Predictors for Cerebral Edema in Acute Ischemic Stroke Treated With Intravenous Thrombolysis

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Background and Purpose—Cerebral edema (CED) is a severe complication of acute ischemic stroke. There is uncertainty regarding the predictors for the development of CED after cerebral infarction. We aimed to determine which baseline clinical and radiological parameters predict development of CED in patients treated with intravenous thrombolysis.

Methods—We used an image-based classification of CED with 3 degrees of severity (less severe CED 1 and most severe CED 3) on postintravenous thrombolysis imaging scans. We extracted data from 42 187 patients recorded in the SITS International Register (Safe Implementation of Treatments in Stroke) during 2002 to 2011. We did univariate comparisons of baseline data between patients with or without CED. We used backward logistic regression to select a set of predictors for each CED severity.

Results—CED was detected in 9579/42 187 patients (22.7%: 12.5% CED 1, 4.9% CED 2, 5.3% CED 3). In patients with CED versus no CED, the baseline National Institutes of Health Stroke Scale score was higher (17 versus 10; $P<0.001$), signs of acute infarct was more common (27.9% versus 19.2%; $P<0.001$), hyperdense artery sign was more common (37.6% versus 14.6%; $P<0.001$), and blood glucose was higher (6.8 versus 6.4 mmol/L; $P<0.001$). Baseline National Institutes of Health Stroke Scale, hyperdense artery sign, blood glucose, impaired consciousness, and signs of acute infarct on imaging were independent predictors for all edema types.

Conclusions—The most important baseline predictors for early CED are National Institutes of Health Stroke Scale, hyperdense artery sign, higher blood glucose, decreased level of consciousness, and signs of infarct at baseline. The findings can be used to improve selection and monitoring of patients for drug or surgical treatment. **(*Stroke*. 2017;48:2464-2471. DOI: 10.1161/STROKEAHA.117.018223.)**

Key Words: cerebral edema ■ cerebral infarct ■ intracerebral hemorrhage ■ outcome ■ thrombolysis

Cerebral edema (CED) is a severe complication of acute ischemic stroke and is the cause of death in 5% of all patients with cerebral infarction.[1,2] CED is caused by endothelial dysfunction of the capillaries, resulting in breakdown of the blood–brain barrier (BBB).[3] Edema causes tissue shifts and increased intracranial pressure that can cause death, usually between the second and fifth day after stroke onset.[4,5] A large and potentially life-threatening infarct of the territory of the middle cerebral artery territory is often called a malignant middle cerebral artery infarct.[1] If treated conservatively, ≈50% to 80% of patients with this condition die.[6–8] Surgical treatment by early decompressive hemicraniectomy decreases mortality in selected patients, and decompressive hemicraniectomy is recommended by leading practice guidelines.[9]

Clinical studies show no apparent increase of risk of CED in ischemic stroke patients receiving intravenous thrombolysis (IVT). However, there is experimental evidence that IVT could impair the BBB and cause CED.[10]

There are few data on risk factors for the development of CED after acute ischemic stroke, including patients receiving IVT. A review article found that the major determinants for life-threatening CED after middle cerebral artery infarction were size of infarct, size of perfusion deficit, and need for mechanical ventilation.[11] Previous studies in patients treated

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with IVT found that baseline National Institutes of Health stroke scale (NIHSS), onset-to-treatment time (OTT), hyperdense artery sign (HAS) and early infarct signs on first computed tomography,[12] and presence of a large ischemic core at baseline[13] were independent predictors of CED.

We aimed to determine which baseline clinical and radiological parameters predict development of early CED in patients with acute ischemic stroke treated with IVT.

Methods

Subjects

We extracted data collected in the SITS-ISTR (Safe Implementation of Treatments in Stroke – International Stroke Thrombolysis Registry), an internet-based academic interactive, prospective registry for the monitoring of thrombolytic treatment in acute ischemic stroke. The methods of data collection have been described in detail elsewhere.[14] Patients with presumed ischemic stroke treated with IVT recorded during years 2002 to 2011 were extracted.

Variables

Data collected for this study were baseline characteristics including demographic, risk factors, medications, stroke severity as measured by NIHSS, impaired consciousness as measured by NIHSS item 1a, imaging data regarding signs of current ischemia and hyperdense artery sign, post-IVT imaging data on cerebral hemorrhages and edema and functional outcome at 3 months as measured by modified Rankin Scale (mRS). Follow-up computed tomography or magnetic resonance imaging brain imaging was performed between 22 and 36 hours after alteplase treatment, or earlier if clinically indicated, and at additional points in time at the discretion of the treating clinicians.

