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# Effect of Hyperthermia on Prognosis After Acute Ischemic Stroke

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*Background and Purpose*—Experimental studies have shown that hyperthermia is a determinant of poor outcome after ischemic stroke. Clinical studies evaluating the effect of temperature on poststroke outcome have, however, been limited by small sample sizes. We sought to evaluate the effect of temperature and timing of hyperthermia on outcome after ischemic stroke.

*Methods*—Data of 5305 patients in acute stroke trials from the Virtual International Stroke Trials Archive (VISTA) data set were analyzed. Data for temperatures at baseline, eighth, 24th, 48th, and 72nd hours, and seventh day were assessed in relation to outcome (poor versus good) based on the modified Rankin Scale at 3 months. Hyperthermia was defined as temperature $>37.2°C$ and poor outcome as 90-day modified Rankin Scale $>2$. Hazard ratios with 95% CIs were reported for hyperthermia in relation to the outcome. Logistic regression models, in relation to hyperthermia, were fitted for a set of preselected covariates at different time points to identify predictors/determinants of hyperthermia.

*Results*—The average age of patients was $68.0±11.9$ years, 2380 (44.9%) were females, and 42.3% (2233) received thrombolysis using recombinant tissue plasminogen activator. After adjustment, hyperthermia was a statistically significant predictor of poor outcome. The hazard ratios (95% CI) for poor outcome in relation to hyperthermia at different time points were: baseline 1.2 (1.0 to 1.4), eighth hour 1.7 (1.2 to 2.2), 24th hour 1.5 (1.2 to 1.9), 48th hour 2.0 (1.5 to 2.6), 72nd hour 2.2 (1.7 to 2.9), and seventh day 2.7 (2.0 to 3.8). Gender, stroke severity (National Institutes of Health Stroke Scale score $>16$), white blood cell count, and antibiotic use were significantly associated with hyperthermia ($P≤0.01$).

*Conclusions*—Hyperthermia, in acute ischemic stroke, is associated with a poor clinical outcome. The later the hyperthermia occurs within the first week, the worse the prognosis. Severity of stroke and inflammation are important determinants of hyperthermia after ischemic stroke. In patients with acute ischemic stroke, aggressive measures to prevent and treat hyperthermia could improve the clinical outcomes. (*Stroke*. 2009;40:3051-3059.)

**Key Words:** acute stroke ■ hyperthermia ■ ischemic ■ clinical outcome

Stroke remains one of the leading causes of mortality and morbidity worldwide. Poststroke disability and handicap have a significant physical and economic impact.[1,2] Recombinant tissue plasminogen activator (rtPA) remains the only agent that has proven clinical efficacy in improving outcomes after ischemic stroke; however, only 5% of patients receive rtPA due to various reasons.[3] Attempts to find neuroprotective agents that may reduce ischemic brain damage have been unrewarding to date.[4] Identification of potentially modifiable factors that determine recovery and functional outcomes after stroke are thus essential for minimization of poststroke deficits.

Several factors determine the outcome and extent of recovery after ischemic stroke. Data from preclinical studies provided a link between hyperthermia and stroke outcomes,

and robust experimental evidence for detrimental effects of hyperthermia on ischemic brain injury is available.[5–7] Fever (temperature $>38°C$) has been included as an independent prognostic marker in validated prognostic models for prediction of mortality and functional outcome after an acute ischemic stroke.[8,9] A recent meta-analysis suggested that pyrexia after stroke was significantly associated with mortality and morbidity. This analysis included patients with both ischemic and hemorrhagic stroke.[10] A few clinical studies have evaluated body temperature in relation to type, location, severity, and mechanism of stroke.[11–13] The Copenhagen Stroke Study group showed that body temperature was an independent predictor of good functional outcome after stroke; a 1°C decrease in temperature corresponded to almost doubling (OR, 1.8) the chance of a good outcome.[11] Simi-

larly, Reith et al showed that the relative risk of poor outcome increased by 2.2 times for each 1°C increase in body temperature.[12] Although the relation of timing of hyperthermia in relation to stroke outcome has been evaluated previously, the relation is not clear.[13]

Previous studies evaluating the effect of temperature have been limited by small numbers of patients and have used temperatures recorded at diverse times from stroke onset. Also, a range of definitions of hyperthermia was used in the studies included in the analysis, which may have a bearing on the results. We sought to determine the effect of temperature, in relation to time, on outcome after ischemic stroke using data from the Virtual International Stroke Trials Archive (VISTA).

