Clinical characteristics and outcome of aneurysmal subarachnoid hemorrhage with intracerebral hematoma

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OBJECTIVE Intracerebral hematoma (ICH) with subarachnoid hemorrhage (SAH) indicates a unique feature of intracranial aneurysm rupture since the aneurysm is in the subarachnoid space and separated from the brain by pia mater. Broad consensus is lacking regarding the concept that ultra-early treatment improves outcome. The aim of this study is to determine the associative factors for ICH, ascertain the prognostic value of ICH, and investigate how the timing of treatment relates to the outcome of SAH with concurrent ICH.

METHODS The study data were pooled from the SAH International Trialists repository. Logistic regression was applied to study the associations of clinical and aneurysm characteristics with ICH. Proportional odds models and dominance analysis were applied to study the effect of ICH on 3-month outcome (Glasgow Outcome Scale) and investigate the effect of time from ictus to treatment on outcome.

RESULTS Of the 5362 SAH patients analyzed, 1120 (21%) had concurrent ICH. In order of importance, neurological status, aneurysm location, aneurysm size, and patient ethnicity were significantly associated with ICH. Patients with ICH experienced poorer outcome than those without ICH (OR 1.58; 95% CI 1.37–1.82). Treatment within 6 hours of SAH was associated with poorer outcome than treatment thereafter (adjusted OR 1.67; 95% CI 1.04–2.69). Subgroup analysis with adjustment for ICH volume, location, and midline shift resulted in no association between time from ictus to treatment and outcome (OR 0.99; 95% CI 0.94–1.07).

CONCLUSIONS The most important associative factor for ICH is neurological status on admission. The finding regarding the value of ultra-early treatment suggests the need to more robustly reevaluate the concept that hematoma evacuation of an ICH and repair of a ruptured aneurysm within 6 hours of ictus is the most optimal treatment path.

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STUDIES indicate that 2 of every 10 subarachnoid hemorrhage (SAH) patients sustain a simultaneous intracerebral hematoma (ICH) and outcomes tend to be poorer among these patients.^{1,3,7,9,15,18,22} No guidelines are currently available as to the best approach to manage these patients. Though some studies have focused on comparing the incidence and prognosis of SAH patients who have concurrent ICH to those of patients without ICH, the available studies reflect the experiences of single centers and small patient cohorts, or present crude data on the relationship of clinical and aneurysm characteristics to outcomes.^{1,3,7,9,22} Addressing questions pertaining to whether well-known

risk factors for SAH confer additional risk for the development of ICH and how much prognostic risk could be attributed to the additional effect of ICH could better inform treatment and individual patient management.

The few studies that investigated the optimal management practices for SAH patients with concurrent ICH suggest that ultra-early intervention within 6 hours of ictus conferred relatively better outcomes for this patient cohort.^{7,20} Some, therefore, have advocated for an aggressive approach to treatment in these patients that involves ultra-early craniotomy with clot evacuation and occlusion of the ruptured aneurysm; however, this is a practice that is not

ABBREVIATIONS ACA = anterior cerebral artery; BP = blood pressure; C-1 = CONSCIOUS-1 trial; DBP = diastolic blood pressure; DM = diabetes mellitus; EBI = early brain injury; GOS = Glasgow Outcome Scale; ICA = internal carotid artery; ICH = intracerebral hematoma; IVH = intraventricular hemorrhage; MCA = middle cerebral artery; MI = myocardial infarction; PCA = posterior cerebral artery; SAH = subarachnoid hemorrhage; SAHIT = SAH International Trialists; SBP = systolic blood pressure; SHOP = SAH Outcomes Project; WFNS = World Federation of Neurosurgical Societies.

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adhered to by others.^{7,20} To ascertain the optimal timing of treatment for patients with SAH who present with additional ICH, further research is needed to improve the understanding on how time to treatment relates to clinical outcome in these patients.

Recently, SAH researchers around the globe have been collaborating to establish a repository of prospective studies on SAH, including randomized clinical trials and well-designed observational studies and registries from multiple centers, in order to more reliably address issues related to SAH prognosis than previously and model the application of novel approaches in trial design in the context of SAH.^{10,16} Using these data, we sought to 1) identify the clinical and aneurysm characteristics that are associated with SAH that present with ICH as a component; 2) ascertain the prognostic value of ICH; and 3) investigate the relationship between the timing of treatment and outcome in this cohort of SAH.