Outcomes

The primary outcome measure for this study was CED on imaging at 22 to 36 hours and additional post-treatment scans, rated by local investigators. If present, CED was classified into 3 CED types based on the radiological appearance: CED 1 (focal edema up to one third of the hemisphere), CED 2 (focal edema greater than one third of the hemisphere), and CED 3 (edema with midline shift). The SITS-MOST edema grading (SITS Monitoring Study) was partly based on ECASS-2 (Second European Co-Operative Acute Stroke Study) and expertise from the SITS-MOST brain imaging committee. Although not explicitly mentioned in the study protocol, signs of focal edema usually are defined as narrowing of the cerebrospinal fluid space, for example, effacement of cortical sulci or ventricular compression.[15]

Secondary outcome measures were the proportion of patients with symptomatic intracerebral hemorrhage (SICH), according to 3 definitions, and functional outcome as assessed by mRS score at 3 months. SICH per SITS-MOST was defined as local or remote parenchymal hemorrhage type 2 on the 22 to 36 hours post-treatment imaging, combined with a neurological deterioration of ≥4 points on the NIHSS from baseline, or from the lowest NIHSS value between baseline and 24 hours, or leading to death.[14] SICH per ECASS 2 was defined as any hemorrhage plus a neurological deterioration of ≥4 points on the NIHSS from baseline, or from the lowest NIHSS value after baseline to 7 days, or leading to death.[14] SICH per NINDS was defined as a hemorrhage that leads to any neurological deterioration (NIHSS score ≥1) or death within 7 days.[14]

Ethics approval was obtained from the Stockholm Regional Ethics Committee for this project as part of the SITS-MOST II study framework. Ethics approval and patient consent for participation in the SITS-ISTR were obtained in countries that required this; other countries approved the registry for anonymized audit.

Statistical Analysis

In an initial descriptive analysis, we compared baseline factors between patients with and without CED and between CED types. Linear regression methods and Pearson's χ^2 test were used. Estimation of proportions was based on reported cases, excluding unknown or uncertain values from the denominator, as previously reported. A significance level of $P<0.05$ was used throughout the whole study.

Using logistic regression, we investigated univariable relationships between baseline variables and each CED type (versus no CED). To study the relationship over a range of values, we categorized continuous variables into quartiles and used logistic regression to address 2 questions: first, whether odds ratios (ORs) differed across categories (test of homogeneity) and, second, whether there was a linear trend in the odds of the outcome with increasing values (test for trend).

To find the most important predictors for CED types 1, 2, and 3 (versus no CED), we entered all statistically significant variables from the univariable analysis into multivariable logistic regression models, one for every type. Backward elimination ($P<0.05$ to retain) was used to select a final set of predictors for each CED type. We evaluated the predictive ability of these models by calculating the area under the curve by receiver operating characteristic analyses and the Hosmer–Lemeshow test.

Results

In total, 45 071 ischemic stroke patients treated with IVT across 41 countries worldwide from a total of 752 centers were recorded in the SITS-ISTR during 2002 and 2011. For 2884 of these patients, data on CED at 22 to 36 hours (or any extra investigation) was either missing or uncertain. The remaining 42 187 patients were included in the study. Any type of CED was seen in 9579 patients (22.7% of the study cohort). Of these, CED 1 was present in 5260 patients (12.5% of study cohort and 54.9% of all edema), CED 2 in 2073 (4.9% of study cohort and 21.6% of all edema), and CED 3 in 2246 (5.3% of study cohort and 23.4% of all edema). Of all edema, >99% was seen on the 22 to 36 hours examination. A minority of patients, 3.5%, had their edema status changed between the 22 and 36 hours examination and any extra examination. There were no changes into a lower grade of edema.

Baseline and demographic characteristics are shown in Table 1. Almost all baseline variables showed statistically significant ($P<0.05$) differences between patients with and without any type of CED, the only exceptions being age and any antiplatelet treatment. The median NIHSS score was 7 points higher in any CED patients than in no CED patients. Patients with CED had an 18% absolute higher frequency of impaired consciousness, 9% higher frequency of signs of current ischemia on baseline imaging, 23% higher frequency of HAS and 0.4 mmol/L higher median blood glucose than patients without edema. Furthermore, diabetes mellitus, hypertension, atrial fibrillation, and congestive heart failure were more common in the CED group. There were more patients on oral anticoagulant in patients with CED versus no CED; nevertheless, this variable was omitted from further analyses because of an overall low prevalence (2.5%), as expected in patients who receive IVT.

In univariable analysis (Table 2), the following clinical or radiological baseline variables were positively associated (increased risk of edema development) with all 3 edema types ($P<0.05$) compared with no edema: NIHSS, impaired consciousness, signs of current ischemia on imaging, HAS, and blood glucose. Point estimates of ORs in most cases increased with severity of edema. Highest OR was observed for HAS in CED 1 and CED 3. In addition, history of diabetes mellitus, hypertension, atrial fibrillation, and congestive heart failure were positively associated with all 3 CED types. ORs for these

Table 1. Baseline Variables in Patients Without and With Edema

Variable	N	No CED (n=32 608)	Any CED (n=9579)	*P* Value
Age, y, median (IQR)	42 169	70 (60–77)	70 (60–77)	0.65*
Male sex, %	42 187	57.5	56.1	0.01†
OTT, min, median (IQR)	41 543	147 (117–175)	145 (117–170)	<0.001*
NIHSS score, median (IQR)	41 595	10 (6–15)	17 (13–20)	<0.001*
NIHSS item 1a ≥1, %	41 591	16.6	34.2	<0.001†
Infarct signs on imaging, %	39 482	19.2	27.9	<0.001†
Hyperdense artery sign, %	39 294	14.6	37.6	<0.001†
Blood glucose, mmol/L, median (IQR)	39 777	6.44 (5.60–7.80)	6.8 (5.83–8.30)	<0.001*
Mean arterial pressure, mm Hg, median (IQR)	41 304	106 (97–115)	105 (95–114)	<0.001*
Previous stroke, %	41 566	13.7	11.3	<0.001†
Previous TIA, %	7354	8.2	5.5	<0.001†
Current smoker, %	38 878	23.1	20.7	<0.001†
Diabetes mellitus, %	41 576	16.6	19.6	<0.001†
Hypertension, %	41 426	62.9	66.1	<0.001†
Hyperlipidemia, %	38 295	34.3	35.9	0.005†
Atrial fibrillation, %	41 222	23.2	30.5	<0.001†
Congestive heart failure, %	41 292	8.1	10.7	<0.001†
Any antiplatelet treatment, %	41 614	36.2	36.1	0.99†
Statin treatment, %	7356	28.5	25.7	0.03†
Oral anticoagulant treatment, %	41 932	2.36	3.06	<0.001†