## Methods

Data were obtained for patients with acute ischemic stroke from the VISTA database. Details of the VISTA collaboration have been previously published; the database includes data from trials that had documented entry criteria and monitoring processes for validation of data.[14] VISTA holds data from 28 trials involving more than 28 000 patients, aged between 18 and 103 years, who experienced an index acute stroke due to either ischemia or intracerebral hemorrhage. Data have been collected prospectively and include demographic characteristics, baseline neurological assessment, and 90-day Barthel Index modified Rankin Scale (mRS), and National Institutes of Health Stroke Scale (NIHSS).

VISTA regulations preclude the identification of trial source(s); however, for the purpose of our analysis, data were extracted for patients with ischemic stroke with records of body temperatures at various time intervals after the index event. The diagnosis of ischemic stroke was confirmed by imaging (CT/MRI) in all patients. Demographic details and medical history, including diabetes, hypertension, prior stroke, myocardial infarction (MI), and baseline stroke severity, as determined by NIHSS, have been recorded for all patients.

### Temperature Measurement

In most patients, the method of temperature measurement was an axillary recording. It was assumed that normal diurnal variation of body temperature is ≤1°C. Data from a recent review, on normal body temperature in adults, were used for defining hyperthermia.[15] Hyperthermia was defined as temperature >37.2°C.

Values for body temperature at baseline and thereafter at 8, 24, 48, 72 hours and 7 days were extracted from the database. For determining the effect of temperature on the outcome, temperature was dichotomized to normothermia (≤37.2°C) versus hyperthermia (>37.2°C). To further analyze the effect of temperature on outcomes, temperature differences were calculated at various time points with reference to the baseline temperature. Body temperature was further categorized as quartiles (<36.4, 36.4 to <36.78, 36.78 to <37.1, and ≥37.1°C). The highest quartile (37.1+°C) was taken as the reference.

### *Stroke Topography and Severity*

The side of hemispheric involvement (right versus left) was recorded for patients based on imaging (CT/MRI). Stroke severity was determined using the NIHSS at baseline and at 24 hours. Stroke was classified as severe (NIHSS >16) and mild to moderate (NIHSS <16). To further analyze the relation of stroke severity and hyperthermia at various time points, the 24-hour NIHSS was categorized into 3 groups: 0 to 10, 10 to 20, and >20. Lesion volume was measured on CT/MRI between 24 hours and 7 days of onset of ictus.

### *Inflammation and Infection*

White blood cell (WBC) and platelet count were used as markers of inflammation. These were classified as normal (WBC <11 000/mm³ and platelet <230/mm³) and abnormal (WBC >11 000/mm³ and

platelet >230/mm³). The use of antibiotics was considered as a surrogate marker for infection.

### Clinical Outcome Measurement

The long-term clinical outcome was measured at 3 months (90 days) using mRS. Functional outcome was dichotomized, poor versus good, based on the mRS at 3 months. Poor outcome was defined as mRS >2. Poststroke mortality up to 90 days was measured. For patients who died during this time period, the mRS was defined as 6 for the analysis.

### Statistical Analysis

Demographic statistics (number of patients, mean, SD, median, and interquartile range) of the study patients with an acute ischemic stroke were summarized. Univariate analyses for demographic variables (age and gender), temperatures (at baseline, 24th hour, 48th hour, 72nd hour, and seventh day), baseline NIHSS, and other potential covariates (MI, hypertension, diabetes, smoking status, and rtPA) by outcome variable ("good" versus "poor") were performed. Probability values were computed to compare "good versus poor" outcome. To quantify model's ability to discriminate between "good" outcome versus "poor" outcome, we computed the area under the receiver operating characteristic curve. Usually, a model having area under the receiver operating characteristic curve >0.8 has some ability in predicting the responses of individual subjects. Also, we used the area under the receiver operating characteristic curve to evaluate the cutoff for body temperature, which eventually categorized patients into hyperthermia and nonhyperthermia. To assess the relation between outcome variable and temperature at specific times (baseline, eighth hour, 24th hour, 48th hour, 72nd hour, or seventh day), simple and multivariable logistic regression analysis were performed. Unadjusted and adjusted ORs with 95% CIs were reported. Adjustments were made for age, gender, MI, hypertension, diabetes, rtPA, smoking status, and baseline NIHSS.

We carried out Kaplan-Meier survival analysis to perceive the change in survival for patients with hyperthermia versus patients without hyperthermia with temperatures over time. To evaluate how survival was influenced by temperature over time, both univariable and multivariable analyses were performed using Cox proportional hazard models. Unadjusted and adjusted hazard ratios with 95% CIs were reported. Similar to adjusted ORs, adjusted hazard ratios associated with temperature were computed after taking account the effects of age, gender, MI, hypertension, diabetes, rtPA, smoking status, and baseline NIHSS.

