

Relationship Between Temperature, Hematoma Growth, and Functional Outcome After Intracerebral Hemorrhage

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Abstract

Background Fever and hematoma growth are known to be independent predictors of poor outcome after intracerebral hemorrhage (ICH). We sought to assess the distribution of temperature at different stages in relation to hematoma growth and functional outcome at 90 days in a cohort of ICH patients.

Methods Data of patients registered in the Virtual International Stroke Trials Archive—ICH were analyzed. Temperatures at baseline, 24, 48, 72, and 168 h were assessed in relation to the hematoma growth and functional outcome at 90 days. We calculated the daily linear variation of each subject's temperature by subtracting 37 °C from the maximal daily recorded temperature (delta-temperature). We used logistic regression and mixed-effects models to identify factors associated with hematoma growth, poor outcome, and temperature elevation after ICH.

Results 303 patients were included in the analysis. The average age was 66 ± 12 years, 200 (66 %) were males,

median admission NIHSS was 13 [Interquartile range (IQR), 9–18], median GCS was 15 (IQR, 14–15). Hematoma growth occurred in 22 % and poor functional outcome at 90-days occurred in 41 % of the patients. Cumulative delta-temperature at 72 h was associated with hematoma growth; age, ICH score, hematoma growth, and cumulative delta-temperature at 168 h were associated with poor outcome at 90 days. Factors associated with fever in mixed-models were day after onset of ICH, hypertension, base hematoma volume, intraventricular-hemorrhage, pneumonia, and hematoma growth.

Conclusions There is a temporal and independent association between fever and hematoma growth. Fever after ICH is associated with poor outcome at 90 days. Future research is needed to study the mechanisms of this phenomenon and if early protocols of temperature modulation would be associated with improved outcomes after ICH.

Keywords Fever · Stroke · VISTA

This study was conducted on behalf of the VISTA Collaboration. The members of Collaboration committee are listed in [Appendix](#).

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Introduction

Early hematoma growth after spontaneous intracerebral hemorrhage (ICH) is common and associated with neurological deterioration and poor clinical outcome [1, 2]. Prior studies indicate that hematoma growth occurs in up to 38 % of ICH patients when re-scanned within 3 h of onset, and in 16 % of those scanned between 3 and 6 h, even in the absence of coagulopathy [1, 3–5]. The mechanisms that lead to early hematoma growth during the acute stage of ICH remain unclear but many factors such as vascular engorgement related to a reduction in venous outflow, early transient ischemia, activation of pro-inflammatory cytokines, ongoing bleeding, and a local coagulopathic state

secondary to increased levels of fibrinolytic proteins and decreased level of coagulation proteins [6–15] have been implicated. In addition to the relative mass effect, the hematoma itself induces early pathophysiologic changes in the surrounding brain tissue such as breakdown of the brain-blood barrier, vasogenic edema, and neuronal and glial cell death due to apoptosis and inflammation [10, 16, 17].

As an adaptive response to injury and inflammation, fever may therefore be seen with the development of the hematoma after ICH [18, 19]. More important to clinical practice, is that fever [20–22] is considered to have detrimental effects after all types of brain injury including ICH [18, 23], because this response is known to increase the metabolism of the brain and can exacerbate neuronal injury, events that occur around the hematoma [7–15, 24, 25]. However, a temporal or independent association between hematoma growth and fever has not been discerned by prior studies that have evaluated the effects of fever on outcomes after ICH [18, 19], while considering the effects of other factors associated with fever. In this study, we sought to assess the distribution of temperature at different stages in relation to hematoma growth and functional outcome at 90 days in a cohort of ICH patients. Specifically, we sought to determine: (a) whether fever was a common occurrence after ICH; (b) whether the presence of fever was associated with hematoma growth; (c) whether fever was associated with poor functional outcome at 90 days; (d) whether the exposure to fever remained significantly associated with hematoma growth and poor functional outcome after adjustment for confounding variables in a multivariate analysis; and (e) to identify independent predictors of fever after ICH. We hypothesized that fever would be temporally associated with hematoma growth and poor outcome after ICH.