Methods

Study Cohort

For the present analysis, we included studies in the SAH International Trialists (SAHIT) repository that collected data on the presence of ICH on an admission CT scan. The studies included 4 randomized controlled trials of tirilazad mesylate (tirilazad),^{8,12–14} the SAH Outcomes Project (SHOP),²³ and the CONSCIOUS-1 trial (C-1).¹⁷ Specific details pertaining to these studies, including the inclusion and exclusion criteria, have been published.^{8,12–14,17,23} The tirilazad trials enrolled SAH patients between 1991 and 1997 to evaluate the efficacy of tirilazad mesylate on cerebral vasospasm and outcome. SHOP is a prospective database that accrues data on SAH patients who have been admitted to the Columbia University Medical Center Neurological Intensive Care Unit (data obtained between 1996 and 2013 are included in the SAHIT repository). The C-1 trial was an international multicenter randomized control trial that was conducted between 2005 and 2006 to evaluate the efficacy and safety of clazosentan for preventing vasospasm. The trials failed to show the efficacy of the treatment agent, thereby allowing for the pooling of both trial arms in this analysis.

Baseline Characteristics

In C-1, the volume of ICH was measured as $xyz/2$ where x, y, and z are the 3 maximum orthogonal diameters of a clot. Midline shift was measured in millimeters. In the SHOP and tirilazad data, ICH was recorded as present or absent. In the pooled data, ICH was categorized qualitatively as either present or absent. The considered baseline characteristics included age, sex, ethnicity, hypertension, angina, myocardial infarction (MI), diabetes mellitus (DM), smoking, admission World Federation of Neurosurgical Societies (WFNS) grade, systolic blood pressure (SBP), diastolic blood pressure (DBP), Fisher grade, intraventricular hemorrhage (IVH), rupture location, aneurysm size, treatment modality, and time from ictus to treatment. Hypertension, angina, MI, and DM were recorded as a preexisting medical condition in all studies. Prior history of smoking was only available in C-1 and

SHOP. Systolic BP and DBP were measured at admission for SHOP and tirilazad, and at time of eligibility screening for C-1. Fisher grading of the SAH was recorded on the admission CT scan in SHOP.⁴ For standardization across studies, baseline SAH clot descriptions were converted to the Fisher scale for tirilazad and C-1.⁶ Admission CT scans were also reviewed for ICH and IVH in all studies. Ruptured aneurysm size and location were determined using digital subtraction angiography. Due to the differences in the coding of the aneurysm sizes in the original studies, we classified aneurysms into 3 categories: small (tirilazad and SHOP, ≤ 12 mm; C-1, ≤ 15 mm); medium (tirilazad and SHOP, 13–24 mm; C-1, 16–25 mm); or large (tirilazad and SHOP, ≥ 25 mm; C-1, > 25 mm). In tirilazad, the ruptured aneurysms were repaired via clipping or treated conservatively, and less than 5% were treated endovascularly. In SHOP, the aneurysms were clipped, coiled, or treated conservatively. All aneurysms in C-1 were clipped or coiled. The time from SAH to aneurysm occlusion was available in tirilazad and C-1.

Outcome Measures

The primary outcome was the patient score on the 5-category Glasgow Outcome Scale (GOS) at 3 months. The secondary outcome was the presence or absence of new cerebral infarcts.

Handling of Missing Values

Most variables had less than 5% missing data, except for aneurysm size (5.8%) and GOS score at 3 months (7.2%). Multiple imputations by chained equations were used to impute missing values and generate 20 data sets for the analysis.²⁵ The imputation models consisted of the outcome variables, covariates in the analysis models, other baseline variables, and a dummy variable for the three studies.

Statistical Analyses

Patient clinical and aneurysm characteristics were computed by comparing patients with SAH who had concurrent ICH to those without ICH using frequency tables for categorical variables and the mean with standard deviation for the continuous variables. The clinical and aneurysm characteristics were studied for their association with ICH by fitting the backward stepwise logistic regression model (exclusion criteria $p > 0.2$). The variables included in the model were age, sex, ethnicity, hypertension, angina or MI, DM, WFNS grade on admission, ruptured aneurysm size, and location. Bias-corrected confidence intervals were computed using the bootstrap resampling technique (1000 resamples). We ranked the relative importance of the variables in the model using dominance analysis based on R^2 as the test statistic. Dominance analysis is a method used to determine the relative importance of predictors included in a regression model.² It compares the effects of the predictor variables for all possible subsets of models based on goodness-of-fit statistics. Effect sizes are reported as the odds ratios and 95% confidence intervals.

The univariable and multivariable analyses were per-

formed to investigate the association of ICH with outcome. For the univariable analysis, we fitted proportional odds logistic regression models to obtain unadjusted odds ratios of the effect of ICH on GOS score by study. The odds ratios were pooled using a random effects model and between-study variability was tested using I^2 statistics. For the multivariable analysis, we fitted a proportional odds logistic regression model to adjust for the fixed effects of study, age, sex, WFNS grade, aneurysm size, location (which was dichotomized into anterior vs posterior circulation aneurysm, whereas an aneurysm that arose at the origin of the posterior communicating artery from the internal carotid artery [ICA] was classified as anterior) and treatment modality (clipping, coiling, or conservatively treated). We assessed the added incremental predictive value of ICH above the other predictor variables in the adjustment model as the percentage increase in Nagelkerke's R^2 of the adjustment model with and without ICH (partial R^2). We further examined if the prognostic effect of ICH varied with age or WFNS grade by performing likelihood ratio tests in order to compare the model with and without interaction terms (interaction of ICH with age or WFNS grade).

