

Epidemiology and Outcomes of Fever Burden Among Patients With Acute Ischemic Stroke

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Background and Purpose—Although fever following ischemic stroke is common and has been associated with poor patient outcomes, little is known about which aspects of fever (eg, frequency, severity, or duration) are most associated with outcomes.

Methods—We used data from a retrospective cohort of acute ischemic stroke patients who were admitted to 1 of 5 hospitals (1998–2003). A fever event was defined as a period with a temperature $\geq 100.0^{\circ}\text{F}$ (37.8°C). Fever burden was defined as the maximum temperature (T_{max}) minus 100.0°F , multiplied by the number of days with a fever. Fever burden (in degree-days) was categorized as low (0.1–2.0), medium (2.1–4.0), or high (≥ 4.0). Logistic regression was used to evaluate the adjusted association of any fever episode and fever burden with the combined outcome of in-hospital mortality or discharge to hospice.

Results—Among 1361 stroke patients, 483 patients (35.5%) had ≥ 1 fever event. Among febrile patients, the median T_{max} was 100.9°F (range, 100.0 – 106.6°F), 87% had ≤ 2 events and median total fever days was 2. Patients with any fever event had higher combined outcome rates after adjusting for demographics, stroke severity, and clinical characteristics: adjusted odds ratio (aOR), 2.7 (95% CI, 1.6–4.4). Higher fever burden was also associated with the combined outcome: high burden aOR, 6.7 (95% CI, 3.6–12.7); medium burden aOR, 3.9 (95% CI, 1.9–8.2); and low burden aOR, 1.2 (95% CI, 0.6–2.3) versus no fever.

Conclusions—This study confirms that poststroke fever occurs commonly and demonstrates that patients with high fever burden have a 6-fold increased odds of death or discharge to hospice. (*Stroke*. 2011;42:3357–3362.)

Key Words: fever ■ epidemiology ■ outcomes ■ mortality

Fever occurs in approximately one third of patients with acute ischemic stroke^{1,2} and has been associated with poor outcomes following stroke,^{1,3–6} including increased mortality and disability, and longer hospital and intensive care unit stays.⁷ In addition, fever has been found to be an independent risk factor for developing in-hospital stroke.⁸ Previous studies have identified an infectious cause in 40% to 80% of poststroke patients with fever^{3,7,9}; the rest are of unknown etiology, and some are presumed to have a central cause.^{2,10}

Despite the evidence of poor poststroke outcomes with fever, little is known about the epidemiology of fever after stroke, or to what extent the severity of fever affects outcomes. Patterns of fever poststroke have not been described in terms of degree of temperature elevation, duration, and timing and frequency after stroke onset. The studies that have evaluated the association between temperature and poststroke outcomes^{1–6} have not taken into account other aspects of

fever, including the duration or number of fever events. It is unknown whether low-grade elevations of temperature for multiple days have similar deleterious effects on outcomes after stroke as do high temperature for a few days.

Fever burden, a calculation measuring the combined effect of temperature and duration of fever, has been examined in a study of subarachnoid hemorrhage,¹¹ but has not, to our knowledge, been studied in ischemic stroke. Our objectives were to: describe the pattern of poststroke fever among patients hospitalized with acute ischemic stroke and examine the association between number of fever events and fever burden with stroke outcomes.

Methods

Patients and Setting

Data from the Quality Evaluation in Stroke and transient ischemic attack (QUEST) study were used in these analyses.¹² Briefly, this

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retrospective cohort included consecutive patients who were admitted to any of 3 Department of Veterans Affairs (VA) or 2 non-VA hospitals with a stroke or transient ischemic attack between the years 1998 to 2003. A medical record review was conducted by trained abstractors.