Methods

Study Design and Patient Data

A retrospective cohort study using a prospectively compiled and maintained registry from the Virtual International Stroke Archive (VISTA) [26]. Details and methods of the VISTA collaboration have been previously published [26, 27]. In brief, this database includes data from clinical trials that had documented entry criteria and monitoring processes for validation of data. VISTA holds data from 31 trials involving more than 28,000 patients, age range 18–103 years, who experienced an index acute stroke due to either ischemia or ICH [27]. Eligibility for VISTA required the following: (1) documented entry criteria into a trial, with a minimum of 100 patients; (2) local ethics board

approval; (3) baseline assessment within 24 h of stroke; (4) baseline assessment of neurologic deficit; (5) confirmation of stroke with imaging; (6) outcome assessment between 1 and 6 months with a validated stroke scale; and (7) data validation through monitoring [27]. Our sample cohort consisted of patients presenting with CT-proven ICH within 6 h of symptom onset. All patients had baseline and 24 h National Institutes of Health Stroke Scale (NIHSS) score [28], Glasgow Coma Scale (GCS) [29], ICH Score [30], follow-up CT scan at 72 h, and 90-days modified Rankin Scores (mRS) [31]. For this analysis, patients were selected from the control arm of the only registered ICH trial: the CHANT trial [32]; all patient data were de-identified by VISTA, and all studies included into the VISTA database required patient consent and local ethics or Institutional Review Board (IRB) approval; this analysis was exempted from full review by the IRB of Thomas Jefferson University Hospital.

Definition of Exposure and Outcome Variables

Our exposure variable was temperature measured in Celsius degrees (T °C), which was recorded daily from either one of the following locations: rectal (3 %), oral (20 %), tympanic (26 %), or axillary (51 %). We defined fever as any daily recorded maximal temperature $T \geq 37.5$ °C at baseline, 24, 48, 72, or 168 h after onset of ICH symptoms. This cutoff was defined a priori and conforms to published results from clinical studies [20, 33] and practice guidelines for initiating antipyretic therapy and diagnostic evaluation of fever or infection causes in the Intensive Care Unit [22]. We also calculated the linear variation of each subject's temperature by subtracting 37 °C from the maximal daily recorded temperature (delta-temperature); when the maximal daily temperature was below 37.0 °C, a score of 0 was assigned [34, 35]. The analysis of change in volume from baseline to 72 h was adjusted for baseline volume as originally defined by the methods of the source trial [32]. ICH volumes were measured on the baseline and 72 h scan using semi-automated computerized planimetry; scans were read centrally and by blind assessors [32]. Our secondary outcome of interest was a measure of "poor outcome" at 90 days, defined a priori as a mRS [31] of 4–6 [27].

Statistical Analysis

Continuous data are presented as means and standard deviations (SD) or medians and interquartile ranges (IQR) as appropriate based on the distribution of the data; categorical data are reported as number of subjects and proportions. The t test for normally distributed data, the Mann–Whitney-U test for non-parametric data, or the χ^2 or

Fisher exact tests for proportions were used for determination of predictors and potential confounders of hematoma growth and poor outcome. In the initial bivariate analysis, we assessed the relationship of each of the potential predictors of hematoma growth and 90-days mRS. As our main predictor of interest, the cumulative delta-temperature was not normally distributed, we log-transformed it for all subsequent multivariate analyses and mixed models and to allow for evaluation of linear relationships. Multivariate models were fitted to assess for predictors of hematoma growth and poor outcome by means of logistic regression and with mixed-effects models to assess for predictors of temperature elevation after hospital admission. The multivariate analysis proceeded in two stages. In the first stage, significant factors were identified from the candidate variables. All patient data in Table 1 were considered as candidate variables for the models. In constructing our multivariate models, we included covariates with bivariate p values of <0.2 as seen in Table 2. We also tested for interactions between all independent predictors of outcome in the final models. To determine the relative contributions of the individual covariates in the model, we compared changes in the likelihood ratio value of the entire model (an estimation of the overall fitness of the model) after individual addition of each significant co-variate. Finally, tests for co-linearity were performed with correlation analysis and the Homer–Lemeshow test was used to assess for the goodness of fit. In the second stage, we evaluated for predictors of temperature elevation with mixed-effects models to identify admission and hospital predictors of fever, with the variable “subject” as a random effect, and the fixed linear effect “ICH day” nested within each subject [34]. An autoregressive pattern (AR1) was tested, assuming decreasing correlation of delta-temperatures within each subject. Statistical analyses were conducted using standard statistical software [SAS Version 9.2 (SAS Institute, Cary, NC) and SPSS Version 19.0 for Macintosh] and significance was judged for $p < 0.05$ unless indicated.

