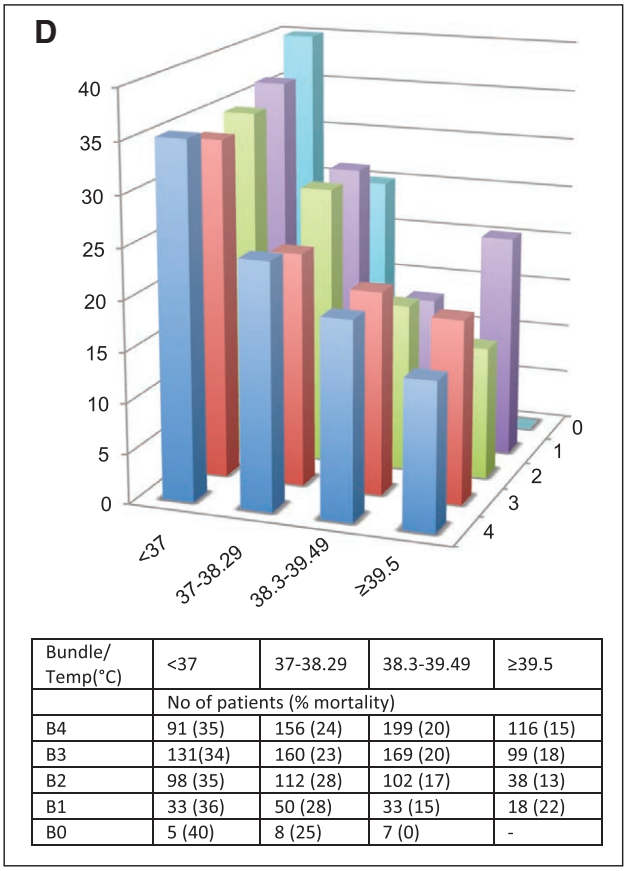
Age/ Temp (°C)	<37	37-38.29	38.3-39.49	≥39.5
	No of patients (% mortality)			
18-54	107 (6)	141 (12)	145 (5)	90 (7)
55-64	90 (23)	136 (18)	110 (20)	66 (11)
65-74	150 (43)	187 (25)	191 (14)	100 (21)
75-84	129 (50)	170 (36)	184 (31)	81 (17)
>85	31 (61)	39 (54)	54 (44)	24 (33)



Lactate (mmol/L)/ Temp (°C)	<37	37-38.29	38.3-39.49	≥39.5
	No of patients (% mortality)			
<2.5	96 (34)	155 (18)	157 (11)	87 (9)
2.5-3.99	70 (34)	122 (26)	132 (18)	78 (19)
≥4	166 (38)	177 (32)	194 (30)	110 (17)



Pathogen/ Temp (°C)	<37	37-38.29	38.3-39.49	≥39.5
	No of patients (% mortality)			
Grampos	193(33)	256 (21)	239 (19)	142 (17)
Gramneg	133(33)	213 (25)	250 (22)	123 (14)
Unknown	165(43)	184 (29)	158 (20)	82 (17)
Other	16 (44)	20 (35)	37 (16)	14 (7)



Bundle/ Temp(°C)	<37	37-38.29	38.3-39.49	≥39.5
	No of patients (% mortality)			
B4	91 (35)	156 (24)	199 (20)	116 (15)
B3	131(34)	160 (23)	169 (20)	99 (18)
B2	98 (35)	112 (28)	102 (17)	38 (13)
B1	33 (36)	50 (28)	33 (15)	18 (22)
B0	5 (40)	8 (25)	7 (0)	-

Figure 2. Temperature and mortality stratified by (**A**) age, (**B**) lactate levels, (**C**) microbiological etiology, and (**D**) sepsis bundle completion (B0–B4 signifies achieved bundle components).

Sensitivity Analyses

Sensitivity analyses, using a logistic regression model with ICU as fixed covariate (non-GEE), yielded results similar to the main GEE-analyses (results not shown). The effect of temperature on in-hospital mortality remained essentially unchanged, when assessed in models adjusting for the

additional factors not known in the ED: incorrect antibiotic, treatment limitations at 48 hours, and final diagnoses; OR per °C increase was 0.70 (0.63–0.81; $p = 0.001$). Mortality was slightly higher in patients with any missing variable (who were not included in the final model) than complete cases, 26.8% versus 23.2% ($p = 0.05$), but there was no difference in the crude temperature-mortality association between these subgroups, ORs per °C increase were 0.77 (0.70–0.85) versus 0.76 (0.69–0.83), respectively ($p = 0.51$).

In a sensitivity analysis, based on 956 subjects with complete information on all variables, adding lactate levels to the adjusted model did not confound the temperature-mortality association, the estimate changed 4%, ORs changed from 0.72 (0.64–0.82) to 0.75 (0.66–0.85).

Finally, we confirmed results by imputing missing values for lactate and time to antibiotics (**Table S4**, Supplemental Digital Content 1, http://links.lww.com/CCM/C311).

We found no difference in the temperature-mortality association between secondary and tertiary care hospitals, OR, 0.74 (0.65–0.86) and 0.68 (0.58–0.82), respectively ($p = 0.76$).

DISCUSSION

In this large national multicenter study, in patients with severe sepsis or septic shock, we found a strong and linear inverse association between increased BT and mortality. Among survivors, patients with lower admission temperature required longer LOS. To our knowledge, this is the first study to focus on the prognostic significance of fever upon ED arrival in patients subsequently admitted to the ICU.

