JoS JOURNAL OF STROKE

Journal of Stroke 2023;25(1):101-110
https://doi.org/10.5853/jos.2022.01956

Original Article

Cerebral Edema in Patients with Severe Hemispheric Syndrome: Incidence, Risk Factors, and Outcomes—Data from SITS-ISTR

Irene Escudero-Martínez,[a,b] Magnus Thorén,[c,d] Peter Ringleb,[e] Ana Paiva Nunes,[f] Manuel Cappellari,[g] Viiu-Marika Rand,[h] Piotr Sobolewski,[i] Jose Egido,[j] Danilo Toni,[k] Shih-Yin Chen,[l] Nicole Tsao,[l,*] Niaz Ahmed[d,m]

[a]Department of Neurology, University Hospital La FE, Valencia, Spain
[b]Neurovascular Research Laboratory, Biomedicine Institute IBiS, Sevilla, Spain
[c]Department of Neurology, Danderyd Hospital, Stockholm, Sweden
[d]Department of Clinical Neuroscience, Karolinska Institute, Stockholm, Sweden
[e]Department of Neurology, Heidelberg University Hospital, Heidelberg, Germany
[f]Department of Neurology, Sao Jose Hospital, University Hospital Lisboa, Lisboa, Portugal
[g]Department of Neuroscience, Integrate University Hospital, Verona, Italy
[h]Department of Neurology, North Estonia Medical Centre Foundation, Tallinn, Estonia
[i]Department of Neurology and Stroke Unit in Sandomierz, Collegium Medicum, Jan Kochanowski University in Kielce, Kielce, Poland
[j]Stroke Unit, Department of Neurology, San Carlos Clinic Hospital, Madrid, Spain
[k]Department of Human Neurosciences, Sapienza University of Rome, Rome, Italy
[l]Biogen, Cambridge, MA, USA
[m]Department of Neurology, Karolinska University Hospital, Stockholm, Sweden

Background and Purpose Cerebral edema (CED) in ischemic stroke can worsen prognosis and about 70% of patients who develop severe CED die if treated conservatively. We aimed to describe incidence, risk factors and outcomes of CED in patients with extensive ischemia.

Methods Observational study based on Safe Implementation of Treatments in Stroke-International Stroke Treatment Registry (2003–2019). Severe hemispheric syndrome (SHS) at baseline and persistent SHS (pSHS) at 24 hours were defined as National Institutes of Health Stroke Score (NIHSS) >15. Outcomes were moderate/severe CED detected by neuroimaging, functional independence (modified Rankin Scale 0–2) and death at 90 days.

Results Patients (n=8,560) presented with SHS and developed pSHS at 24 hours; 82.2% received intravenous thrombolysis (IVT), 10.5% IVT+thrombectomy, and 7.3% thrombectomy alone. Median age was 77 and NIHSS 21. Of 7,949 patients with CED data, 3,780 (47.6%) had any CED and 2,297 (28.9%) moderate/severe CED. In the multivariable analysis, age <50 years (relative risk [RR], 1.56), signs of acute infarct (RR, 1.29), hyperdense artery sign (RR, 1.39), blood glucose >128.5 mg/dL (RR, 1.21), and decreased level of consciousness (RR, 1.14) were associated with moderate/severe CED (for all P<0.05). Patients with moderate/severe CED had lower odds to achieve functional Independence (adjusted odds ratio [aOR], 0.35; 95% confidence interval [CI], 0.23 to 0.55) and higher odds of death at 90 days (aOR, 2.54; 95% CI, 2.14 to 3.02).

Conclusion In patients with extensive ischemia, the most important predictors for moderate/severe CED were age <50, high blood glucose, signs of acute infarct, hyperdense artery on baseline scans, and decreased level of consciousness. CED was associated with worse functional outcome and a higher risk of death at 3 months.