ANOVA indicates analysis of variance; CED, cerebral edema; IQR, interquartile range; and NIHSS, National Institutes of Health Stroke Scale.
*ANOVA.
†Pearson χ^2 test.

associations were modest, <1.6. Previous stroke and current smoker were negatively associated (lower risk of edema development) with all 3 types. The following variables had a negative association with only 1 or 2 CED types: male sex (CED 1 and CED 3), OTT (CED 1 and CED 2), mean arterial pressure (CED 1), previous transient ischemic attack (CED 1 and CED 3), and statin treatment (CED 1). Age and antiplatelet treatment were not statistically associated with any edema type.

When categorized in quartiles (Table III in the online-only Data Supplement), baseline NIHSS and blood glucose were associated ($P<0.05$) with all 3 edema types in tests for both trend and homogeneity. There was a clear tendency for higher OR of edema with higher values of NIHSS and blood glucose. Age showed a positive association in tests for both homogeneity and trend only for CED 2. There was a weak negative association between OTT and mean arterial pressure and edema, with higher values of OTT and mean arterial pressure showing somewhat lower ORs for edema.

Table 3 shows results from the stepwise regression analysis with continuous variables categorized in quartiles. Because few patients had information on previous transient ischemic attack and statin treatment, these variables were excluded from multivariable analyses. All final models contained baseline total NIHSS score, impaired consciousness, signs of current ischemia on imaging, HAS, and baseline blood glucose. The final model for prediction of CED 3 contained only these variables. The model for CED 1 additionally contained sex, OTT, previous stroke, hyperlipidemia, and atrial fibrillation. The model for CED 2 additionally contained age, previous stroke, diabetes mellitus, hypertension, atrial fibrillation, and congestive heart failure. Baseline total NIHSS score was the strongest predictor for all types of CED, with a highest OR of 16.5 for CED 3 in patients with NIHSS score ≥17. The second strongest predictor for CED was HAS at baseline imaging with a highest OR of 2.5 for CED 3. Baseline blood glucose ≥7.9 mmol/L significantly predicted all types of edema with an OR of 1.9 for CED 3. ORs for other variables ranged between 1 and 2. Previous stroke had a significantly lower OR for CED 1 and CED 2. Receiver operating characteristic analysis resulted in similar area under the curves for all 3 models, 0.72 to 0.82, indicating good to strong discrimination ability. The Hosmer–Lemeshow test ruled out gross lack of fit for the CED 1 and CED 2 models but not for CED 3.

The most common etiologies of stroke, according to *International Classification of Diseases* Tenth Revision, were cardiac emboli (30.2%) and large vessel disease, including carotid stenosis (35.2%). As patients with more severe edema tended to die early, a large proportion of them did not receive an *International Classification of Diseases* diagnosis in the registry.

The proportions of patients with various definitions of SICH are shown in Figure 1. The frequency of all types of

Table 2. Univariable Associations Between Baseline Variables and CED Types

	CED 1		CED 2		CED 3	
Variable	OR	95% CI	OR	95% CI	OR	95% CI
Age	1.00/10 y	0.98–1.02	1.06/10 y	1.02–1.10	0.97/10 y	0.94–1.00
Male sex	0.94	0.88–0.99	0.99	0.91–1.09	0.90	0.83–0.99
OTT	0.97/30 min	0.95–0.98	0.96/30 min	0.94–0.99	0.99/30 min	0.96–1.02
NIHSS score	1.12/point	1.11–1.12	1.16/point	1.15–1.17	1.19/point	1.18–1.20
NIHSS item 1a ≥1	2.04	1.91–2.19	2.98	2.72–3.28	3.89	3.56–4.25
Infarct signs on imaging	1.49	1.39–1.60	1.63	1.47–1.81	1.99	1.80–2.19
Hyperdense artery sign	3.05	2.85–3.26	3.66	3.32–4.03	4.65	4.24–5.10
Blood glucose	1.04/mmol	1.03–1.05	1.05/mmol	1.03–1.06	1.09/mmol	1.08–1.11
Mean arterial pressure, mm Hg, median (IQR)	0.93/10 mm Hg	0.91–0.95	0.99/10 mm Hg	0.95–1.02	1.03/10 mm Hg	1.00–1.06
Previous stroke	0.81	0.74–0.88	0.80	0.69–0.92	0.83	0.72–0.95
Previous TIA	0.68	0.50–0.94	0.82	0.53–1.27	0.41	0.21–0.77
Current smoker	0.92	0.85–0.99	0.77	0.68–0.87	0.84	0.75–0.94
Diabetes mellitus	1.13	1.05–1.22	1.34	1.20–1.50	1.34	1.21–1.49
Hypertension	1.09	1.03–1.16	1.24	1.13–1.37	1.22	1.12–1.34
Hyperlipidemia	1.09	1.02–1.16	1.11	1.00–1.22	1.01	0.92–1.11
Atrial fibrillation	1.36	1.28–1.45	1.59	1.45–1.75	1.55	1.41–1.70
Congestive heart failure	1.34	1.21–1.48	1.59	1.38–1.83	1.24	1.07–1.43
Any antiplatelet treatment	0.95	0.90–1.01	1.09	0.99–1.19	1.03	0.94–1.12
Statin treatment	0.83	0.70–0.99	0.96	0.74–1.23	0.87	0.67–1.14

Reference: no CED. CED indicates cerebral edema; CI, confidence interval; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; OTT, onset-to-treatment time; and TIA, transient ischemic attack.