Patients with higher temperature received more timely and better quality of care. In Sweden, the triage systems Medical Emergency Triage and Treatment System and Adaptive Process Triage are used in 65% and 19% of EDs (16). These award no extra priority for patients with temperatures 35–38.5°C (95–101.3°F) and 36–38°C (96.8–100.4°F), respectively—intervals in which 53% and 38% of patients in this study were found. Better care, however, did not explain the fever-mortality association which remained firm when tested in multivariate models adjusted for quality of care and a wide range of covariates concerning severity of illness, which could have confounded the association. The ORs were also stable across different subgroups according to age, sex, comorbidity, and whether antibiotics were given within an hour. Among all clinical signs, BT was the best predictor of survival in this group of patients.

It is well known that subnormal BT is a bad omen in critically ill septic patients (17–19), but that elevated temperature is a good sign is not a common perception, as evidenced by the concurrent rise of BT and quality of care and also by the routine practice of fever control in septic ICU patients (20, 21). In line with our findings, studies on bacteremic patients (22–25) have shown lower mortality in those with elevated BT compared with normal or low BT. One study on two ICU databases investigated the association between maximum recorded temperature over the first 24 hours in the ICU and mortality and found decreased mortality in infected patients with elevated BT (10) but, in agreement with other studies, increased mortality in noninfected patients (5, 26). Furthermore, the recently developed sepsis severity score prognosticates an increased risk of death for BT less than 36.0°C (96.8°F) and a decreased risk for BT greater than 38.3°C (100.9°F) (27). However, all these studies included diverse hospital populations, such as patients with postoperative infections, and BT was measured at varying time points or on multiple occasions, and no firm conclusions can be drawn concerning the relevance of arrival BT in critically ill ED patients. There are two studies, both single center, based on ED patients; the first investigated risk factors for death in patients with severe sepsis/septic shock and found an increased risk in those who lacked fever (> 38.0°C [100.4°F]) (28), but it included relatively few patients, impeding detailed analysis. The second focused on patients with suspected bacterial infection and found a decreased risk of death in temperature intervals exceeding 36°C compared with patients below that threshold (29), but it adjusted for few confounders. Also, in this study, as in almost all studies on BT, no adjustment was made for differences in quality of care why it cannot be ruled out that the reported decreased risks were attributable to better care of patients with higher BT. Nevertheless, despite limitations, the current literature supports our findings of fever being an important, hitherto underrecognized, survival factor.

It is currently unclear if fever-reducing therapy is beneficial or harmful in critically ill patients. In a recent study, 700 intensive care patients with probable infection were randomized to acetaminophen (paracetamol) IV or placebo and no differences were found in ICU-free days or mortality (30). Other studies have used external cooling (31, 32) or ibuprofen (33, 34). No study has conclusively shown a difference in ICU mortality with or without temperature regulation.

Our study has a number of strengths. First, the study is based on a large, multicenter register comprising patients from all parts of Sweden. Second, multiple experienced investigators collected data as part of quality control, why biased recording of parameters is unlikely. Third, we adjusted models for a wide range of potential confounders. Fourth, the robustness of our results is further supported by the fact that the association remained stable in all models and by the similarity of results achieved in sensitivity analyses based on imputed values.

BT was measured during variable circumstances—during stressful triaging, by different measurers using different thermometers—making measurement errors likely. Random measurement errors would, however, dilute the association; therefore, our findings are remarkably robust. The registry mirrors routine care; as a result, there was a large proportion of missing values and only 58% of patients had complete information on all variables and could be included in the final fully adjusted analyses. However, there was no difference in the crude temperature-mortality association across the subgroups of patients with no missing values versus patients with any missing values.

Nine percent of patients did not have their BT registered. Their mortality rate was in the range of patients with low temperatures. Missing values were more prevalent in patients without fever, in line with lower quality of care in that group. We therefore believe that those with no registered BT had lower temperatures,

suggesting that the true temperature-mortality association is even stronger than here reported.

Other weaknesses of the study include the lack of severity scores such as Sequential Organ Failure Assessment or Acute Physiology and Chronic Health Evaluation (not recorded in the NQSR), which would have allowed more precise adjustment for disease severity than vital parameters and comorbidity. Information concerning the use of antipyretics or immunomodifying drugs prior to measurement of temperature is lacking, why residual confounding cannot be ruled out. And although analyses were adjusted for quality of care, it is possible that the temperature-mortality association was related to other differences in treatment not captured in the database. Furthermore, the NQSR does not capture all eligible patients in Sweden, since it only comprises hospitals where infectious disease physicians are present and registration rates vary between centers (35). However, we found no difference in the temperature-mortality association between secondary and tertiary care hospitals. We therefore believe that our results are valid and generalizable to many settings.

CONCLUSIONS

Contrary to common perceptions and triage guidelines, this study shows a strong inverse association between BT at ED admission and mortality and LOS in septic patients admitted to the ICU. Quality of care, including prompter antibiotic treatment, improved with rising BT, but this did not explain lower mortality. Among vital signs, temperature was the best predictor of death. It is essential that healthcare personnel learn to recognize signs of severe sepsis in the absence of fever, and that patients with normal or subnormal temperatures, once recognized, should be given highest priority.

ACKNOWLEDGMENTS

We want to express our deep gratitude to dedicated colleagues throughout Sweden who painstakingly keep the quality register up to date.

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