To identify for predictors/determinants of hyperthermia, logistic regression models in relation to hyperthermia are fitted for a set of preselected covariates at different time points. The preselected covariates are patients' age, gender (male/female), smoking status (nonsmoker/current-smoker/exsmoker), congestive heart failure (yes/no), atrial fibrillation (yes/no), NIHSS at baseline, NIHSS at the 24th hour (<16, ≥16), hemispheric stroke (right/left), lesion volume (0 to 110, <110 mm³), rtPA use (yes/no), antibiotic use (yes/no), and WBC count (0 to 11, >11 in 10³/mm³). The covariate, lesion volume, is categorized using the average lesion volume (approximately 110 mm³) in the nonhyperthermia patients. We have performed this analysis for patients whose body temperatures are available at or after the 24th hour because one of our covariates of interest is NIHSS at the 24th hour. All of the analyses were executed in SAS (Version 9.1.3).

## Results

Data were extracted for 5305 patients with an acute ischemic stroke. The average age of patients was 68.0±11.9 years and 2380 (44.9%) were females. Baseline characteristics of the patients are summarized in Table 1 . Temperature measurements were available for the following number of patients: 5128 (96.3%) at baseline, 1702 (31.9%) at the eighth hour, 3058 (56.7%) at the 24th hour, 1688 (31.6%) at the 48th hour, 1829 (34.3%) at the 72nd hour, and 1631 (30.6%) at the

**Table 1. Demographics of Study Patients With an Acute Ischemic Stoke (n=5305)**

| Variable | Statistics |
| --- | --- |
| Age, years, mean (SD) | 68.0 (11.9) |
| Females, n (%) | 2380 (44.9) |
| Atrial fibrillation, n (%) | 1367 (25.8) |
| MI, n (%) | 569 (10.7) |
| Previous transient ischemic attack or stroke, n (%) | 454 (8.6) |
| Diabetes, n (%) | 1181 (22.3) |
| Hypertension, n (%) | 3704 (69.8) |
| Baseline NIHSS, median (IQ range) | 12 (8–18) |
| Received rtPA, n (%) | 2233 (42.1) |
| mRS at 90 days, median (IQ range) | 3 (1–5) |
| Barthel Index 90 days, median (IQ range) | 90 (55–100) |
| Smoking status, n (%) | 758 (14.3) |
| Mortality within 90 days, n ( %) | 880 (16.6) |
| Temperature, °C, median (IQ range) | |
| At baseline | 36.8 (36.4–37.1) |
| At eighth hour | 36.7 (36.4–36.9) |
| At 24th hour | 36.7 (36.5–37.1) |
| At 48th hour | 36.7 (36.5–37.1) |
| At 72nd hour | 36.7 (36.5–37.1) |
| At seventh day | 36.6 (36.4–36.8) |

IQ indicates interquartile.

**Table 2. Characteristics of Study Patients by 'Good' versus 'Poor' Outcome**

| Variable | Good (mRS $\leq$2) (n=2209) | Poor (mRS >2) (n=3096) | P Value |
| --- | --- | --- | --- |
| Age, years, mean (SD) | 64.8 (12.0) | 70.3 (11.3) | <0.001 |
| Age category, n (%) | | | |
| <70 years | 1375 (50.2) | 1366 (49.8) | <0.001 |
| 70 years and older | 834 (32.5) | 1730 (67.5) | |
| Baseline NIHSS, mean (SD) | 8.9 (4.9) | 16.0 (6.4) | <0.001 |
| Gender, n (%) | | | |
| Male | 1301 (44.5) | 1624 (55.5) | <0.001 |
| Female | 908 (38.2) | 1472 (61.8) | |
| MI, n (%) | | | |
| Yes | 205 (36.0) | 364 (64.0) | <0.01 |
| No | 2004 (42.3) | 2732 (57.7) | |
| Hypertension, n (%) | | | |
| Yes | 1504 (40.6) | 2200 (59.4) | 0.02 |
| No | 705 (44.0) | 896 (56.0) | |
| Diabetes, n (%) | | | |
| Yes | 429 (36.3) | 752 (63.7) | <0.001 |
| No | 1780 (43.2) | 2344 (56.8) | |
| rtPA, n (%) | | | |
| Yes | 999 (44.7) | 1234 (55.3) | <0.001 |
| No | 1210 (39.4) | 1862 (60.6) | |
| Smoking status | | | |
| Yes | 384 (50.7) | 374 (49.3) | <0.001 |
| No | 1825 (40.1) | 2722 (59.9) | |
| Temperature, °C, mean (SD) | | | |
| At baseline | 36.81 (0.5) | 36.84 (0.6) | <0.001 |
| At eighth hour | 36.63 (0.4) | 36.76 (0.5) | <0.001 |
| At 24th hour | 36.71 (0.5) | 36.82 (0.6) | <0.001 |
| At 48th hour | 36.62 (0.5) | 36.81 (0.6) | <0.001 |
| At 72nd hour | 36.66 (0.5) | 36.93 (0.7) | <0.001 |
| At seventh day | 36.52 (0.4) | 36.64 (0.6) | <0.001 |