Results

Description of the Cohort and Distribution of Temperatures

At the time of this analysis, the VISTA—ICH repository contained 603 patients enrolled in one ICH trial: the CHANT trial [32]. The final study cohort consisted of 303 patients participating in the placebo arm of this source trial [32]. Mean age was 66 ± 12 years, of which 66 % were men; median NIHSS on admission was 13 (IQR, 9–18); median GCS was 15 (IQR, 14–15); median ICH score was

Table 1 Characteristics of the study cohort

	Overall ($n = 303$)
Demographics	
Age (years)	66 ± 12
Sex (man)	200 (66)
Affected hemisphere (left)	145 (48)
Chronic medical conditions	
Myocardial infarction	9 (3)
Atrial fibrillation	20 (7)
Hypertension	252 (82)
Diabetes mellitus	63 (21)
Coronary artery disease	30 (15)
Congestive heart failure	8 (3)
Tobacco (current or ex-smoker)	131 (43)
Hypercholesterolemia	31 (10)
Stroke	33 (11)
Transient ischemic attack	15 (5)
Anticoagulation (warfarin)	21 (7)
Antiplatelet use	77 (25)
Admission characteristics	
NIHSS	13 (9–18)
GCS	15 (14–15)
ICH score	1 (0–1)
ICH score ($n = 300$)	
0	110 (37)
1	120 (40)
2	53 (18)
3	15 (5)
4	2 (0.6)
Stroke onset to treatment time (placebo)	4.4 ± 1
Hemoglobin (Hb gr/dL)	14 ± 1.5
White blood cell count (GI/L)	9.2 (7–11)
Neutrophils (GI/L)	7 (6–9)
Platelet count (GI/L)	217 (185–261)
Activated PTT (sec)	24 (18–28)
INR	1 (0.9–1.2)
ALT (U/L)	20 (15–29)
AST (U/L)	23 (19–30)
Alkaline phosphatase (U/L)	80 (67–94)
Creatinine (mmol/L)	76 (62–89)
Blood urea nitrogen (mmol/L)	6 (5–7)
Sodium Na (mmol/L)	140 ± 4
Potassium K (mmol/L)	4 ± 0.6
Calcium (mmol/L)	2.3 ± 0.1
Bilirubin (mmol/L)	7 (5–11)
Temperature variables (°C)	
Baseline ($n = 288$)	36.5 (36.2–36.7)
24 h ($n = 276$)	37.0 (36.6–37.3)
48 h ($n = 267$)	37.0 (36.6–37.4)
72 h ($n = 278$)	36.9 (36.5–37.3)
168 h ($n = 258$)	36.8 (36.5–37.1)

Table 1 continued

	Overall (<i>n</i> = 303)
Fever baseline (<i>n</i> = 288)	2 (0.6)
Fever 24 h (<i>n</i> = 276)	48 (17)
Fever 48 h (<i>n</i> = 267)	66 (25)
Fever 72 h (<i>n</i> = 278)	51 (18)
Fever 168 h (<i>n</i> = 258)	2 (12)
Blood pressure (MAPs mmHg)	
Baseline	119 ± 22
24 h (<i>n</i> = 285)	107 ± 16
48 h (<i>n</i> = 276)	107 ± 17
72 h (<i>n</i> = 288)	107 ± 17
168 h (<i>n</i> = 261)	101 ± 15
CT scan characteristics	
Scan time baseline (hour)	2 (1–3)
Volume base (cc) (<i>n</i> = 300)	15 (8–33)
IVH base (y/n)	104 (34)
Scan time 72 h (<i>n</i> = 285)	72 (69–73)
Volume 72 h (cc) (<i>n</i> = 283)	17 (8–39)
IVH 72 h (y/n) (<i>n</i> = 285)	126 (44)
Hematoma growth volume (cc) (<i>n</i> = 282)	0.8 (–0.4–5.6)
Primary outcome	
Hematoma growth (≥33 %) (<i>n</i> = 282)	63 (22)
Secondary outcomes	
NIHSS 90 days (<i>n</i> = 237)	4 (2–7)
mRS ≥4 90 days (<i>n</i> = 239)	98 (41)
Seizure prophylaxis	
Phenytoin	11 (4 %)
Infectious adverse events	
Pneumonia	15 (5)