Patients were included in the current project if they had an acute ischemic stroke, neurological symptom onset within 2 days of admission, a neurological deficit on admission (National Institute of Health Stroke Scale ≥ 2), and were age ≥ 18 years. Patients were excluded if they had a transient ischemic attack, were residing in a nursing home or extended care facility at the time of stroke symptom onset, were already admitted to the hospital at the time of stroke symptom onset, were transferred from another acute-care facility, or were not admitted to the hospital. This project received human subjects approval.

Definitions

Because there is no accepted standard definition of fever,^{3,13,14} it was defined for this study based on a comprehensive review of studies of body temperature, as any temperature measurement $\geq 100.0^{\circ}\text{F}$ (37.8°C). A fever event was defined as a period with a body temperature $\geq 100.0^{\circ}\text{F}$, where the event ended when the temperature fell below 100.0°F for ≥ 24 hours. Fever burden was defined as the maximum temperature measured during hospitalization (T_{max}) minus 100.0°F , multiplied by the number of days with a temperature $\geq 100.0^{\circ}\text{F}$.¹¹ For example, 2 days of fever with a T_{max} of 102°F would give a fever burden of 4 degree-days ($[102^{\circ}\text{F} - 100^{\circ}\text{F}] \times 2 \text{ days} = 4 \text{ degree-days}$). Fever burden (in degree-days) was categorized as low (0.1–2.0), medium (2.1–4.0), or high (>4.0). Therefore, patients who had many days with fever at a low T_{max} (eg, 4 days at T_{max} of $101^{\circ}\text{F} = 4 \text{ degree-days}$) would have the equivalent fever burden as patients with shorter periods at a high T_{max} (eg, 1 day at $104^{\circ}\text{F} = 4 \text{ degree-days}$).

The mechanism by which temperature was measured varied between and within sites. Hospital staff members were interviewed for practices of temperature measurement in their hospitals; although a variety of instruments were used, the majority of patients had their temperature taken via the tympanic route. Data were not collected on the route of temperature measurement because this was rarely documented.

Outcome

The primary outcome was the combined end point of in-hospital mortality or discharge to hospice. We selected this combined end point because it represents clinically important events that are generally considered the poorest outcomes after stroke, and is reliably obtained from medical records. Discharge disposition was determined from the medical record. Patients discharged either to home hospice or to inpatient hospice were classified as discharged to hospice.

Patient and Clinical Variables for Risk Adjustment

The variables considered for risk adjustment were based on a priori clinical judgment and the existing literature and included: age, race, comorbidity based on past medical history (Charlson comorbidity score),¹⁵ preadmission symptom course (worsening preadmission course versus other descriptions of the symptom course), prestroke functional status (independent or no record compared with dependent in any activity of daily living), admission code status (do not resuscitate, do not intubate, or comfort measures only compared with full code), baseline stroke severity (retrospective National Institutes of Health Stroke Scale),¹⁶ stroke subtype (classified as atherothrombotic, cardioembolic, lacunar, other, unclassified), edema on brain imaging, hypoxia on admission (oxygen saturation $<90\%$ or $\text{PaO}_2 < 60 \text{ mm Hg}$), pneumonia on admission chest radiograph, pressure ulcer on admission, antipyretics on admission and during hospitalization (including aspirin, acetaminophen, nonsteroidal anti-inflammatory medications, steroids), modified Acute Physiology,

Age, Chronic Health Evaluation (APACHE III) score,¹⁷ and length of hospital stay.

Analytic Plan

Descriptive statistics (eg, mean with standard deviation, median, range for dimensional data, and proportions for dichotomous data) were used to describe patterns of fever, independent variables, and outcome rate.

To identify variables that were associated with fever occurrence, the baseline characteristics of patients with any versus no episode of fever were compared using χ^2 for categorical variables and t-tests for continuous variables. To identify variables associated with the combined outcome, the same analysis was repeated for each baseline characteristic. Variables that were significant ($P < 0.05$) in either bivariate analyses were included in 2 logistic regression models with backward elimination to assess the association of any fever and fever burden with the combined outcome. An event-per-variable ratio of $\geq 10:1$ was maintained for all multivariate models.