seventh day. The absolute difference in baseline temperatures between patients with missing and available follow-up temperature recordings was 0.35°C, 0.19°C, 0.33°C, 0.30°C, and 0.33°C at the eighth hour, 24th hour, 48th hour, 72nd hour, and seventh day, respectively ($P<0.01$). Patients with missing data at follow-up had lower baseline temperatures. A total of 976 (18.2%) of the study patients died within 1 week from baseline.

Hyperthermia (temperature >37.2°C) was recorded in 15.9% (n=817), 11.0% (n=188), 17.2% (n=521), 19.1% (n=323), 17.9% (n=328), and 9.3% (n=152) of the study patients at baseline, eighth hour, 24th hour, 48th hour, 72nd hour, and seventh day, respectively. Any increase in temperature, as compared with baseline, was seen in 26.4% patients at the eighth hour and 39.5% of patients at the 24th hour after the index event. A greater than 1°C increase in temperature was seen in 3.0% patients at the eighth hour and 5.6% patients at the 24th hour.

Characteristics of the study patients by outcome variable (univariate analysis) are summarized (Table 2). Older patients (>70 years), females, and patients with MI and diabetes were more likely to have a poor outcome. There were statistically significant associations between temperature and poor outcome ($P<0.0001$) at baseline, eighth hour, 24th hour, 48th hour, 72nd hour, and seventh day. Unadjusted and unadjusted ORs with 95% CIs of preselected covariates (risk factors) are provided in Table 3. Based on the multivariate analysis, age ($P<0.001$), baseline NIHSS ($P<0.001$), intravenous rtPA administration ($P<0.001$), and temperatures at the eighth hour ($P<0.01$), 48th hour ($P<0.01$), 72nd hour ($P<0.001$),

and seventh day ($P<0.001$) appeared to be statistically significant predictors of a poor long-term outcome of patients with an acute ischemic stoke (Table 3). The areas under the receiver operating characteristic curve of the models with the mentioned time points were consistently >0.8. It indicates models' ability to discriminate subjects into poor versus good outcome as well as high sensitivity and specificity of the body temperature cutoff we used to define hyperthermia.

A total of 996 (18.8%) patients died during the 3-month follow-up period. Kaplan-Meier survival curves at various time points for hyperthermia are shown in Figure 1. No significant difference was observed in the mortality rate between patients with hyperthermia versus normothermia at baseline ($P=0.68$). However, compared with normothermic patients, the mortality rates were significantly higher ($P<0.001$) in the patients with hyperthermia at and after the eighth hour (Figure 1).

After adjusting for age, gender, hypertension, diabetes, MI, smoking status, baseline NIHSS, and intravenous rtPA ad-

**Table 3.** Unadjusted and Adjusted ORs for Potential Covariates and Temperature at Specific Time Point (baseline, eighth hour, 24th hour, 48th hour, 72nd hour, or seventh day) in Relation to 'Poor' Long-Term Outcome (mRS >2)