The relationship between time from SAH to aneurysm treatment and the outcomes of the SAH patients with ICH was investigated in the tirilazad and C-1 cohorts for whom the time from SAH to treatment was recorded ($n = 857$). First, we constructed restricted cubic spline plots to visually examine the relationship between the timing of treatment and outcome and identify potential inflection points in the relationship. Next, we fitted a proportional odds logistic regression model with time from ictus to treatment, which was dichotomized using 6 hours from SAH as the cut point, while adjusting for the effects of age, WFNS grade, aneurysm size and location, and treatment modality. This cut point was adopted to ensure consistency with previous studies. The relationship of the variables to time from ictus to treatment was investigated using Kaplan-Meier survival curve analysis and proportional Cox models. Statistical significance was set at the 5% significance level. All statistical analyses were performed using Stata (version 13; Stata Corp.) and R (version 3.1.1; R Core Team).

Results

Clinical Characteristics

We evaluated a pooled cohort of 5362 SAH patients, 1120 (20.9%) of whom presented with concurrent ICH on admission CT. Fifty-one patients (12.5%) in the C-1 study, 263 (18.6%) in the SHOP study, and 806 (22.8%) in the tirilazad study presented with ICH. The baseline characteristics of the study cohort are shown in Table 1. The average age of the patients was 52.4 years. SAH patients with ICH were slightly older than those without (53.9 vs 52.0 years; $p < 0.001$). The proportion of patients with SAH and ICH who were WFNS Grade I (i.e., the best grade) was 13.4% in comparison with 45.2% for patients who presented with only SAH. The proportion of patients with SAH and ICH who were WFNS Grade V (the worst grade) was 28.4% in comparison with 9.7% for patients

TABLE 1. Baseline characteristics comparing SAH patients with ICH to patients without ICH*

Variable	ICH Absent	ICH Present	Total
No. of patients	4242 (79.1)	1120 (20.9)	5362 (100)
Age in yrs	52.0 $\pm$ 13.7	53.9 $\pm$ 12.8	52.4 $\pm$ 13.5
Female	3296 (77.7)	879 (78.5)	4175 (77.9)
Ethnicity			
White	3226 (76.0)	913 (81.5)	4139 (77.2)
Black	437 (10.3)	84 (7.5)	521 (9.7)
Other	579 (13.7)	123 (11.0)	702 (13.1)
WFNS grade			
I	1893 (45.2)	148 (13.4)	2041 (38.5)
II	1095 (26.1)	250 (22.6)	1345 (25.4)
III	332 (7.9)	134 (12.1)	466 (8.8)
IV	466 (11.1)	258 (23.4)	724 (13.7)
V	406 (9.7)	314 (28.4)	720 (13.6)
SBP in mm Hg	143.9 $\pm$ 29.0	148.2 $\pm$ 30.7	144.83 $\pm$ 29.4
DBP in mm Hg	78.8 $\pm$ 17.8	79.9 $\pm$ 19.2	79.019 $\pm$ 18.1
Hypertension	1530 (36.8)	449 (41.4)	1979 (37.8)
Smoking†	818 (56.6)	169 (60.1)	987 (57.2)
Angina or MI	204 (4.9)	56 (5.2)	260 (4.9)
Diabetes	214 (5.1)	50 (4.6)	264 (5.0)
Fisher grade			
1	461 (11.0)	68 (6.1)	529 (10.0)
2	723 (17.3)	68 (6.1)	791 (15.0)
3	2490 (59.6)	771 (69.5)	3261 (61.6)
4	507 (12.1)	202 (18.2)	709 (13.4)
IVH	1976 (47.3)	652 (58.7)	2628 (49.7)
Location			
ACA	1070 (26.3)	361 (33.2)	1431 (27.8)
ICA	1119 (27.5)	167 (15.4)	1286 (24.9)
MCA	600 (14.8)	387 (35.6)	987 (19.2)
Posterior	685 (16.8)	48 (4.4)	733 (14.2)
Other	594 (14.6)	123 (11.3)	717 (13.9)
Size			
Small	3227 (80.8)	732 (69.2)	3959 (78.3)
Medium	659 (16.5)	278 (26.3)	937 (18.5)
Large	109 (2.7)	48 (4.5)	157 (3.1)
Treatment			
None	475 (11.2)	135 (12.1)	610 (11.4)
Clip	3309 (78.2)	920 (82.2)	4229 (79.1)
Coil	446 (10.5)	64 (5.7)	510 (9.5)
GOS score			
1	574 (14.6)	292 (28)	866 (17.4)
2	53 (1.3)	31 (3.0)	84 (1.7)
3	434 (11.0)	208 (20.0)	642 (12.9)
4	717 (18.2)	205 (20.0)	922 (18.5)
5	2155 (54.8)	307 (29.4)	2462 (49.5)
Cerebral infarction	1112 (26.5)	411 (37.0)	1523 (28.7)

* Data are presented as number of patients (%) or mean $\pm$ SD.