Data is presented as mean ± SD, median (IQR), or *N* (%). *N* = 303 unless otherwise noted

NIHSS National Institutes of Health Stroke Scale, GCS Glasgow coma scale, INR international normalized ratio, IVH intraventricular-hemorrhage, fever ($T \geq 37.5$ °C)

1 (IQR, 0–1); median hematoma volume was 15 cc (IQR, 8–33 cc); intraventricular-hemorrhage (IVH) was seen in 34 % of the patients; other baseline characteristics are shown in Table 1. Hematoma growth occurred in 22 % and poor functional outcome at 90 days occurred in 41 % of the patients (Table 1).

Daily temperatures were measured from rectal (3 %), oral (20 %), tympanic (26 %), or axillary (51 %) routes. The proportion of hyperthermic patients increased over time in relation to hematoma growth and functional outcome (Fig. 1; Table 2). The proportion of fever at 24 ($p = 0.009$) and 72 h ($p = 0.004$) was significant in those patients with hematoma growth but this was not seen at baseline, 48, or 168 h (Fig. 1; Table 2). Similarly, the proportion of fever at 24 ($p = 0.003$), 48 ($p = 0.02$), and

168 h ($p = 0.01$) was higher in those patients with poor outcome at 90 days but not at baseline or 72 h, though there was a trend at 72 h ($p = 0.06$) (Fig. 1; Table 2). The cumulative delta-temperatures were also higher at 72 h ($p = 0.08$) in those patients with hematoma growth and significantly higher at 168 h in those with poor functional outcome at 90 days ($p < 0.001$) (Table 2).

Predictors of Hematoma Growth and Poor Outcome

In the bivariate analysis, hematoma growth was associated with: history of atrial fibrillation, hypertension (HTN), international normalized ratio (INR), anticoagulation with warfarin, fever at 24 and 72 h, and cumulative delta-temperature at 72 h (Table 2). Poor outcome was associated with: age, history of HTN and diabetes mellitus, admission NIHSS, GCS, ICH score, INR, white blood cell count, baseline hematoma volume, presence of IVH, fever at 24, 48, 72, and 168 h; cumulative delta-temperature at 168 h; and hematoma growth (Table 2).

In multivariate analysis, history of anticoagulation with warfarin ($p = 0.03$) and the cumulative delta-temperature at 72 h in log-scale ($p = 0.04$) was associated with hematoma growth (Table 3). Predictors of poor outcome at 90 days were age ($p = 0.03$), ICH score ($p < 0.001$), hematoma growth ($p = 0.02$), and the total cumulative delta-temperature at 168 h in log-scale ($p = 0.04$). We did not observe significant interactions between our co-variables.

Predictors of Temperature Elevation After ICH

Independent factors associated with temperature elevation in the mixed-effects analysis were: day after onset of ICH, history of HTN, base hematoma volume ≥ 15 cc, IVH, pneumonia, and hematoma growth (Table 4). Though we found nine patients exposed to anti-epileptic drugs for seizure prophylaxis, of which 8 (4 %) received phenytoin, our mixed-effect models did not find a significant association between phenytoin exposure and temperature elevation.

Discussion

In this study, we observed that fever was a common occurrence after ICH and independently associated with hematoma growth and poor functional outcome at 90 days. Most importantly, we found that fever was temporally associated with hematoma growth, after adjustment for additional predictors of temperature elevation including: white blood cell count, infectious complications (pneumonia), phenytoin exposure, hematoma volume, and IVH.