| Variable | Univariate Analysis | | Multivariable Analysis* | |
|---|---|---|---|---|
| | OR (95% CI) | P Value | OR (95% CI) | P Value |
| Gender | | | | |
| Female | 1.0 | | 1.0 | |
| Male | 1.3 (1.2–1.5) | <0.001 | 1.1 (1.0–1.3) | 0.10 |
| Age | | | | |
| <70 years | 1.00 | | 1.0 | |
| ≥70 years | 2.1 (1.9–2.3) | <0.001 | 2.2 (1.9–2.5) | <0.001 |
| MI | | | | |
| No | 1.00 | | 1.0 | |
| Yes | 1.3 (1.1–1.6) | <0.01 | 1.0 (0.8–1.3) | 0.99 |
| Hypertension | | | | |
| No | 1.00 | | 1.0 | |
| Yes | 1.2 (1.0–1.3) | 0.02 | 1.1 (0.9–1.3) | 0.25 |
| Diabetes | | | | |
| No | 1.00 | | 1.0 | |
| Yes | 1.3 (1.2–1.5) | <0.001 | 1.2 (1.0–1.4) | 0.10 |
| rtPA | | | | |
| Yes | 1.00 | | 1.0 | |
| No | 1.2 (1.1–1.4) | <0.001 | 1.8 (1.5–2.0) | <0.001 |
| Smoking status | | | | |
| No | 1.00 | | 1.0 | |
| Yes | 1.5 (1.3–1.8) | <0.001 | 1.2 (1.0–1.5) | 0.05 |
| Baseline NIHSS | 1.3 (1.2–1.3) | <0.001 | 1.3 (1.2–1.3) | <0.001 |
| Temperature at baseline, °C | | | | |
| ≤37.2 | 1.00 | | 1.0 | |
| >37.2 | 0.8 (0.7–0.9) | <0.001 | 0.9 (0.7–1.1) | 0.27 |
| Temperature at eighth hour, °C | | | | |
| ≤37.2 | 1.00 | | 1.0 | |
| >37.2 | 2.5 (1.8–3.6) | <0.001 | 1.9 (1.3–2.7) | <0.01 |
| Temperature at 24th hour, °C | | | | |
| ≤37.2 | 1.00 | | 1.0 | |
| >37.2 | 1.7 (1.4–2.1) | <0.001 | 1.2 (1.0–1.6) | 0.10 |
| Temperature at 48th hour, °C | | | | |
| ≤37.2 | 1.00 | | 1.0 | |
| >37.2 | 3.0 (2.3–3.9) | <0.001 | 1.7 (1.2–2.3) | <0.01 |
| Temperature at 72nd hour, °C | | | | |
| ≤37.2 | 1.00 | | 1.0 | |
| >37.2 | 4.3 (3.2–5.9) | <0.001 | 2.7 (1.9–3.8) | <0.001 |
| Temperature at seventh day, °C | | | | |
| ≤37.2 | 1.00 | | 1.0 | |
| >37.2 | 5.7 (3.6–9.1) | <0.001 | 4.5 (2.7–7.5) | <0.001 |

*Temperatures at baseline, eighth hour, 24th hour, 48th hour, 72nd hour, and seventh day are adjusted for gender, age, MI, hypertension, diabetes, rtPA, smoking status, and baseline NIHSS separately.

ministration, in the Cox proportion hazard model, hyperthermia appeared as a statistically significant predictor of poor outcome. The hazard ratios (95% CI) for temperatures at different time points were: baseline 1.2 (1.0 to 1.4), eighth hour 1.7 (1.2 to 2.2), 24th hour 1.5 (1.2 to 1.9), 48th hour 2.0 (1.5 to 2.6), 72nd hour 2.2 (1.7 to 2.9), and seventh day 2.7 (2.0 to 3.8). The likelihood of a poor outcome appeared to be greater the later the hyperthermia. In addition, any increase in temperature, with relation to the baseline, was a significant predictor of poor outcome. The hazard ratios for poor

**Figure 1.** Kaplan-Meier survival curves for hyperthermia versus normothermia. Y-axis: survival distribution fraction.

outcome (95% CI), for patients in whom a rise in temperature was recorded, were: 1.5 (1.2 to 1.9) at the eighth hour, 1.5 (1.2 to 1.8) at the 24th hour, 2.1 (1.6 to 2.7) at the 72nd hour, and 2.4 (1.8 to 3.1) at seventh day. The baseline body temperature was categorized as quartiles (<36.4°C, 36.4°C to <36.78°C, 36.78°C to <37.1°C, and ≥37.1°C). After adjusting for gender, age, MI, hypertension, diabetes, rtPA, smoking status, and baseline NIHSS, no overall significant difference was observed between quartiles (P=0.66) and even at individual quartile level in relation to poor long-term outcome.

Further analysis was performed to determine predictors of hyperthermia. Univariate analysis for variables in relation to hyperthermia at 24 hours showed no significant difference in age and prevalence of hypertension, diabetes, and MI between patients with and without hyperthermia (P>0.5). A total of 20.8% (n=273) females and 14.1% (n=248) males had hyperthermia at 24 hours (P<0.001). Nonsmokers/exsmokers and patients with atrial fibrillation and congestive heart failure were more likely to have hyperthermia (P<0.001). The mean NIHSS was 13.9 (±7.6) and 14.7 (±7.8) in patients with hyperthermia versus 12 (±7.2) and 8.9 (±6.2) in nonhyperthermic patients at baseline and 24 hours, respectively (P<0.001). Hyperthermia (at 24 hours) was recorded in 36.8% (n=127) patients with 24 hour NIHSS ≥16 compared with 14.3% (n=195) of patients with 24-hour NIHSS <16 (P<0.001). Patients with hyperthermia were

more likely to have abnormal WBC counts compared with patients without hyperthermia (58.4% versus 43.9%; P<0.001); however, no significant difference was seen in platelet counts in the 2 groups (P=0.33). Among patients who were thrombolyzed, 18.8% (195 of 1034) had hyperthermia compared with 16.1% (326 of 2024) in the nonthrombolyzed patients (P>0.05). Antibiotics were used in 48.1% (225 of 467) of patients with hyperthermia and 33% (769 of 2329) of nonhyperthermic patients (P<0.001).