SICH increased by severity of CED, and the most severe type of SICH, that is, SICH per SITS-MOST, was detected in 15.9% of patients with CED 3 compared with 0.5% in patients with no edema.

Follow-up with mRS scoring at 3 months was completed for 33 737 patients, that is, 80% of the study cohort (Figure 2). The proportions of deaths (mRS score 6) at follow-up were 8% (no CED), 18% (CED 1), 39% (CED 2), and 65% (CED 3). The proportions of patients having reached mRS score 0 to 2 at follow-up were 66% (no CED), 34% (CED 1), 12% (CED 2), and 5% (CED 3).

Discussion

This is an extensive study examining the predictors for CED after acute ischemic stroke treated with IVT. We found that 5 variables at baseline independently predicted CED of all types, including the most severe edema with midline shift, CED 3: stroke severity at baseline as measured by NIHSS, level of consciousness, baseline blood glucose, HAS, and signs of acute ischemia on baseline imaging.

The main outcome measurement, presence of edema classified into 3 types, has been used previously in the ECASS-2 and ECASS-3 trials (although not mentioned in the final publication),[16,17] in a phase II clinical trial of imatinib[18] and in an analysis of local data from Helsinki.[12] Furthermore, variants of similar edema scales, with 2 or 3 degrees of edema, have been used in several publications.[13,19–21]

Among the predictors in our study, baseline NIHSS score was the strongest predictors of any type of CED. NIHSS correlates with infarct volume and, thus, with development of edema.[22,23] The categorical use of NIHSS score in our study is more helpful in the clinical situation compared with merely showing NIHSS as continuous variable.

Our findings that baseline NIHSS, signs of current ischemia, and HAS on baseline imaging predicted CED development are consistent with a single center data from Helsinki.[12] Because the HAS and signs of early ischemia are themselves associated with more proximal vessel occlusions and, thus, to larger infarct volume, our results are also consistent with previous findings that in both IVT and non-IVT patients, a major predictor for severe brain edema is the presence of a large ischemic core at baseline, as measured by computed tomography or magnetic resonance imaging.[13,19,24–27]

For 2 independent predictors, blood glucose and level of consciousness, this study adds confirmation of previous observations. Baseline blood glucose was an independent predictor for CED development in our study, including severe edema, as was indicated but not statistically significantly associated in some earlier studies.[12,28,29] One explanation for this may be an impaired BBB caused by high levels of glucose.[30] Level of consciousness has been found to be an independent predictor of all types of CED.[19]

History of previous stroke was the only independent predictor that was associated with lower risk of development of

Table 3. Final Multivariable Models for Prediction of CED Types

	CED 1*			CED 2†			CED 3‡		
Variable	OR	95% CI	*P* Value	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Age				0.99	0.99–1.00	0.001			
Male sex	1.10	1.02–1.18	0.013						
OTT, min									
117–145	1.10	1.00–1.22	0.063						
146–174	1.15	1.04–1.28	0.006						
≥175	1.10	0.99–1.22	0.075						
NIHSS score									
7–11	1.85	1.61–2.13	<0.001	2.83	2.09–3.84	<0.001	2.10	1.52–2.90	<0.001
12–16	3.75	3.27–4.29	<0.001	7.86	5.87–10.51	<0.001	8.11	6.02–10.91	<0.001
≥17	5.64	4.92–6.46	<0.001	15.41	11.55–20.56	<0.001	16.50	12.3–22.11	<0.001
NIHSS item 1a ≥1	1.11	1.02–1.21	0.019	1.36	1.22–1.53	<0.001	1.58	1.42–1.76	<0.001
Infarct signs on imaging	1.27	1.17–1.39	<0.001	1.31	1.15–1.48	<0.001	1.52	1.35–1.70	<0.001
Hyperdense artery sign	2.09	1.92–2.26	<0.001	2.13	1.90–2.39	<0.001	2.51	2.25–2.79	<0.001
Blood glucose, mmol/L									
5.67–6.53	1.07	0.96–1.19	0.233	0.97	0.83–1.13	0.715	1.08	0.92–1.27	0.319
6.54–7.89	1.21	1.09–1.34	<0.001	1.05	0.95–1.29	0.209	1.30	1.11–1.51	0.001
≥7.90	1.35	1.22–1.50	<0.001	1.22	1.08–1.48	0.004	1.93	1.67–2.24	<0.001
Previous stroke	0.81	0.72–0.90	<0.001	0.84	0.71–0.99	0.034			
Diabetes mellitus				1.23	1.06–1.42	0.005			
Hypertension				1.19	1.06–1.42	0.005			
Hyperlipidemia	1.11	1.03–1.19	0.007						
Atrial fibrillation	1.12	1.03–1.21	0.006	1.21	1.07–1.36	0.002			
Congestive heart failure				1.23	1.04–1.46	0.014			

Reference: no CED. For continuous variables, odds ratio reference (OR 1.00) is the lowest quartile. AUC indicates area under the curve; CED, cerebral edema; CI, confidence interval; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; and OTT, onset-to-treatment time.