Table 2 Bivariate analysis of factors associated with hematoma growth (>33 %) and modified Rankin Scale (mRS 4–6) at 90 days

Hematoma growth	No N = 219	Yes N = 63	p value
Atrial fibrillation	11 (5)	8 (12)	0.04
Hypertension	179 (82)	58 (92)	0.04
Anticoagulation (warfarin)	8 (4)	9 (14)	0.004
INR	0.9 (0.9–1.1)	1.1 (0.9–1.3)	0.002
Fever baseline	1 (0.4 %)	1 (2 %)	NS
Fever 24 h	28 (13)	16 (29)	0.009
Fever 48 h	46 (22)	17 (32)	NS
Fever 72 h	30 (14)	19 (31)	0.004
Cumulative delta-temperature °C at 72 h*	0.3 (0–0.8)	0.5 (0–1.7)	0.08
Functional outcome	mRS 1-3 N = 141	mRS 4-6 N = 98	p value
Age (year)	62 ± 11	67 ± 11	0.001
Hypertension	112 (79)	86 (88)	0.088
Diabetes mellitus	22 (16)	28 (29)	0.016
NIHSS	10 (7–14)	16 (13–19)	<0.001
GCS	15 (14–15)	14 (13–15)	<0.001
ICH score	0 (0–1)	1 (1–2)	<0.001
White blood cell count (G/L)	8.7 (7–11)	9.7 (8–12)	0.044
INR	0.9 (0.8–1.1)	1 (0.9–1.1)	0.019
Fever baseline	0	0	NS
Fever 24 h	10 (7)	19 (21)	0.003
Fever 48 h	24 (18)	29 (31)	0.02
Fever 72 h	18 (13)	21 (22)	0.06
Fever 168 h	8 (6)	16 (17)	0.01
Cumulative delta-temperature °C at 168 h**	0.2 (0–0.8)	0.6 (0.1–1.4)	<0.001
Volume baseline (cc) (n = 237)	14 ± 12	25 ± 20	<0.001
IVH Baseline (n = 238)	34 (24)	34 (35)	0.08
Volume 72 h (cc) (n = 235)	16 ± 14	30 ± 25	<0.001
IVH 72 h (n = 236)	36 (26)	51 (53)	<0.001
Hematoma growth >33 % (n = 282)	16 (12)	29 (30)	<0.001

Data are presented as mean ± SD, median (IQR), or N (%). N = 303 unless otherwise noted

INR international normalized ratio, fever ($T \geq 37.5$ °C), NIHSS National Institutes of Health Stroke Scale, GCS Glasgow coma scale, IVH intraventricular-hemorrhage

* Cumulative delta-temperature in relation to hematoma growth was measured at this time-point as the source trial [32] measured hematoma growth at 72 h and not before; similarly

** Cumulative delta-temperature in relation to poor outcome was measured at this time-point as the source trial did not record further temperatures and reflects all temperature data available during hospital admission

Fig. 1 Proportion of fever ($T \geq 37.5$ °C) during the study period by hematoma growth and modified Rankin Scale (1–3 vs. 4–6). (* $p \leq 0.01$, ** $p \leq 0.05$)

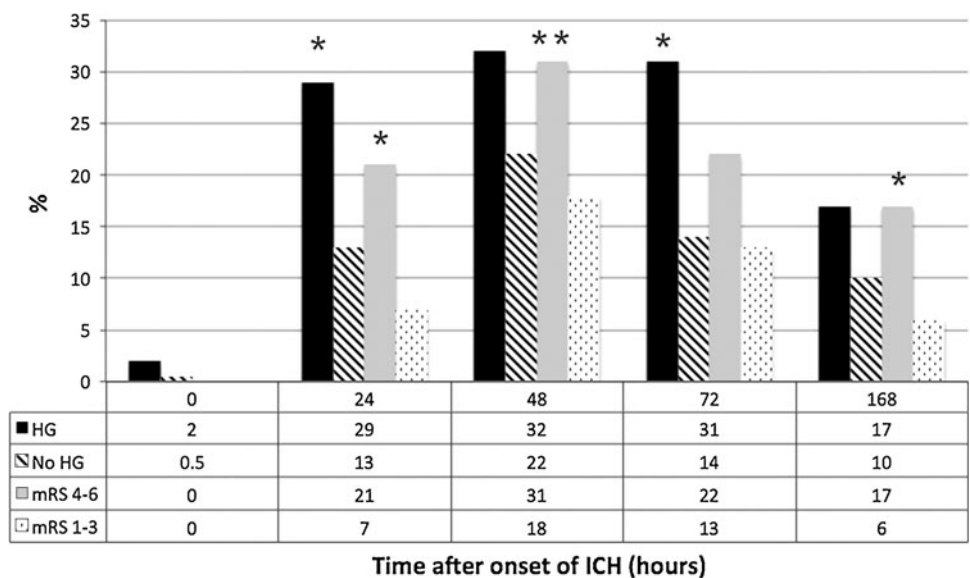


Table 3 Multivariate analysis of predictors of hematoma growth measured at 72 h (per methods of source trial [32]) and 90-days mRS 4–5