The results of the multivariate analysis, for hyperthermia at 24 hours and 7 days and the adjusted OR are summarized in Table 4. Female gender (OR, 1.58), presence of atrial fibrillation (OR, 1.39), left hemispheric stroke (OR, 1.25) and severe stroke (24-hour NIHSS ≥16; OR, 2.76) were independent predictors of hyperthermia at 24 hours. Severe stroke (NIHSS >16) and presence of congestive heart failure showed significant association with hyperthermia at 7 days (OR, 2.31 and 1.88, respectively). At 7 days, females (OR, 0.57) and patients who received thrombolytic therapy (OR, 0.52) were less likely to have hyperthermia. Antibiotic use was significantly associated with hyperthermia both at 24 hours and 7 days (P<0.001). WBC counts were available at 24 hours only and showed a significant association with hyperthermia at 24 hours (P<0.01). The lesion volume did not show any significant correlation with hyperthermia at 24 hours (P>0.5); a borderline significant association was seen with hyperthermia at 7 days. Because the severity of stroke

**Table 4.   Adjusted ORs in Relation to Hyperthermia (temperature >37.2°C) at 24th hour and 7 Days**

| Variable | Hyperthermia at 7 Days | | | Hyperthermia at 24 Hours | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | *P* Value | OR | 95% CI | *P* Value |
| Age | 1.02 | 1.00–1.03 | 0.06 | 0.99 | 0.98–0.99 | 0.50 |
| Gender | | | | | | |
|   Male | 1.00 | | | 1.00 | | |
|   Female | 0.57 | 0.38–0.85 | 0.01 | 1.58 | 1.28–1.95 | <0.001 |
| Smoking | | | | | | |
|   Nonsmoker | 1.00 | | | 1.00 | | |
|   Current smoker | 0.69 | 0.41–1.17 | 0.17 | 0.55 | 0.38–0.81 | <0.01 |
|   Exsmoker | 0.62 | 0.37–1.03 | 0.07 | 1.51 | 1.08–2.12 | 0.02 |
| Congestive heart failure | | | | | | |
|   No | 1.00 | | | 1.00 | | |
|   Yes | 1.88 | 1.07–3.29 | 0.03 | 1.16 | 0.73–1.82 | 0.54 |
| Atrial fibrillation | | | | | | |
|   No | 1.00 | | | 1.00 | | |
|   Yes | 0.61 | 0.39–0.96 | 0.03 | 1.39 | 1.10–1.75 | 0.01 |
| NIHSS at baseline | 1.03 | 0.98–1.08 | 0.19 | 1.08 | 0.96–1.22 | 0.22 |
| NIHSS at 24th hour | | | | | | |
|   <16 | 1.00 | | | 1.00 | | |
|   ≥16 | 2.31 | 1.36–3.95 | <0.01 | 2.76 | 2.04–3.73 | <0.001 |
| Hemispheric stroke | | | | | | |
|   Right | 1.00 | | | 1.00 | | |
|   Left | 1.07 | 0.74–1.54 | 0.72 | 1.25 | 1.03–1.53 | 0.03 |
| Lesion volume | | | | | | |
|   0–110 mm$^3$ | 1.00 | | | 1.00 | | |
|   >110 mm$^3$ | 0.48 | 0.24–0.96 | 0.04 | 0.80 | 0.45–1.42 | 0.44 |
| rtPA use | | | | | | |
|   No | 1.00 | | | 1.00 | | |
|   Yes | 0.52 | 0.29–0.95 | 0.03 | 1.21 | 0.96–1.54 | 0.11 |
| Antibiotic use | | | | | | |
|   No | 1.00 | | | 1.00 | | |
|   Yes | 3.93 | 2.50–6.17 | <0.001 | 1.66 | 1.34–2.05 | <0.001 |
| WBC count | | | | | | |
|   0–11 (10$^3$/mm$^3$) | NA | NA | NA | 1.00 | | |
|   >11 (10$^3$/mm$^3$) | | | | 1.63 | 1.18–2.25 | <0.01 |

NA indicates not available.

emerged as the strongest clinical predictor of hyperthermia, the 24-hour NIHSS was further categorized into 3 groups: 0 to 10, 10 to 20, and >20; and OR for hyperthermia at various time points were calculated for the prespecified time points. The odds of hyperthermia rose with the increasing severity of stroke at all time points (Figure 2).