Some exploratory analyses were conducted focusing on: the timing of fever (occurring <72 hours of admission versus >72 hours), the etiology of fever using available data on infectious sources (including urine/blood/sputum/stool cultures; chest x-rays; and diagnoses of pneumonia, urinary tract infection, and septicemia), the antipyretic treatment of fever, and the association of T_{max} with the combined outcome.

Results

Among 1363 acute ischemic stroke patients in the QUEST cohort, 2 patients were excluded because of missing temperature data. Among the 1361 patients in this analysis, 483 patients (35.5%) had any episode of fever during their hospital stay. Eighty-seven patients (6.4%) died in hospital and 53 patients (3.9%) were discharged to hospice; therefore, a total of 140 patients (10.3%) had the combined outcome (Table 1). The demographics and clinical characteristics of the cohort are presented in Table 1. The distribution of maximum temperatures of the entire cohort during the hospitalization was as follows: 64.5% had a $T_{\text{max}} < 100.0^{\circ}\text{F}$, 20.8% had a T_{max} of 100.0 to 101.0°F , 9.3% had a T_{max} of 101.1 to 102.0°F , and 5.4% had a $T_{\text{max}} > 102.0^{\circ}\text{F}$. Among the total cohort, 131 patients (9.6%) had a high fever burden, 81 patients (5.9%) had a medium burden, 271 patients (19.9%) had a low burden, and 878 patients (64.5%) had no fever during hospitalization.

Among the 483 patients with any fever event, the mean T_{max} was 101.1°F (SD, 1.1°F ; median, 100.9°F ; range, 100.0 – 106.6°F ; Table 2). The mean total number of days with fever was 2.9 (SD, 2.9; median, 2 days). Eighty-seven percent of patients had ≤ 2 fever episodes. Twelve percent of patients with fever had it documented within 24 hours of admission, and 58% of fever events occurred within 72 hours of admission. The average fever burden was 3.9 degree-days (SD, 6.2; median, 1.6; range, 0.1–49). The patient with a fever burden of 49 had a fever episode lasting 14 days that had a T_{max} of 103.5 .

Among patients with any fever, 103/483 patients (21.3%) died or were discharged to hospice compared with 37/878 patients (4.2%) without fever ($P < 0.0001$). The combined outcome was more common with increasing fever burden; 4.2%, no fever; 9.2%, low; 24.7%, medium; and 44.3% with high burden ($P < 0.0001$ for trend; Figure).

The factors that were independently associated with the combined outcome included stroke severity, symptom course,