	OR	95 % CI low	95 % CI high	<i>p</i> value
Model 1. Hematoma growth >33 %				
Anticoagulation with warfarin	2.0	1.1	3.8	0.03
Cumulative delta- temperature at 72 h, in log-scale*	1.5	1.02	2.1	0.04
Model 2. mRS 4-5 at 90 days				
Age	1.1	1.01	1.1	0.03
Hematoma growth >33 %	1.8	1.1	3.0	0.02
ICH score \geq 1	2.4	1.6	3.5	<0.001
Cumulative delta- temperature at 168 h, in log-scale*	1.4	1.01	2.0	0.04

* The variable delta-temperature was log-transformed based on its non-normal distribution

Table 4 Independent predictors of temperature elevation after ICH

	Affected <i>N</i> = 303	Main fixed effect	Interaction by day (linear)
Day after ICH	–	<0.001	–
Hypertension	252 (82)	0.011	–
Hematoma volume > 15 cc	148 (50)	<0.001	<0.001
Presence of IVH at 72 h (<i>n</i> = 283)	126 (44)	<0.001	<0.001
Pneumonia	15 (5)	<0.001	<0.001
Hematoma growth >33 % (<i>n</i> = 282)	63 (22)	0.011	–

Data are *N* (%) and *p* values. Mixed-effects analysis was used to predict temperature elevation above 37 °C. Each subject was treated as a random effect. Delta-temperature values were assumed to be correlated within each subject and were modeled using an autoregressive process (AR1 diagonal = 0.1; AR1 rho = 0.13)

Fever is frequently seen after all types of brain injury [18, 20, 36] including ICH, where it can be seen in up to 91 % of the patients [33]. Schwarz et al. [33] reported that the incidence of fever (defined as temperature \geq 37.5 °C) was higher during the first 72-h after ICH and that this proportion decreased over time. We observed a smaller incidence of fever in our cohort (Table 2), which may have been explained by the less severe forms of ICH patients enrolled in the source trial [32] as compared to the more severe cohort seen in the Schwarz et al. [33] study, where 50 % of patients had GCS of less than 14 and at least 40 % had ICH volumes >60 cm³. In agreement with Schwarz et al. [33], we also observed that the proportion of fever increased significantly after the first 24 h and trended down later on (Fig. 1). We did not find a significant difference in the proportion of fever at baseline, suggesting that the onset of inflammatory mechanisms associated with the hematoma and its growth, reminiscent of a systemic inflammatory response as seen in other types acute injury (trauma, stroke, sepsis, among others), may be implicated in this phenomenon [10, 16, 17] (Table 2). In support of this observation, is that both hematoma volume and growth remained independently associated with temperature elevation in our mixed-analysis after adjustment for other predictors of fever (Table 4). Because the source trial recorded only maximal daily temperatures

and assessed hematoma growth at 72 h, we cannot definitely conclude that the peak temperatures seen after 24 h of onset of ICH in our study were related to the expansion of the hematoma. However, our mixed-analysis included those plausible factors that may have been associated with fever after ICH including: hematoma growth, day after onset of ICH [33], IVH [33], hematoma volume, infections, and drug exposure (Table 4), and provides some evidence of the temporal association of hematoma growth with a febrile response. Similarly, as most of hematoma growth after ICH occurs within the first 6 h [1, 3–5] and less likely beyond 12 h [1, 3–5], and the ascertainment of hematoma growth occurred at 72 h in the source trial [32], we cannot definitely conclude that the proportion of fever observed during the first 24 h (Table 2) was a consequence of hematoma growth. However, it is still possible that fever was a manifestation of hematoma growth [37] and possibly related to several physiopathological mechanisms such as breakdown of the brain-blood barrier, vasogenic edema, and neuronal and glial cell death due to apoptosis and inflammation [10, 16, 17]. We also found a significant association between fever and poor functional outcome at 90 days even when considering the effects of hematoma growth and other predictors of poor functional outcome, supporting the results of other observational studies [18, 19, 33].