## Discussion

Our study demonstrates that hyperthermia is associated with a poor outcome in patients with acute ischemic stroke. A novel observation that emerged from this analysis is that delayed hyperthermia is more strongly associated with poor outcomes than that seen in the early hours after stroke, which suggests that a wide window of opportunity is available for prevention and management of hyperthermia or its cause(s).

Preclinical studies have provided ample evidence for the harmful effects of elevated temperature on ischemic brain tissue.[4–7] An increase in brain temperature, before and after the ischemic insult, has been shown to increase the total infarct volume.[16,17] Temperature elevation may have an all-or-none response with a defined threshold beyond which increased temperature aggravates ischemic injury.[17] Hyperthermia leads to physiological and structural changes, including alteration of enzyme activity and damage to cytoskeletal proteins. Release of neurotoxic excitatory neurotransmitters (glutamate and glycine) and production of free radicals have also been proposed as mechanisms through which hyperthermia leads to tissue injury.[18–22]

Clinical studies have reported hyperthermia in 18% to 61% of patients after ischemic stroke[23–25]; only one study reported
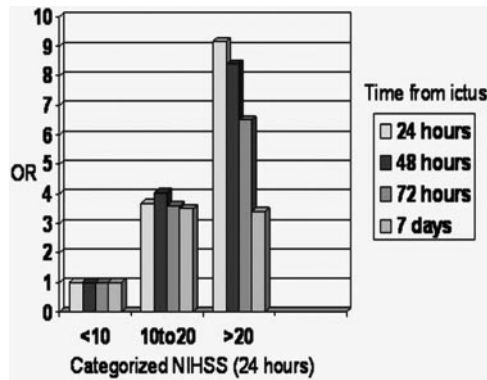
**Figure 2.** Unadjusted OR for hyperthermia at various time points for severity of stroke as assessed by categorized NIHSS.

a low prevalence (5.3%) of hyperthermia.[10] This wide variation may be partly dependent on variable times since stroke onset and difference in definitions of hyperthermia. Our analysis showed that 9.3% to 17.9% of patients with ischemic stroke had temperatures exceeding 37.2°C depending on time elapsed from baseline. The largest body of evidence to date, evaluating the effect of hyperthermia on poststroke outcomes, is that from a meta-analysis that included 9 studies with a total of 3790 patients.[10] Patients with both ischemic and hemorrhagic stroke, admitted 6 to 24 hours after stroke, were included; temperature limits for defining hyperthermia varied from 37.4°C to 38°C. The combined OR for mortality, as assessed by mortality during hospital stay to within 1 year after stroke, was 1.19 for patients with hyperthermia. The findings in our analysis are in line with those from this meta-analysis; however, we restricted our analysis to patients with ischemic stroke.

Previously, although small and large analysis have highlighted that hyperthermia is a prognostic marker for adverse outcomes after stroke,[10–13,23–27] evidence for the influence of timing of hyperthermia in relation to outcome is not clear (see Supplemental Table I, available at http://stroke.ahajournals.org). Castillo et al reported higher mortality rates in patients with hyperthermia recorded in the first 48 hours than later; also, the relationship between high temperature and adverse outcome was greater the earlier the increase in temperature.[24] Boysen and Christenson observed that hyperthermia in the first 8 hours after ischemic stroke did not have any significant impact on 3-month outcomes; however, hyperthermia at >8 hours up to 24 hours was a predictor of poor 3-month outcomes.[13] The data may partly be influenced by the timing of measurement of temperatures since stroke onset. The present analysis has extended the time window to 7 days after stroke, and the results suggest that delayed hyperthermia has a greater adverse association with long-term outcomes and mortality compared with that seen in the early period after an ischemic stroke. An interesting observation in this analysis was a lack of association between baseline hyperthermia and clinical outcomes. This seems to suggest that the adverse effects of hyperthermia are not purely dependent on aggravation of ischemic injury. Why is delayed hyperthermia more serious than that seen in the early phase? It may, in part, be determined by the etiology underlying the increase in temperatures. Although hyperthermia in the early period after stroke may

be determined by severity of stroke and an inflammatory response to the infarcted tissue, infections may be an important cause of the hyperthermia seen in the later stages. Another possibility is that delayed hyperthermia may adversely impact physiological procedures necessary for tissue healing and neural plasticity. The fact remains intriguing and warrants further investigation.