Table 1. Cohort Demographics and Clinical Characteristics

Characteristics	Total	Fever Episode	No Fever Episode	<i>P</i>
No. of patients (%)	1361	483 (35.5)	878 (64.5)	
Age, y, mean±SD	71.4±13.2	73.8±13.6	70.1±12.8	0.09
Female, n (%)	578 (42.5)	228 (47.2)	350 (39.9)	0.009
Race				0.07
White, n (%)	1069 (78.6)	396 (82.0)	673 (76.7)	
Black, n (%)	206 (15.1)	64 (13.3)	142 (16.2)	
Hispanic, n (%)	42 (3.1)	15 (3.1)	27 (3.1)	
Other/unknown, n (%)	44 (3.2)	8 (1.7)	36 (4.1)	
In-hospital mortality	87 (6.4)	66 (13.7)	21 (2.4)	<0.0001
Length of hospital stay, d, mean±SD*	6.6±7.0	9.3±9.7	5.1±4.4	<0.0001
Discharge to hospice, n (%)	53 (3.9)	37 (7.7)	16 (1.8)	<0.0001
Combined mortality or hospice, n (%)	140 (10.3)	103 (21.3)	37 (4.2)	<0.0001
Baseline NIHSS, mean±SD	9.4±7.3	13.2±8.6	7.3±5.4	<0.0001
Baseline NIHSS score				<0.0001
0–9, n (%)	884 (65.0)	203 (42.0)	681 (77.6)	
10–19, n (%)	342 (25.1)	175 (36.2)	167 (19.0)	
20+, n (%)	135 (9.9)	105 (21.8)	30 (3.4)	
Charlson comorbidity index				0.54
1, n (%)	457 (33.6)	163 (33.8)	294 (33.5)	
2, n (%)	318 (23.4)	105 (21.7)	213 (24.3)	
≥3, n (%)	586 (43.1)	215 (44.5)	371 (42.3)	
Stroke subtype				<0.0001
Atherothrombotic, n (%)	289 (21.5)	136 (28.2)	153 (17.5)	
Cardioembolic, n (%)	217 (16.0)	102 (21.1)	115 (13.1)	
Lacunar, n (%)	231 (17.0)	45 (9.3)	186 (21.2)	
Other, n (%)	20 (1.5)	5 (1.0)	15 (1.7)	
Unclassified	603 (44.3)	195 (40.4)	408 (46.5)	
Pre-admission symptom				<0.0001
Course				
Stable, n (%)	465 (34.7)	187 (39.4)	278 (32.1)	
Improving, n (%)	392 (29.2)	95 (20.0)	297 (34.3)	
Worsening, n (%)	266 (19.8)	122 (25.7)	144 (16.6)	
Fluctuating, n (%)	218 (16.3)	71 (14.9)	147 (17.0)	
History of hypertension, n (%)	982 (72.2)	345 (71.4)	637 (72.6)	0.66
History of atrial fibrillation, n (%)	258 (19.0)	119 (24.6)	139 (15.8)	<0.0001
Independent in activities of daily living, n (%)	1084 (88.2)	358 (85.2)	726 (89.7)	0.02
DNR order at admission, n (%)	122 (9.0)	66 (13.7)	56 (6.4)	<0.0001
Edema on admission head CT, n (%)	118 (8.7)	58 (12.0)	60 (6.8)	0.001
Hypoxia on admission, n (%)	52 (3.8)	34 (7.0)	18 (2.0)	<0.0001
Skin lesion on admission†, n (%)	98 (7.2)	51 (10.6)	47 (5.4)	0.0004
Antipyretics on admission, n (%)	751 (55.2)	248 (51.4)	503 (57.3)	0.03
Antipyretics during hospitalization, n (%)	603 (44.3)	285 (59.0)	318 (36.2)	<0.0001
Pneumonia on admission chest X-ray, n (%)	86 (6.3)	46 (9.5)	40 (4.6)	0.0003
Modified APACHE III score, mean±SD	19.7±10.5	22.7±12.3	18.0±9.0	<0.0001

SD indicates standard deviation; NIHSS, National Institutes of Health Stroke Scale; DNR, do not resuscitate; APACHE, acute physiology, age, chronic health evaluation.

*N=1345.

†Includes pressure ulcer or open skin wound.

Table 2. Characteristics of Fevers

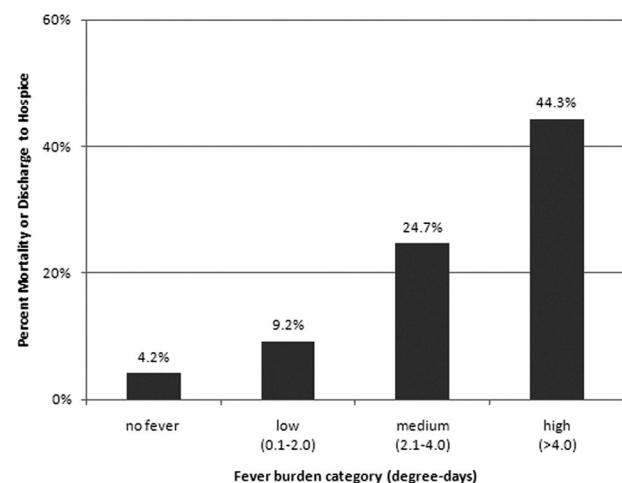
Characteristics	Mean±SD	Median (Range)	N	%
Maximum temperature, °F	101.1±1.1	100.9 (100–106.6)		
Length of fever, d	2.9±2.9	2 (1–23)		
Fever burden (degree-days)	3.9±6.2	1.6 (0.1–49)		
No. of fever events, total			483	100
1			314	65.0
2			108	22.4
3			35	7.2
4			13	2.7
5+			13	2.7
Timing of fever events*				
<24 h			59	12.2
<48 h			150	31.0
<72 h			282	58.4
<7 d			430	89.0