† History of cigarette smoking was only available in the SHOP and C-1 data sets.

who presented with only SAH. Patients with SAH who had a concurrent ICH had relatively higher incidences of a history of hypertension, cigarette smoking, angina and MI, IVH, and cerebral infarction in comparison with patients with only SAH (Table 1). The most common location of rupture in those patients with ICH was the middle cerebral artery (MCA; 35.6%), followed by the anterior cerebral artery (ACA; 33.2%). The least common site of rupture was posterior circulation (4.4%). In patients with only SAH, the most common site of rupture was the ICA (27.5%), followed by the ACA (26.3%), posterior cerebral artery (PCA), and lastly the MCA. Patients with SAH and ICH were more frequently treated by clipping in comparison with patients with SAH only (82.2% vs 78.2%) and less frequently treated by coiling (5.7% vs 10.5%). Mortality in SAH patients with ICH was 28% in comparison with 14.6% of patients without ICH (Table 1).

Associative Factors For ICH in Patients With SAH

Table 2 shows the variables identified in the backward stepwise regression model to be associated with ICH. Among the 9 variables considered, the dominance analysis based on R^2 as the fit statistic identified neurological status as the most important factor that was predictive of ICH in patients with SAH, the next being ruptured aneurysm location, aneurysm size, and patient ethnicity in order of decreasing importance. Although history of hypertension and DM were selected in the model, their effects were not statistically significant. The presence of ICH was associated with worse neurological status and larger aneurysms. In comparison with ACA, aneurysms of the MCA were more likely to be associated with ICH (OR 1.82; 95% CI 1.50–2.20), whereas aneurysms of the ICA (OR 0.41; 95% CI 0.33–0.51) and PCA (OR 0.16; 95% CI 0.12–0.22) were less likely to be associated with ICH. SAH patients who were black or other ethnicity were less likely than white patients to have concurrent ICH. Age, sex, smoking status, angina or MI, and DM were not significantly associated with the presence of ICH.

Effect of ICH on Outcome of SAH Patients

The occurrence of ICH was significantly associated with poorer outcomes across studies in the univariable analysis, with a pooled unadjusted OR value of 2.86 (95% CI 2.53–3.24) (Fig. 1). There was no significant between-study heterogeneity ($p = 0.678$). The effect of ICH was reduced to an OR value of 1.58 (95% CI 1.37–1.82) after adjusting for the fixed effect of study, age, history of hypertension, WFNS grade, aneurysm size and location, and treatment modality (Table 3). The partial R^2 of ICH was 1.45%, which suggests some added incremental value for predicting outcome. The effect of ICH did not significantly differ with age or patient neurological grade (interaction: $p = 0.101$ and 0.428 , respectively). Patients with concurrent ICH were more likely to develop cerebral infarction than those without ICH (OR 1.22; 95% CI 1.04–1.42).

Time to Treatment and Outcome of SAH Patients With ICH

Most patients (99%) had aneurysm occlusion performed within 72 hours of SAH. Patients with ICH were

TABLE 2. Predictors of ICH in patients with SAH ranked in order of decreasing importance

Predictor	OR (95% CI)
WFNS grade	
I	1
II	3.01 (2.42–3.76)
III	4.88 (3.72–6.41)
IV	7.89 (6.23–9.99)
V	10.53 (8.33–13.30)
Location	
ACA	1
ICA	0.41 (0.33–0.51)
MCA	1.82 (1.50–2.20)
Other	0.63 (0.49–0.81)
PCA	0.16 (0.12–0.22)
Size*	
Small	1
Medium	1.57 (1.31–1.88)
Large	1.60 (1.09–2.34)
Ethnicity	
White	1
Black	0.68 (0.52–0.90)
Other	0.71 (0.56–0.91)
Hypertension	1.14 (0.98–1.34)
Diabetes	0.77 (0.54–1.08)

* Small is defined as ≤ 12 mm in tirilazad and SHOP, or ≤ 15 mm in C-1.

Medium is defined as 13–24 mm in tirilazad and SHOP, or 16–25 mm in C-1.