*Model AUC=0.72. Hosmer–Lemeshow *P*=0.19.

†Model AUC=0.79. Hosmer–Lemeshow *P*=0.59.

‡Model AUC=0.82. Hosmer–Lemeshow *P*=0.02.

edema, in our cohort CED 1 and CED 2. This finding remains largely unexplained. However, a loss of brain tissue because of previous stroke might speculatively cause a lower risk of midline shift and, thus, explain a lower risk of CED 3, which was seen as a univariable relationship but not in the final multivariable model.

The frequency of CED is consistent with other published cohorts, taking into account that the definitions of CED vary. In the Helsinki cohort, which used the same imaging definition of edema, 28% had any type of CED compared with the 23% in ours. This moderate difference could partly be explained by a wider and clear definition of infarct sign and single center reading of imaging data in the Helsinki cohort compared with local reading of imaging scans in a large number of centers in our study cohort who might have missed subtle sign of current ischemia in the imaging scans. In support of this, the frequency of signs of current ischemia in baseline imaging was higher in Helsinki cohort (50%–71%) compared with that in our study (26%–32%). Also, frequency of CED 2 and 3 was similar between our and Helsinki cohort (10%). Only limited data are available on frequency and outcome of CED in IVT versus non-IVT patients. Using a definition of symptomatic infarct swelling, a meta-analysis found around 10% symptomatic infarct swelling in both IVT and non-IVT patients.[31] Again, this is similar to the frequency of CED 2 and CED 3 in our study. Another cohort study of IVT patients, using a 3-level edema imaging grading scheme different from ours, found a 45%, that is, clearly higher, frequency of any CED.[13,32] Despite this, the frequency of the most severe edema type, 6.8%, was similar to the 5.3% that we found. This is also similar to reported result from IST-3 (The Third International Stroke Trial) where 4% of patients had the most severe edema type, symptomatic swelling with midline shift, within the first 7 days.

Patients with CED had a worse 3-month functional outcome than patients without edema. Functional outcome at 3 months progressively worsened with increasing CED. This is consistent with previously reported data.[12] The deleterious effect of CED may not only be because of larger infarcts because a study indicates that the presence of CED (as measured by magnetic resonance imaging) independently predicts

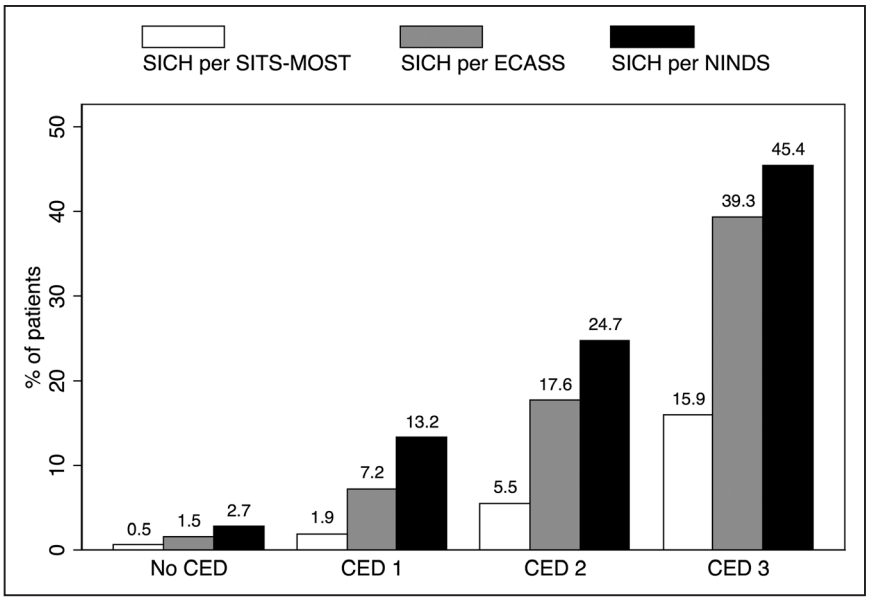

Figure 1. Distribution of symptomatic intracerebral hemorrage (SICH) among patients with different cerebral edema (CED) types on imaging at follow-up. ECASS indicates Second European Co-Operative Acute Stroke Study; NINDS, National Institute of Neurological Disorders and Stroke; and SITS-MOST, SITS Monitoring Study.

worse outcome also in smaller infarcts.[33] The absolute excess mortality at 3 months, compared with patients without edema, was between 10% and 57%. The 65% mortality at 3 months was comparable to that of previous observational studies, as well as control groups of clinical trials of early decompressive hemicraniectomy.[1,6]

This study adds support to the hypothesis, tested in animal studies, that both CED and SICH share a common pathway of impaired BBB. Animal studies have suggested that IVT using tPA (tissue-type plasminogen activator) disrupts the BBB, thus, increasing the risk for both CED and hemorrhage.[10] Furthermore, animal studies and a pilot clinical study indicate that drugs that maintain the integrity of BBB may improve clinical outcome after acute ischemic stroke in tPA-treated patients.[18,34,35] In our study, CED was associated with all types of SICH. Our data do not allow conclusions about the risk of CED in IVT patients versus non-IVT patients. From published studies, there is no definite clinical evidence that the risk of CED is increased by IVT.[11,31] In-depth analysis of the association of SICH and CED in IVT patients, and the impact of individual and combined effect of these variables on long-term functional outcome, will be the subject of a separate analysis.