SD indicates standard deviation.

*In timing of fever events, numbers and percentages are cumulative.

admission code status, length of stay, and hypoxia on admission. After adjusting for these variables, any fever event was associated with the combined outcome (adjusted odds ratio [aOR], 2.7 (95% CI, 1.6–4.4). Fever burden was also associated with the combined outcome: low: aOR, 1.2 (95% CI, 0.6–2.3); medium: aOR, 3.9 (95% CI, 1.9–8.2); and high: aOR, 6.7 (95% CI, 3.6–12.7). The number of fever events during admission for stroke was not significantly associated with the combined outcome (Table 3).

Exploratory analyses results included the following: the combined outcome rate did not differ statistically among patients with early (<72 hours) versus late (>72 hours) initial fever (20.0% versus 24.2%; $P=0.30$). Including fever timing in the logistic regression as an interaction did not change the results. In terms of fever etiology, using the available data for infectious etiology (because not all fevers had an infectious work-up), 66.3% of patients with fever and 30.0% of patients without a fever event had evidence of an infection. Among those with fever, the combined outcome

**Figure.** In-hospital mortality or discharge to hospice and fever burden.**Table 3. Death or Hospice by Fever Episode, Number of Fever Episodes, Fever Burden, and Significant Covariates**

Characteristics	Adjusted OR	CI
Any fever episode	2.7	1.6–4.4
Fever burden		
None	ref	
Low	1.2	0.6–2.3
Medium	3.9	1.9–8.2
High	6.7	3.6–12.7
No. of fever episodes		
1	ref	
2	1.2	0.7–2.2
3	1.4	0.5–3.4
4	0.9	0.2–4.2
5	1.2	0.3–4.8
Age, y		
<65	ref	
65–74	0.9	0.4–1.9
75–80	1.1	0.5–2.2
>80	2.4	1.2–4.6
Baseline NIHSS score	1.1	1.1–1.2
Worsening course on admission	2.1	1.3–3.4
Admission DNR order	2.2	1.2–4.0
Hypoxia on admission	2.6	1.1–5.9
Length of stay, d	0.95	0.92–0.99

OR indicates odds ratio; CI, confidence interval; NIHSS, National Institutes of Health Scale Score; DNR, do not resuscitate.

was more frequent among patients with evidence of an infection (26.6% versus 11.0%; $P<0.0001$), but when included as an interaction term in the logistic regression, evidence of infection was nonsignificant ($P=0.11$) and did not change overall results. When examining antipyretic treatment of fever, the combined outcome was not significantly different among those receiving antipyretics ($n=332$) and those not receiving ($n=151$) antipyretics (25.0% versus 13.3%; $P=0.10$). When included in the logistic model, antipyretic treatment was not significant ($P=0.49$). In addition, compared with T_{max} alone, the calculated fever burden fit the data better (c-statistic, 0.90 versus 0.85).

Discussion

These data demonstrate that the burden of a poststroke fever event differentially influences outcomes; in addition, this study confirms that fever occurs commonly poststroke and is associated with poor patient outcomes. Patients with a high fever burden, whether that is high fever for a brief period or low-grade fever for an extended period, have at least 6-fold increased odds of death or discharge to hospice, whereas low-grade fevers for short periods of time do not seem to be associated with the combined outcome.