Large is defined as ≥ 25 mm in tirilazad and SHOP, or > 25 mm in C-1.

treated earlier than those without ICH (median time 23 hours vs 27 hours, respectively); the difference in time was statistically significant after adjusting for age, neurological grade on admission, treatment modality, and the fixed effect of study in the proportional Cox model (HR 1.12; 95% CI 1.03–1.22; $p = 0.005$). The spline plot indicated that the probability of poor outcome declined with longer time to aneurysm treatment in patients with concurrent ICH (Fig. 2). The inflection point in the effect of time to treatment was approximately 18 hours. The median time for patients with ICH who had aneurysm occlusion within 6 hours of ictus was 4.75 hours, and it was 25.8 hours for those treated after 6 hours. A proportional odds model that was adjusted for the fixed effect of study only indicated that patients who presented with ICH who had intervention within 6 hours of ictus experienced poorer outcomes than those who had intervention after 6 hours (OR 2.58; 95% CI 1.67–3.98; $p = 0.001$). After further adjustment for age, WFNS grade on admission, aneurysm location, aneurysm size, and treatment modality, the OR was reduced to 1.67 (95% CI 1.04–2.69). We did a sensitivity analysis and excluded patients who received treatment after 72 hours, as such a delay may reflect late presentation, probably due to transfer from other facilities or logistic or treatment challenges, among others. The results were essentially comparable (OR 1.68; 95% CI 1.04–2.72; $p =$

FIG. 1. Forest plot showing the unadjusted effect of ICH on outcome in SAH patients stratified by study. ES = effect size.

0.035). We further performed a subgroup analysis with the C-1 cohort to include other factors in the adjusted analysis that might confound the time to treatment effect, such as midline shift, ICH volume, and location. The mean ICH volume in the C-1 cohort was 14.0 ± 21.7 ml. Intracerebral hematoma was more commonly located in the subcortical region (42.3%), frontal lobe (39.4%), and right temporal lobe (16.3%). Patients with a larger ICH volume had more timely occlusion of their aneurysms (HR 1.02; 95% CI 1.00–1.03); however, ICH volume did not significantly affect outcome (OR 1.02; 95% CI 0.99–1.04; $p = 0.089$). Including ICH volume and location and the presence of midline shift as adjustment factors in the multivariable analysis resulted to a lack of significant association between time from ictus to treatment and outcome (OR 0.99; 95% CI 0.94–1.07).

Discussion

Few studies have addressed the aneurysm and clinical characteristics in SAH patients who present with additional ICH. Abbed and Ogilvy¹ retrospectively reviewed 460 SAH patients, but their cohort included only Fisher Grade 3 and 4 patients who were surgically treated. Bruder et al.³ analyzed 174 patients with additional ICH, focusing on the effect of hematoma location on outcome. The proportion of clipped patients was 67%, which is similar to our series. Tokuda et al.²² analyzed data on 512 patients, 98 of whom presented with ICH, and all patients underwent clipping of the aneurysm. Liu and Rinkel¹⁵ studied 310 SAH patients, 75 of whom had ICH, to identify the risk factors for the ICH. Another series by Hauerberg et al. involved 815 patients who were treated prior to the introduction of endovascular coiling.⁹ Indeed, prior to our present effort, data were scarcely available, including those on patients treated by endovascular coil embolization. Our findings

support those of previous studies that suggested that factors pertaining to the aneurysm and its rupture rather than pre-ictal clinical characteristics are more critical to the pathogenesis of SAH with concurrent ICH.^{3,9,22} We found, as others have reported previously, poorer admission clinical status and a higher preponderance of MCA aneurysms in patients with ICH in comparison with patients without ICH, and the lack of an association of patient age, sex, cigarette smoking, angina or MI, hypertension, and DM with the occurrence of ICH.^{1,3,7,9,15,18,22} Our study further raises the intriguing possibility that ethnicity may play some role, as we found a 50% higher risk for concurrent ICH in white patients than other ethnic groups. The reasons for this are unknown, given in part that this analysis may be the first study to use current statistical techniques to illustrate the relative importance of the factors associated with ICH in SAH patients. The most important and only factor that strongly predicted ICH was neurological status on admission, which overwhelmed the other factors included in the model. This finding most probably reflects brain damage due to ICH, associated brain shift, and increased intracranial pressure, as well as the effect of early brain injury (EBI) that occurs immediately following SAH, which is thought to be mediated, in part, by increased intracranial pressure causing transient global cerebral ischemia.^{5,24} The additional mass effect of ICH may further contribute to raised intracranial pressure and consequentially global ischemia associated with EBI. One value of our finding may be its potential to inform triaging for emergency CT in patients who present with a history consistent with SAH, by knowing that those patients with ICH might need an urgent craniotomy and clot evacuation.