There are some limitations to this study. First, the definition of edema is imaging-based, done mostly with computed tomography, and not based on other clinical findings or tissue analysis. As with other similar definitions, we have no data on its sensitivity. Moreover, the edema classification we used is 2 decades old and needs a modification in the future, in combination with modern imaging and clinical data by prospective study. As a part of the ischemic process, early or mild edema may be difficult to distinguish from infarction.[36] However, we think that this could potentially be problematic only in CED 1 where the radiological findings are more subtle. Second, because of the timing of imaging, our results are relevant for the prediction edema at 22 to 36 hours, that is, early, using data available at baseline. Third, it is an observational study based on retrospective analysis, although data were collected

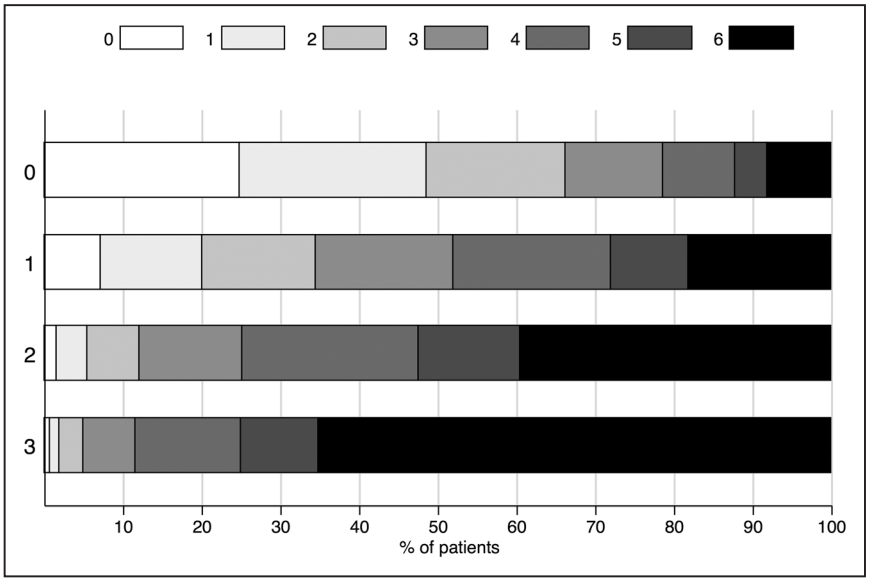

Figure 2. Distribution of modified Rankin Scale at 3 months among patients with different cerebral edema (CED) types.

prospectively. The outcomes were self-reported by local investigators who, furthermore, had varying degrees of training. However, the relatively simple definitions of edema should help to avoid a potential information bias. Fourth, missing and unknown data may have influenced the results. Thus, there is a potential bias of patient selection. However, the rate of missing data was low for most variables. Fifth, we did not record until recently the rates of anti-edema treatment such as decompressive hemicraniectomy and medical therapy. However, no medical therapy has proven effective in controlled trials, and the rates of decompressive hemicraniectomy have been low in published studies.[37–40] Sixth, we did not analyze infarct volume. In the SITS database, there is an optional data entry possibility for volume of ischemia or infarction. However, infarct volume is rarely entered in the database by the centers, and hence, we could not perform an analysis of impact of infarct size on the development of CED. Finally, we do not claim that this is a study of causal relationships. Although we did multivariable analysis to adjust for recorded baseline differences, there is still a potential for residual confounding because of factors not recorded among the baseline variables.

In conclusion, we found that the most important baseline predictors for early CED were baseline NIHSS, hyperdense artery sign, signs of current ischemia, level of consciousness, and higher blood glucose. We conclude that some of these predictors are associated with a large infarct at baseline or BBB damage. Based on these clinical predictors, patients at risk of CED can potentially be selected for close monitoring or treatment. Before routinely doing this, our findings may need to be confirmed in a prospective study with a standardized reading of image data.

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Disclosures

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Predictors for Cerebral Edema in Acute Ischemic Stroke Treated With Intravenous Thrombolysis

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SUPPLEMENTAL MATERIAL

Predictors for cerebral edema in acute ischemic stroke treated with IV thrombolysis