Keywords Brain edema; Thrombolytic therapy; Thrombectomy; Reperfusion; Registries; Cerebral hemorrhage

Correspondence: Irene Escudero-Martínez
Stroke Unit, Department of Neurology, University Hospital La Fe, Av. Fernando Abril 106, 46026, Valencia, Spain
Tel: +34-96-124-4000
E-mail: escudero_ire@gva.es
https://orcid.org/0000-0003-1838-0235

Received: June 14, 2022
Revised: August 2, 2022
Accepted: August 11, 2022

*Current affiliation: Sanofi Genzyme, Cambridge, MA, USA

Introduction

Cerebral edema (CED) in acute ischemic stroke worsens the prognosis and can, if severe, cause life-threatening intracranial tissue shifts.[1] In patients presenting with cerebral ischemia, the size of the ensuing infarct is dependent on several factors, including treatment aimed at reperfusion of the occluded artery. Infarct size is a major determinant of the extent and clinical severity of the ensuing edema and potential hemorrhage. Severe hemispheric syndrome (SHS) is defined as having a high National Institutes of Health Stroke Score (NIHSS) score at baseline, as a marker of a large area of cerebral ischemia.[2] In cerebral ischemia caused by supratentorial large vessel occlusion (LVO), the risk of life-threatening edema is highest in occlusion of terminal internal carotid artery or the main trunk of the middle cerebral artery (MCA). This condition is called large hemispheric infarction (LHI). The most common guideline-supported definition of LHI refers to "a large ischemic stroke affecting the total or subtotal territory of the MCA, involving the basal ganglia at least partially, with or without involvement of the adjacent territories."[3,4] Among patients with supratentorial ischemia, approximately 1 in 10 develops a subtotal or complete MCA infarction.[2] The clinical deterioration caused by edema after a large MCA infarction is usually observed within 48 hours after symptom onset with one third of the patients undergoing early deterioration within 24 hours.[5] The rate of mortality is close to 80% within a few days, unless treated with early surgery.[6]

Data from previous studies indicate that the risk for life-threatening CED is strongly associated with increasing infarct size, or other variables correlated to infarct size such as need for mechanical ventilation, large perfusion deficit and involvement of more than one vascular territory.[7-9] A previous Safe Implementation of Treatments in Stroke (SITS)-International Stroke Treatment Registry (ISTR) paper reported that the most important baseline predictors for CED were higher NIHSS score, hyperdense artery sign (HAS), higher blood glucose, decreased level of consciousness (LOC) and signs of infarct at baseline imaging scan.[10]

Aims and hypothesis

Although patients with SHS and LHI are at particular risk of CED, published data describing the burden and outcomes are limited. The aim of this study is to describe incidence, clinical characteristics, complications, and long-term outcome of CED in patients with SHS and persistent SHS (pSHS) after reperfusion treatment in a real-world setting population.

Methods

Study design

We included a subset of patients from the SITS-ISTR, an ongoing, prospective, internet-based, academic driven, multinational, primarily European Union-based, stroke register. Methods of data collection in SITS-ISTR have been described in detail elsewhere.[10,11] For this study, we have collected data from pre-specified intravenous thrombolysis (IVT) and or endovascular treatment (EVT) data entry forms of SITS-ISTR. All patients had presumed ischemic stroke treated with IVT and/or EVT and were recorded from January 2003 to September 2019. A study protocol and statistical analysis plan were developed before data extraction and analysis. According to the study protocol, we selected centers that included at least 10 patients in the SITS IVT and or EVT data entry forms and that had at least 70% complete data for modified Rankin Scale (mRS) score at 90 days follow-up.

The number of patients included in the study is not driven by a formal sample size calculation but rather by available patient numbers.

We included patients that:

- had a presumed ischemic stroke treated with IVT and/or EVT.
- were recorded at SITS-ISTR from January 2003 to September 2019.
- had a recorded NIHSS score at baseline.
- had a recorded indirect (HAS) or direct radiological evidence (computed tomography [CT] or magnetic resonance imaging angiography) of a cerebral arterial occlusion at baseline.

We defined the primary population study as patients with SHS at baseline (NIHSS score >15) and pSHS after reperfusion treatment (NIHSS score >15 at 24 hours).

Outcomes and covariates

The primary outcome measure was CED which was rated by local investigators on post-treatment imaging scans at 22 to 36 hours. We used the SITS-Monitoring Study (MOST) edema scale which has been described previously.[12] We defined mild CED as focal brain swelling up to one-third of the hemisphere (grade 1), moderate CED as focal brain swelling greater than one-third of the hemisphere (grade 2), and severe CED as focal brain swelling with midline shift (grade 3). Although not explicitly mentioned in the SITS-MOST study protocol, signs of focal brain edema usually are defined as narrowing of the cerebrospinal fluid space, e.g., effacement of cortical sulci or ventricular compression. We specified in advance that the two higher

 https://doi.org/10.5853/jos.2022.01956

grades of the scale would be put together into a compound outcome so that moderate to severe edema would be compared to no or mild edema.