Previous studies have reported a higher incidence of mortality and unfavorable outcome in SAH patients with

TABLE 3. Results of the multivariable analysis of the effect of ICH on the outcomes of patients with SAH

Variable	Adjusted OR	Lower 95% CL	Upper 95% CL	p Value
ICH	1.58	1.37	1.82	<0.001
Age	1.03	1.03	1.04	<0.001
Sex				
Male	1			
Female	1.02	0.89	1.18	0.734
WFNS grade				
I	1			<0.001
II	1.75	1.51	2.03	<0.001
III	3.96	3.23	4.86	<0.001
IV	4.95	4.15	5.91	<0.001
V	12.06	9.92	14.67	<0.001
Location				
Anterior	1			
Posterior	1.05	0.88	1.25	0.589
Size				
Small	1			
Medium	1.54	1.33	1.79	<0.001
Large	3.03	2.17	4.23	<0.001
Treatment				
Clip	1			
Coil	1.08	0.87	1.35	0.493
None	4.20	3.45	5.11	<0.001
Hypertension	1.49	1.32	1.68	<0.001
Study				
Tirilazad	1			
SHOP	1.54	1.31	1.80	<0.001
C-1	3.52	2.81	4.39	<0.001

CL = confidence limit.

ICH in comparison with patients without ICH.^{1,7,9,22} The present study quantified the effect of ICH on outcome in the largest cohort to date, showing a 58% increase in the risk of poor outcome among patients who presented with SAH and ICH after considering other factors such as patient age, sex, neurological status on admission, aneurysm location and size, and treatment modality. Hematoma volume may be expected to influence the impact of ICH on outcome. Tokuda et al.²² reported ICH volume less than 25 ml as the only factor that was significantly associated with outcome in their cohort; we found no significant association between ICH volume and outcome in the C-1 cohort. The data regarding the added incremental effect of ICH may help guide the construction of prognostic models that incorporate multiple predictors for risk stratification after SAH. Indeed, our analysis of the SAHIT cohort suggests that the added incremental predictive value (measured as partial R^2) of ICH is higher than that of a history of hypertension, aneurysm size and location, and the Fisher grade of SAH volume—predictors that have been more readily used than ICH for building prognostic models of SAH.

FIG. 2. Spline plot showing the relationship between time to treatment and outcome in SAH patients with concurrent ICH.

ICH, therefore, may be a better predictor of outcome than these other factors.

There has been a recurrent interest in the effect of timing of treatment on the outcome of patients with SAH. With respect to patients who present with intraparenchymal extension of the hematoma, the debate has been about whether hematoma evacuation and aneurysm repair within 6 hours in comparison with such treatment after 6 hours results in better outcomes. Our analysis indicated a poorer outcome among those treated within 6 hours, and no difference in outcome after controlling for the ICH-specific characteristics in the subanalysis. Emergency evacuation of intraparenchymal hematoma, particularly large hematomas, appears logical to mitigate secondary brain injury from the mass effect. In a study by Güresir et al.,⁷ which involved 585 patients, of whom 50 (8.5%) presented with an ICH volume greater than 50 cm³, the time to aneurysm obliteration within 6 hours after ictus was the most important factor that predicted outcome at 6 months on the modified Rankin Scale. According to that study, patients who had an intervention within 6 hours are likely to have a 10-fold improvement in outcome compared with those who had a later intervention (OR 10.78; 95% CI 1.4–85.8). While there may be a benefit in outcomes in some patients who are treated within 6 hours of ictus, whether such treatment confers a greater benefit than treatment after 6 hours is unknown; recommending such treatment as standard is another issue.

Some credence to our finding is provided by Shimoda et al.,²⁰ who had previously reported that patients with ruptured MCA aneurysms who presented with diffuse SAH and ICH did not differ in terms of outcomes whether they received ultra-early treatment of the ruptured aneurysm or not; however, those patients with intrasylvian hematomas fared better when treated within 6 hours of the ictus, presumably because of the smaller volume of ICH. It has already been suggested in the cooperative study on the timing of aneurysm surgery that early admission is an adverse prognostic factor for outcome after aneurysm rupture.¹¹ According to that study, SAH patients who underwent sur-

gical intervention within 7 to 10 days of the event had a higher risk of poor outcome than those who had intervention thereafter, and the postoperative complications were comparable in both groups. In our study, some attempt was made to reflect the confounding factors that need be factored in to determine the prognostic benefit of ultra-early intervention, including patient neurological status, ICH volume and location, and the presence of midline shift. Controlling for these confounders revealed no association between poor outcome and ultra-early treatment in the C-1 cohort, suggesting that these clinical factors influenced the decision for emergent treatment and likely explain the poorer outcomes observed in those patients treated emergently in our pooled cohort. In the study by Güresir et al.,⁷ and in ours as well, ICH volume inversely correlated with time to treatment. However, unlike their study, we did not find ICH volume to significantly impact outcome, and overall we showed no benefit in outcome for ultra-early treatment. There may be reasons why patients who have ultra-early intervention may not fare better than those who have “delayed” treatment within 72 hours of ictus. It is well recognized that rebleeding occurs most frequently within 6 hours of ictus and in the presence of ICH;^{7,22} rebleeding could potentially be complicated by ultra-early intervention. Some have recently suggested that rebleeding may not necessarily be from the ruptured aneurysm.²¹ In the study by Güresir et al.,⁷ 16% of patients with ICH had CT-confirmed rebleeding in comparison with 6.3% of those patients without ICH, but the reasons for this are unknown. Additionally, hematoma evacuation during the immediate hours following SAH may aggravate EBI and impede the cerebral autoregulatory mechanisms that may have been activated to mitigate EBI.¹⁹