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Contains Table I – V

Variable	N	No CED n=32608	CED1 n=5260	CED2 n=2073	CED3 n=2246	Overall P
Age, years, median (IQR)	42169	70 (60–77)	70 (60–77)	71 (61–77)	70 (59–77)	.002 *
Male gender, %	42187	57.5	56.0	57.4	55.1	.029 †
OTT, min, median (IQR)	41543	147 (117–175)	145 (116–170)	145 (115–170)	145 (120–175)	<.001 *
NIHSS score, median (IQR)	41595	10 (6–15)	16 (11–19)	17 (14–21)	18 (15–21)	<.001 *
NIHSS item 1a ≥1, %	41591	16.6	28.9	37.2	43.6	<.001 †
Infarct signs on imaging, %	39482	19.2	26.1	27.9	32.0	<.001 †
Hyperdense artery sign, %	39294	14.6	34.3	38.5	44.4	<.001 †
Blood glucose, mmol/l, median (IQR)	39777	6.44 (5.60–7.80)	6.70 (5.80–8.11)	6.80 (5.83–8.30)	7.00 (6.00–8.72)	<.001 *
Mean arterial pressure, mmHg, median (IQR)	41304	106 (97–115)	104 (95–113)	106 (97–115)	107 (97–116)	<.001 *
Previous stroke, %	41566	13.7	11.3	11.2	11.6	<.001 †
Previous TIA, %	7354	8.2	5.7	6.8	3.5	.001 †
Current smoker, %	38878	23.1	21.6	18.8	20.2	<.001 †
Diabetes mellitus, %	41576	16.6	18.3	21.0	21.1	<.001 †
Hypertension, %	41426	62.9	64.9	67.8	67.5	<.001 †
Hyperlipidemia, %	38295	34.3	36.2	36.6	34.5	.018 †
Atrial fibrillation, %	41222	23.2	29.1	32.5	31.9	<.001 †
Congestive heart failure, %	41292	8.1	10.5	12.2	9.8	<.001 †
Any antiplatelet treatment, %	41614	36.1	35.1	38.1	36.8	.089 †
Statin treatment, %	7356	28.5	24.9	27.7	25.8	.144 †

Table I. Baseline variables by CED type.

* ANOVA
† Pearson chi-square test

Variable	Any CED (CED 1, 2 or 3)		CED 2 or 3		CED 3	
	OR	95% CI	OR	95% CI	OR	95% CI
Age	1.00/10 years	0.99–1.02	1.01 /10 years	0.99–1.04	0.97/10 years	0.93–1.00
Male gender	0.94	0.90–0.99	0.95	0.90–1.02	0.91	0.84 –0.99
OTT	0.97/30 min.	0.96–0.99	0.98/30 min.	0.96–1.00	1.00/30 min.	0.97–1.03
NIHSS score	1.15/point	1.15–1.16	1.16/point	1.15–1.17	1.16/point	1.15–1.16
NIHSS item 1a ≥1	2.61	2.48–2.74	3.04	2.85–3.25	3.23	2.96–3.53
Infarct signs on imaging	1.63	1.55–1.72	1.70	1.58–1.83	1.83	1.66–2.01
Hyperdense artery sign	3.51	3.33–3.70	3.38	3.15–3.62	3.51	3.21–3.84
Blood glucose	1.06/mmol	1.05–1.07	1.06/mmol	1.05–1.08	1.08/mmol	1.07–1.10
Mean arterial pressure, mmHg, median (IQR)	0.96/10 mmHg	0.95–0.98	1.02/10 mmHg	0.99–1.04	1.04/10 mmHg	1.01–1.07
Previous stroke	0.81	0.75–0.87	0.84	0.76–0.93	0.86	0.75–0.98
Previous TIA	0.66	0.51–0.84	0.65	0.45–0.93	0.42	0.22–0.80
Current smoker	0.87	0.82–0.92	0.82	0.75–0.89	0.86	0.77–0.97
Diabetes mellitus	1.22	1.15–1.30	1.32	1.22–1.43	1.30	1.17–1.45
Hypertension	1.15	1.10–1.21	1.22	1.14–1.30	1.20	1.09–1.31
Hyperlipidemia	1.07	1.02–1.13	1.04	0.97–1.12	0.99	0.90–1.09
Atrial fibrillation	1.45	1.38–1.53	1.50	1.40–1.61	1.45	1.32–1.59
Congestive heart failure	1.37	1.27–1.48	1.34	1.21–1.49	1.15	1.00–1.33
Any antiplatelet treatment, %	1.00	0.95–1.05	1.06	1.00–1.14	1.03	0.94–1.13
Statin treatment	0.87	0.76–0.99	0.93	0.77–1.13	0.89	0.68–1.16

Table II. Univariable associations between baseline variables and CED outcomes.

Variable	CED 1			CED 2			CED 3		
	OR	95% CI	P *	OR	95% CI	P *	OR	95% CI	P *
Age, years			.41			<.001			.25
60–69	0.94	0.86–1.02		1.06	0.93–1.21		0.90	0.80–1.02	
70–76	0.99	0.91–1.08		1.27	1.12–1.45		0.96	0.85–1.08	
≥77	0.98	0.90–1.06		1.24	1.09–1.41		0.90	0.80–1.01	
OTT, min			<.001			.04			.07
117–145	1.03	0.95–1.12		0.99	0.88–1.13		1.15	1.02–1.30	
146–174	1.06	0.98–1.15		1.01	0.89–1.15		1.04	0.92–1.18	
≥175	0.88	0.81–0.96		0.86	0.76–0.98		1.00	0.89–1.13	
NIHSS score			<.001			<.001			<.001
7–11	2.02	1.79–2.28		3.38	2.55–4.48		2.49	1.85–3.34	
12–16	4.44	3.95–4.98		11.15	8.52–14.57		11.82	9.03–15.48	
≥17	7.69	6.88–8.60		25.57	19.69–33.21		30.35	23.34–39.46	
Blood glucose, mmol/l			<.001			<.001			<.001
5.67–6.52	1.11	1.01–1.21		1.06	0.93–1.22		1.15	1.00–1.33	
6.53–7.89	1.33	1.22–1.45		1.39	1.22–1.59		1.54	1.35–1.76	
≥7.90	1.41	1.30–1.54		1.60	1.41–1.82		2.13	1.87–2.41	
Mean arterial pressure, mmHg			<.001			.84			.28
96.6–105.6	0.90	0.83–0.97		1.00	0.88–1.13		0.99	0.87–1.12	
105.7–114.9	0.81	0.75–0.88		1.00	0.88–1.13		1.08	0.96–1.23	
≥115.0	0.78	0.72–0.84		0.95	0.84–1.08		1.08	0.96–1.22	

Table III. Univariable associations between quartiles of continous variables and CED types. Reference: CED 0.
Odds ratio reference (OR 1.00) is the lowest quartile.