Early secondary outcomes were the proportion of patients with parenchymal hemorrhage (PH) type 2 of the infarct area on follow-up imaging at 22 to 36 hours and the proportion of patients with symptomatic intracranial hemorrhage (SICH). To define SICH, we used the SITS-MOST (a local or remote type 2 PH <22 to 36 hours, or earlier in case of clinical deterioration, in combination with an increase of ≥4 NIHSS points from baseline, or leading to death <24 hours), and European-Australian Cooperative Acute Stroke Study 2 (ECASS-II) (any type of intracerebral hemorrhage with an increase of ≥4 NIHSS points from baseline or leading to death <7 days) definitions.[11,13] Late secondary outcomes, measured at 90 days, were mortality and functional outcome assessed by mRS score. Covariates collected for this study were baseline and demographic characteristics and any acute intervention.

Ethics and informed consent

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 where required; other countries approved the register for anonymized audit.

Statistical analysis

In an initial univariate analysis, we compared baseline characteristics and outcomes between patients according to the presence or absence of CED, for all levels of CED and between the groups of no or mild edema versus moderate to severe edema. We used linear regression methods for numerical variables and Pearson´s chi-square test for categorical variables to compare baseline characteristics and outcomes. Estimation of proportions was based on reported cases, excluding unknown or uncertain values. A significance level of $P<0.05$ was used through the whole study.

We used multivariable regression analysis to identify predictors of CED. The biologically relevant baseline factors (NIHSS score, signs of acute infarction at baseline, HAS, blood glucose at baseline), and the factors associated ($P<0.05$) with CED in the previous univariate analysis were included in the multivariable model. Age was analyzed per 10-year groups and as a dichotomic variable (<50 years vs. ≥50 years). Association of baseline variables with CED were presented as relative risk (RR) with 95% confidence limits. A Poisson regression with generalized estimating equation was used to assess factors associated with CED. Impact of CED on long term outcomes was assessed using logistic regressions presented as an odds ratio. We used the statistical software SPSS version 25 (IBM Co., Armonk, NY, USA).

Results

Patients (n=8,560) that presented with SHS developed pSHS at 24 hours. Figure 1 shows a flowchart of the study. Table 1 shows baseline characteristics and univariate analysis of patients with SHS and pSHS, stratified by grade of CED. Median age was 77 and median NIHSS was 21 (interquartile range, 18 to 23); 46.3% were men. Of the total SHS and LHI patients, 7,035 patients (82.2%) received IVT, 903 (10.5%) IVT and EVT, and 622 (7.3%) EVT alone. Of 7,949 patients with available CED data, 3,780 (47.6%) had any CED and 2,297 (28.9%) were moderate/severe. Supplementary Table 1 shows baseline characteristics and Supplementary Table 2 shows the clinical and radiological outcomes of any SHS, any pSHS, both SHS & pSHS, and no SHS nor pSHS populations. Patients with pSHS had worse outcomes than SHS. pSHS patients had a higher rate of SICH and any type of hemorrhages and death and a lower rate of functional independence than SHS patients.

Univariate analysis

As seen in Tables 1 and 2, patients with moderate or severe CED were significantly younger and had more frequently signs of acute infarction and HAS at baseline imaging scans. Moreover, patients with moderate/severe edema presented higher values of blood glucose at admission and oral antidiabetic treatment. The proportion of patients with previous stroke was lower in the moderate/severe CED group and the percentage of patients with pre-stroke mRS 0 was higher. Decreased LOC as measured by item 1a in the NIHSS score was more frequent in the moderate/severe CED group. In 175 patients (2%) decompressive hemicraniectomy was performed. This percentage ranged from 0.6% in no CED, 0.9% in mild CED, 2.2% in moderate, and 8.2% in severe CED ($P<0.001$).