While our results may challenge the concept that ultra-early aggressive treatment is associated with better outcomes and may raise queries about the idea that such intervention prevents rebleeding, the limitations of our study design, as well as other studies in the literature, preclude the determination of the optimal time to treatment of SAH patients with ICH. We must assume a cautious approach in interpreting the clinical significance and management implications of our findings. Several factors influence how soon emergency hematoma evacuation and obliteration of the ruptured aneurysm is performed; our study and others currently in the literature likely cannot capture all of them. However, we have shown conflicting findings to the literature that highlight the complex and multifactorial nature of determining the optimal timing to intervention. Currently, the timing of management for ICH in SAH patients might best be decided on a case-by-case basis, as there is insufficient evidence to support emergent treatment within 6 hours as a standard of care.

The other limitations of this study include that the majority of our data originated from randomized controlled trials that excluded patients based on some other criteria; hence, our sample may not be entirely representative, though it is by far the largest sample analyzed to date. The time over which the patients were managed is substantial (1991–2013), encompassing periods with significant changes in the practice and management of SAH. Although we accounted for study effects in all analyses in

order to mitigate differences in time, we found no significant study heterogeneity. However, we may not have satisfactorily eliminated residual confounding that resulted from the wide interval over which the patients were managed. Also, heterogeneity between studies in the interpretation of CT scans is not unlikely, which may have resulted in somewhat different rates of ICH detection among studies, although the rates are within the limits seen in the literature.

Conclusions

We have characterized the clinical and aneurysm characteristics that are associated with ICH in patients presenting with SAH from ruptured aneurysms in the largest cohort to date with data derived from multiple centers, thereby highlighting the importance of neurological status on admission, aneurysm location and size, and patient ethnicity. The power and heterogeneity of the study cohort indicate we may have more reliably determined the prognostic value of ICH than any prior attempts. We were unable to determine the benefit of ultra-early intervention in SAH patients with additional ICH, suggesting the need to evaluate such patients on a case-by-case basis. Given the drawback of our study design and those of previous studies, the need therefore arises for prospective studies, including clinical trials, to more completely address the optimal timing of intervention in patients with SAH who have ICH.