The etiology of hyperthermia after stroke may be determined by numerous factors. Previous studies have demonstrated that age, stroke type, lesion topography and volume, stroke severity, infections, and a systemic inflammatory response (secondary to infarction) may be determinants of higher body temperatures after stroke.[25–29] Other causes of increase in temperature after stroke include pre-existing infection, hospital-acquired infections, and poststroke complications like aspiration pneumonia and deep vein thrombosis.[11,30] Superimposed infections have been reported to be a cause of hyperthermia in 40% to 70% of patients after stroke.[31] In our analysis, the severity of stroke, as determined by NIHSS, emerged as the strongest predictor of hyperthermia. The baseline NIHSS did not show significant correlation in contrast to 24-hour NIHSS. We think that the final infarct size/volume, which is well demarcated by 24 hours, may be the determining factor rather than the severity of presenting symptoms (baseline NIHSS). We did not have imaging data regarding hemorrhagic transformation or presence of hematoma and could not therefore analyze relationship of the same with hyperthermia. Lesion volumes were not significantly associated with hyperthermia at 24 hours. However, volumes were available for a very small number of patients (10% [311 of 3058]), the time (between 24 hours and 7 days) and mode (CT or MRI) of measurement of volumes were variable and, therefore, reliable conclusions cannot be drawn based on these results. Also, the degree of inflammation may not only depend on infarct volume, but may be determined by individual variability in the inflammatory response. Previously, studies have reported elevation in inflammatory markers in acute stroke.[32] However, this was a retrospective analysis of data from studies that did not measure markers of inflammation. The WBC counts were significantly correlated with hyperthermia. The increase in WBC counts may be related to inflammation, secondary to the infarct, or may be an indicator of underlying infection/inflammatory state. We did not have access to laboratory investigations (chest x-ray, urine examination) for precise evaluation of infections. Although antibiotic use was significantly greater in patients with hyperthermia, this could have been a response (to fever) rather than a cause (infection).

An association of hyperthermia with cardiac conditions was also seen in our analysis. Although congestive heart failure is known to predispose to respiratory infections, the association between atrial fibrillation and hyperthermia may be determined by the larger infarct size in cardioembolic strokes. Females have been reported to have more severe strokes, and this may explain why females were more likely to be hyperthermic at 24 hours.[33] The gender association with hyperthermia was, however, reversed at 7 days. Whether this is an indicator of greater predisposition to infections in males (eg, pneumonia) remains to be analyzed. As previously

alluded to, the determinants of hyperthermia may vary with time from ictus. In the acute phase, the stroke severity and infarct volume may determine the inflammatory response, and infections may be the primary determinants in the later period.

Our analysis has some limitations. First, the data came from several randomized, controlled trials with inherent selection biases peculiar to each trial. Second, the method of temperature measurement is variable among patients included in this analysis. Our attempt was to select a cutoff for temperature, based on method of measurement, for which we assumed that axillary, oral or tympanic measurements would have been performed. Most patients had axillary measurements, which tends to underestimate oral and core body temperatures; prevalence of hyperthermia therefore may have been underestimated. Patients may have received antipyretic medications, which would affect the temperature measurements and underestimate the number of patients with hyperthermia. Also, the baseline temperature for patients with missing follow-up values was significantly lower. The missing values were random and may be due to either the specific study design or indicative of intensive monitoring in individuals with higher baseline temperatures, creating a selection bias. Although we have addressed the etiology of hyperthermia in our analysis, we did not have access to laboratory investigations needed to reliably evaluate infection as an etiology of hyperthermia. Respiratory and urinary infections are especially common in the early days after stroke and, after adjustment for other prognostic factors, themselves have a significant association with poor outcome.[34] Although we adjusted for other prognostic factors, we did not adjust for infection rates. Of course, the diagnosis of infection is sometimes based largely on pyrexia in the absence of focal symptoms or signs and so some confounding is possible. We cannot distinguish between a causal association and an incidental association between hyperthermia and outcome; however, some of the causes of hyperthermia can be tackled directly, and secondary hyperthermia can also be treated. Both offer scope for intervention during a period when patients are under close hospital observation.

In conclusion, hyperthermia is associated with poor long-term outcomes after ischemic stroke. This association is stronger for delayed hyperthermia as compared with that seen in the hyperacute phase. The adverse impact of hyperthermia, on poststroke outcomes, does not seem to be determined solely by aggravation of ischemic injury. The pathological effects of hyperthermia on poststroke recovery need further investigation. Aggressive steps to prevent and treat hyperthermia should be a part of management protocols for improving clinical outcomes after ischemic stroke. The severity of stroke and inflammation are determinants of hyperthermia after ischemic stroke. Further research is required for understanding the etiology of hyperthermia in relation to time and time-dependent effects of hyperthermia on clinical outcomes.

## Appendix

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## Disclosures

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