An increase in the number of fever events alone did not account for the increase in the odds of worse outcome without an increase in the fever burden. Some studies have demonstrated that every 1°C increase in poststroke admission

temperature is associated with an increase in relative risk of approximately 2 for mortality and disability,^{1,2} but these previous studies did not examine the cumulative effect of fever over a period of time on outcomes. The results of our study indicate that both the duration of fever and the degree of temperature elevation are key factors influencing post-stroke outcomes.

The majority of previous studies examining the effect of poststroke fever have been relatively small, and most were conducted at a single site. Saini et al published a study of 5305 patients,¹⁸ but the data were gathered from several randomized controlled trials and, therefore, may not be representative of the general stroke population. Our study included a relatively large cohort from routine clinical care, and included patients from 5 hospitals that vary in geographic location, stroke care providers, and settings (VA and non-VA), thereby enhancing generalizability.

In general, most of the previous studies on this topic focused on the presence of fever early after hospital admission (<72 hours or <24 hours or at admission)^{4,19}; however, 2 studies^{5,18} examined the occurrence of fever up to 7 days poststroke. Theoretically, elevated temperature is more likely to influence neurological outcomes early after brain ischemia. We were interested in the cumulative effect of fever on the poststroke patient; therefore, we evaluated all episodes of fever during the stroke hospitalization. We found that the majority (58%) of fever episodes occurred within 72 hours of admission, and an exploratory comparison of outcomes among patients with early versus late fever identified no statistically significant differences between the 2 groups.

Although we were interested in the association of fever and outcomes independent of fever etiology, it is possible that fever was a marker of significant infection, which could be a confounder of our results.⁹ Because this study used observational data from real clinical settings, the clinical work-up for infections was not uniformly performed, although in most cases a fever did lead to testing; a secondary analysis using available data on infectious sources did not change the results. Elevated white blood cell count also was not independently associated with adverse outcomes in this cohort, a finding consistent with results from some previous studies^{1,3}; however, elevated white blood cell count has been associated with ischemic stroke mortality in the intensive care unit.⁷

We recognize the following limitations of this study. First, we did not record the total number of temperature measurements per patient, and therefore there may have been a wide variation in these totals. Patients with significant fever, or even just 1 elevated temperature reading, may have had more measurements, possibly making their temperature data more complete and possibly missing higher temperatures in patients receiving fewer readings. Also, given this variation in number of readings, fever duration was estimated in days (as opposed to hours), which might obscure smaller variations in fever burden. Second, although the body temperature in the majority of patients was measured by tympanic membrane, some patients may have had measurements taken by oral or rectal routes. Documentation on the route of temperature measurement in this retrospective cohort was poor; a prospective study would be able to designate a standardized temper-

ature measurement. Third, as described above, we do not have complete data on the etiology of fever events. Last, our method of calculating fever burden may overestimate the true fever burden. Alternative approaches include using the mean or median temperature of the fever episode times the duration, but using these definitions are likely to underestimate the severe aspects of elevated temperature. In addition, if fever burden were used practically to assist in prognosis, mean or median temperature would likely be more difficult to obtain for clinicians than would the maximum temperature.

In summary, the occurrence of fever is associated with poor outcomes after ischemic stroke, but primarily among patients with moderate and high fever burden. Therefore, even low-grade fevers that last for more than a couple of days seem to be detrimental to ischemic stroke patients. Clinicians should consider measuring and monitoring fever burden in poststroke patients. Current recommendations are to treat fever presumptively with antipyretics,²⁰ but there is no evidence as of yet that antipyretics are effective in improving outcomes.²¹ It may also be clinically prudent to seek a fever etiology. Future research should examine the potential benefit of antipyretics or cooling strategies among high-risk stroke patients.

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Disclosures

None.

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