Multivariable analysis

Table 3 shows results from a multivariable model for prediction of moderate to severe CED with RR and 95% confidence intervals. Age <50 years (RR, 1.56), signs of acute infarction on baseline imaging (RR, 1.29), HAS (RR, 1.39), blood glucose >128.5 mg/dL (RR, 1.21), and decreased LOC (RR, 1.14) were associated with moderate/severe CED (for all $P<0.05$).

Long-term outcomes

Table 4 shows multivariable logistic regression models for the effect of CED on long term outcomes. The adjusted odds ratio (aOR) showed that patients with any CED versus no CED (aOR, 0.36), severe CED versus no, mild, or moderate CED combined (aOR, 0.42), and moderate and severe CED versus no or mild CED (aOR, 0.35) were less likely to achieve functional independence defined by mRS 0–2 at 90 days. Regarding mortality, the presence of CED in any degree, moderate and severe and severe were associated with a higher risk for death at 90 days, and the risk increased with the severity of CED (aOR, 1.58 for any; aOR, 2.54 for moderate and severe; and aOR, 3.94 for severe).

Discussion

In this large observational study based on multinational data of acute ischemic stroke patients treated with recanalization therapy, we found that almost half of the patients with severe ischemic stroke according to SHS and pSHS definitions had any degree of CED and almost a third of them had moderate to severe CED. A previous Chinese study found the same rate of severe CED in LHI patients.[14] However, when all types of ischemic strokes irrespective of severity are analyzed, any type of CED, detected by the SITS-MOST Edema Scale[12] at 22 to 36 hours imaging was around one in four patients. The incidence of moderate and severe CED was similar, about 5%.[10] For the purpose of our study, we selected patients with severe stroke symptoms at baseline (SHS) and a clinical proxy using NIHSS score at 24 hours (pSHS) for severe strokes after repersfusion treatment. Our study population with SHS and pSHS are expected to have higher prevalence of CED than the general ischemic stroke population.

In this SHS & pSHS population with high risk of CED, the most important predictors for moderate/severe CED development were young age, high blood glucose levels, signs of acute infarction or HAS on baseline neuroimaging and decreased LOC at admission. Predictors for CED in our study on severe stroke patients are consistent with previous single center and multi-