As an adaptive response to injury and inflammation, fever would be an expected event after ICH, particularly during the first 72 hrs after onset of symptoms [19, 33]. Fever is known to increase the metabolism of the brain and can exacerbate neuronal injury, events that may occur around the hematoma. Several potential physiopathologic mechanisms that may explain this phenomenon include: excitotoxicity from amino-acid and free radical production, cytoskeletal proteolysis, inhibition of protein kinases, and activation of certain matrix metalloproteinases, which could lead to blood–brain barrier breakdown, hematoma growth, and worsening cerebral edema [7–15, 24, 25]. With newer technologies for temperature modulation available in the intensive care unit, and based on the detrimental effects of fever after brain injury [18], aggressive temperature modulation will play a role in the management of ICH patients to improve functional outcomes. Recent experimental data from animal models of ICH that used bacterial collagenase infusions, suggested that temperature modulation improved recovery and lessened neuronal injury when temperature modulation to hypothermia was initiated after 12 h of onset [38], but this effect was not seen in a different animal model of “whole blood” infusion [39]. A recent study of ICH patients suggested that mild induced hypothermia was associated with less cerebral edema without change in hematoma growth or functional outcome when hypothermia was started after 6 h of onset [40]. To this end, our results are important as they provide support for those initiatives that will study the potential therapeutic implications of early protocols of temperature modulation, which may limit secondary neuronal damage after ICH.

We acknowledge that though association does not necessarily imply causation, our data support prior observations showing that fever after ICH may have adverse effects, not only by its independent association with hematoma growth but also on functional outcomes. Whether ultra-early aggressive therapeutic temperature modulation after ICH improves functional outcomes after ICH by modulation of the neuro-inflammatory response as seen in animal models [38], remains to be answered by future clinical studies aimed at answering this particular question. Novel strategies that go beyond control of glucose, blood pressure, and ICP [41], aimed at reducing hematoma growth and neuro-inflammation could be the new frontier in the management of ICH. Finally, our study demonstrates an association between hematoma growth and fever, independent of infectious adverse events; this could be important in clinical practice, as early onset of fever after ICH may not be an indication of empiric antibiotic regimen in the absence of obvious signs of infection.

Our study has limitations. First, our analysis was observational in nature, which limits the inferences that can

be made about etiological or causal relationships. Second, our study is a post hoc analysis of the source trial, which included a heterogeneous population of ICH patients (history of hypertension and exposed to anticoagulants)[32], and was not designed to answer our proposed questions, so our results should be interpreted with caution. Third, we acknowledge our modest sample size and that our exposure variable was measured from different sites allowing for variability or possible underestimation of temperature measurements. Similarly, a single daily measurement of temperature may have not captured the whole burden of fever on our proposed outcomes and most importantly, we did not have temperature data between the baseline and 24 h when hematoma growth after ICH is more likely to occur. However, our results mirror and are in agreement with the findings of earlier observational studies that addressed the effect of fever and functional outcome after ICH [33]. Fourth, our study looked at patient data within 168 h of ICH onset, so the effect of fever on functional outcome after this time may have not been accounted for in our multivariate models. Considering all these shortcomings, our study provides important information about the effects of fever after ICH and its temporal relationship with hematoma growth, implying that this response should not be considered an epi-phenomenon but a possible target for future therapies for the most devastating type of stroke.

In summary, our data confirms the frequent occurrence of fever after ICH. There is a probable temporal association between fever and hematoma growth as early as 24 h. It is also possible that the inflammatory mechanisms implicated in the physiopathology of ICH are responsible for the abnormal early temperature elevation seen in these patients. Future research is needed to study the mechanisms of this phenomenon and if early protocols of temperature modulation would be associated with improved outcomes after ICH.

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Conflict of interest None.

Appendix

VISTA-Acute Steering Committee

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