Appendix

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References

1. Abbed KM, Ogilvy CS: Intracerebral hematoma from aneurysm rupture. **Neurosurg Focus** 15(4):E4, 2003
2. Azen R, Budescu DV: The dominance analysis approach for comparing predictors in multiple regression. **Psychol Methods** 8:129–148, 2003
3. Bruder M, Schuss P, Berkefeld J, Wagner M, Vatter H, Seifert V, et al: Subarachnoid hemorrhage and intracerebral hematoma caused by aneurysms of the anterior circulation: influence of hematoma localization on outcome. **Neurosurg Rev** 37:653–659, 2014
4. Fisher CM, Kistler JP, Davis JM: Relation of cerebral vasospasm to subarachnoid hemorrhage visualized by computerized tomographic scanning. **Neurosurgery** 6:1–9, 1980
5. Frontera JA, Ahmed W, Zach V, Jovine M, Tanenbaum L, Sehba F, et al: Acute ischaemia after subarachnoid haemorrhage, relationship with early brain injury and impact on outcome: a prospective quantitative MRI study. **J Neurol Neurosurg Psychiatry** 86:71–78, 2015
6. Frontera JA, Claassen J, Schmidt JM, Wartenberg KE, Temes R, Connolly ES Jr, et al: Prediction of symptomatic vasospasm after subarachnoid hemorrhage: the modified fisher scale. **Neurosurgery** 59:21–27, 2006
7. Güresir E, Beck J, Vatter H, Setzer M, Gerlach R, Seifert V, et al: Subarachnoid hemorrhage and intracerebral hematoma: incidence, prognostic factors, and outcome. **Neurosurgery** 63:1088–1094, 2008
8. Haley EC Jr, Kassell NF, Apperson-Hansen C, Maile MH, Alves WM: A randomized, double-blind, vehicle-controlled trial of tirilazad mesylate in patients with aneurysmal subarachnoid hemorrhage: a cooperative study in North America. **J Neurosurg** 86:467–474, 1997
9. Hauerberg J, Eskesen V, Rosenørn J: The prognostic significance of intracerebral hematoma as shown on CT scanning after aneurysmal subarachnoid haemorrhage. **Br J Neurosurg** 8:333–339, 1994
10. Jaja BN, Attalla D, Macdonald RL, Schweizer TA, Cusimano MD, Etminan N, et al: The Subarachnoid Hemorrhage International Trialists (SAHIT) Repository: advancing clinical research in subarachnoid hemorrhage. **Neurocrit Care** 21:551–559, 2014
11. Kassell NF, Adams HP Jr, Torner JC, Sahs AL: Influence of timing of admission after aneurysmal subarachnoid hemorrhage on overall outcome. Report of the cooperative aneurysm study. **Stroke** 12:620–623, 1981
12. Kassell NF, Haley EC Jr, Apperson-Hansen C, Alves WM: Randomized, double-blind, vehicle-controlled trial of tirilazad mesylate in patients with aneurysmal subarachnoid hemorrhage: a cooperative study in Europe, Australia, and New Zealand. **J Neurosurg** 84:221–228, 1996
13. Lanzino G, Kassell NF: Double-blind, randomized, vehicle-controlled study of high-dose tirilazad mesylate in women with aneurysmal subarachnoid hemorrhage. Part II. A cooperative study in North America. **J Neurosurg** 90:1018–1024, 1999
14. Lanzino G, Kassell NF, Dorsch NWC, Pasqualin A, Brandt L, Schmiedek P, et al: Double-blind, randomized, vehicle-controlled study of high-dose tirilazad mesylate in women with aneurysmal subarachnoid hemorrhage. Part I. A cooperative study in Europe, Australia, New Zealand, and South Africa. **J Neurosurg** 90:1011–1017, 1999
15. Liu X, Rinkel GJ: Aneurysmal and clinical characteristics as risk factors for intracerebral haematoma from aneurysmal rupture. **J Neurol** 258:862–865, 2011
16. Macdonald RL, Cusimano MD, Etminan N, Hanggi D, Hasan D, Ilodigwe D, et al: Subarachnoid Hemorrhage International Trialists data repository (SAHIT). **World Neurosurg** 79:418–422, 2013
17. Macdonald RL, Kassell NF, Mayer S, Ruefenacht D, Schmiedek P, Weidauer S, et al: Clazosentan to overcome neurological ischemia and infarction occurring after subarachnoid hemorrhage (CONSCIOUS-1): randomized, double-blind, placebo-controlled phase 2 dose-finding trial. **Stroke** 39:3015–3021, 2008
18. Niemann DB, Wills AD, Maartens NF, Kerr RS, Byrne JV, Molyneux AJ: Treatment of intracerebral hematomas caused by aneurysm rupture: coil placement followed by clot evacuation. **J Neurosurg** 99:843–847, 2003
19. Sehba FA, Hou J, Pluta RM, Zhang JH: The importance of early brain injury after subarachnoid hemorrhage. **Prog Neurobiol** 97:14–37, 2012
20. Shimoda M, Oda S, Mamata Y, Tsugane R, Sato O: Surgical indications in patients with an intracerebral hemorrhage due to ruptured middle cerebral artery aneurysm. **J Neurosurg** 87:170–175, 1997
21. Suzuki K, Ueno E, Kasuya H: Origin of sylvian hematoma in patients with subarachnoid hemorrhage: findings of extravasation on multiphase contrast-enhanced computed tomography. **World Neurosurg** 82:e747–e751, 2014
22. Tokuda Y, Inagawa T, Katoh Y, Kumano K, Ohbayashi N, Yoshioka H: Intracerebral hematoma in patients with ruptured cerebral aneurysms. **Surg Neurol** 43:272–277, 1995
23. Wartenberg KE, Schmidt JM, Claassen J, Temes RE, Frontera JA, Ostapkovich N, et al: Impact of medical complications on outcome after subarachnoid hemorrhage. **Crit Care Med** 34:617–624, 2006
24. Wartenberg KE, Sheth SJ, Michael Schmidt J, Frontera JA, Rincon F, Ostapkovich N, et al: Acute ischemic injury on diffusion-weighted magnetic resonance imaging after poor grade subarachnoid hemorrhage. **Neurocrit Care** 14:407–415, 2011
25. White IR, Royston P, Wood AM: Multiple imputation using chained equations: Issues and guidance for practice. **Stat Med** 30:377–399, 2011

Disclosures

Dr. Macdonald reports that he is the Chief Scientific Officer of Edge Therapeutics, Inc., for which he has direct stock ownership.

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Conception and design: all authors. Acquisition of data: Macdonald, Jaja. Analysis and interpretation of data: Wan, Jaja. Drafting the article: Wan, Jaja. Critically revising the article: all authors. Reviewed submitted version of manuscript: Macdonald, Schweizer. Statistical analysis: Wan, Jaja. Study supervision: Schweizer.

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