* Overall P-value for homogeneity (P-value for trend not shown)

Variable	Any CED (CED 1, 2 or 3)			CED 2 or 3			CED 3		
	OR	95% CI	P *	OR	95% CI	P *	OR	95% CI	P *
Age, years			.070			.068			.248
60–69	0.95	0.89–1.02		0.98	0.89–1.07		0.91	0.80–1.02	
70–76	1.04	0.97–1.11		1.09	1.00–1.20		0.95	0.84–1.07	
≥77	1.01	0.95–1.08		1.05	0.96–1.15		0.89	0.79–1.00	
OTT, min			<.001			.072			.113
117–145	1.05	0.98–1.12		1.07	0.98–1.17		1.15	1.02–1.29	
146–174	1.05	0.98–1.12		1.02	0.93–1.12		1.03	0.91–1.17	
≥175	0.90	0.84–0.96		0.95	0.87–1.04		1.03	0.91–1.16	
NIHSS score			<.001			<.001			<.001
7–11	2.23	2.01–2.48		2.81	2.29–3.45		2.34	1.75–3.15	
12–16	6.06	5.49–6.70		9.93	8.20–12.02		9.65	7.37–12.64	
≥17	12.37	11.23–13.62		21.42	17.78–25.81		20.64	15.88–26.83	
Blood glucose, mmol/l			<.001			<.001			<.001
5.67–6.52	1.11	1.03–1.19		1.09	0.99–1.21		1.14	0.99–1.31	
6.53–7.89	1.39	1.30–1.49		1.41	1.28–1.55		1.46	1.28–1.67	
≥7.90	1.60	1.50–1.71		1.77	1.61–1.94		1.98	1.74–2.25	
Mean arterial pressure, mmHg			.001			.359			.094
96.6–105.6	0.94	0.88–1.00		1.01	0.92–1.11		1.00	0.89–1.14	
105.7–114.9	0.91	0.85–0.97		1.07	0.98–1.17		1.11	0.99–1.26	
≥115.0	0.88	0.82–0.94		1.06	0.96–1.15		1.12	1.00–1.27	

Table IV. Univariable associations between quartiles of continous variables and CED outcomes.
Odds ratio reference (OR 1.00) is the lowest quartile.

* Overall P-value for homogeneity

Variable	Any CED (CED 1, 2 or 3) *			CED 2 or 3 †			CED 3 ‡		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Male gender	1.11	1.05–1.18	<.001						
OTT, min									
117–145	1.12	1.03–1.21	.007						
146–174	1.15	1.06–1.25	<.001						
≥175	1.15	1.06–1.25	<.001						
NIHSS score									
7–11	2.00	1.78–2.26	<.001	2.43	1.94–3.03	<.001	2.08	1.50–2.88	<.001
12–16	4.74	4.22–5.33	<.001	7.04	5.70–8.68	<.001	7.09	5.25–9.56	<.001
≥17	8.13	7.23–9.13	<.001	12.67	10.29–15.60	<.001	12.32	9.17–16.55	<.001
NIHSS item 1a ≥1	1.27	1.19–1.36	<.001	1.44	1.33–1.56	<.001	1.54	1.29–1.61	<.001
Infarct signs on imaging	1.35	1.26–1.45	<.001	1.38	1.25–1.48	<.001	1.44	1.44–1.64	<.001
Hyperdense artery sign	2.21	2.06–2.36	<.001	1.97	1.81–2.13	<.001	2.04	1.83–2.26	<.001
Blood glucose, mmol/l									
5.67–6.53	1.04	0.96–1.13	.353	1.03	0.92–1.15	.612	1.08	0.92–1.26	.342
6.54–7.89	1.20	1.10–1.30	<.001	1.18	1.05–1.31	.005	1.26	1.09–1.47	.002
≥7.90	1.45	1.33–1.58	<.001	1.53	1.37–1.70	<.001	1.77	1.53–2.04	<.001
Mean arterial pressure, mmHg									
96.6–105.6							1.11	0.97–1.29	.134
105.7–114.9							1.33	1.15–1.52	<.001
≥115.0							1.45	1.27–1.67	<.001
Atrial fibrillation	1.14	1.07–1.22	<.001	1.12	1.03–1.21	.008			

Table V. Final multivariable models for prediction of CED outcomes. For continuous variables, odds ratio reference (OR 1.00) is the lowest quartile.

* Model AUC=0.76. Hosmer-Lemeshow P=.31
† Model AUC=0.78. Hosmer-Lemeshow P=.91
‡ Model AUC=0.79. Hosmer-Lemeshow P=.86