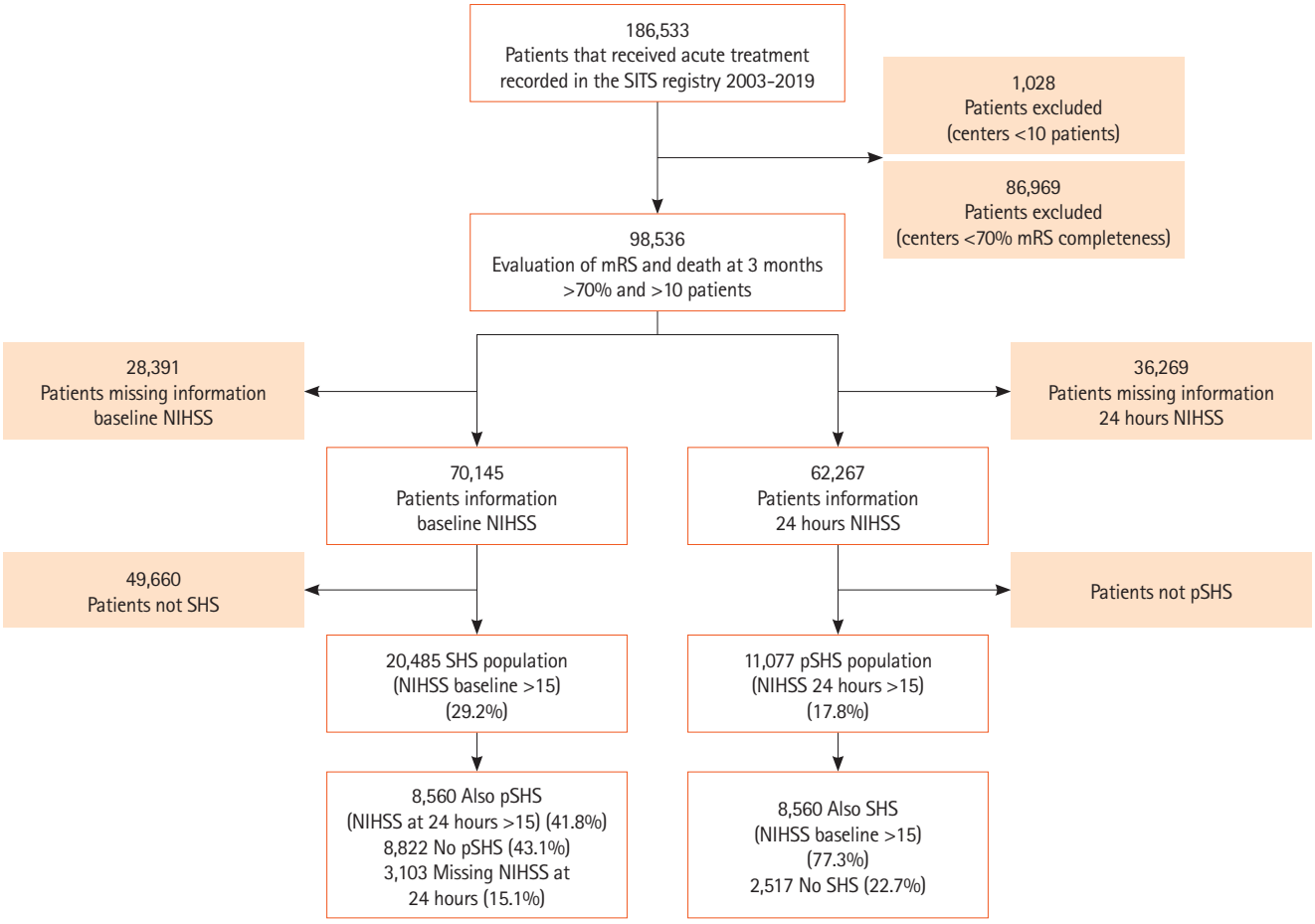

Figure 1. Study flow chart. SITS, Safe Implementation of Treatments in Stroke; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Score; SHS, severe hemispheric syndrome; pSHS, persistent severe hemispheric syndrome.

 https://doi.org/10.5853/jos.2022.01956

Table 1. Baseline characteristics and univariate analysis by grade of cerebral edema

Variable	SHS & pSHS (n=8,560)	No CED (n=4,169)	Mild CED (n=1,483)	Moderate CED (n=1,141)	Severe CED (n=1,156)	Overall *P*
Age (yr)	77 (68–84)	78 (70–84)	77 (68–83)	77 (69–83)	74 (64–82)	<0.001
Age (yr)						<0.001
<50	315 (4)	126 (3)	68 (4.6)	56 (4.9)	65 (5.6)	
50–59	559 (7)	259 (6.2)	105 (7.1)	74 (6.5)	121 (10.5)	
60–69	1,264 (15.9)	611 (14.7)	247 (16.7)	171 (15)	235 (20.3)	
70–79	2,573 (32.4)	1,339 (32.2)	464 (31–3)	408 (35.8)	362 (31.3)	
≥80	3,230 (40.7)	1,828 (43.9)	598 (31.3)	431 (37.8)	373 (32.3)	
Male sex	3,966 (46.3)	1,877 (45)	719 (48.5)	522 (45.7)	572 (49.5)	0.016
Acute treatment						<0.001
IVT only	7,035 (82.2)	3,516 (84.3)	1,145 (77.2)	941 (82.5)	918 (79.4)	
EVT only	622 (7.3)	259 (6.2)	140 (9.4)	93 (8.2)	89 (7.7)	
IVT+EVT	903 (10.5)	394 (9.5)	198 (13.4)	107 (9.4)	149 (12.9)	
NIHSS score	21 (18–23)	21 (18–23)	21 (18–23)	21 (18–23)	21 (18–23)	0.594
OTT for IVT (min)	150 (112–194)	150 (112–195)	150 (113–190)	150 (120–192)	150 (110–195)	0.917
OTT for IVT (min)						0.176
<112	1,800 (24.8)	965 (25.1)	330 (24.8)	228 (22)	277 (24.8)	
112–149	1,815 (25)	951 (24.8)	326 (24.5)	288 (27.7)	250 (23.7)	
150–194	1,880 (25.9)	983 (25.6)	366 (27.5)	274 (26.4)	257 (24.4)	
≥195	1,768 (24.3)	941 (24.5)	308 (23.2)	248 (23.9)	271 (25.7)	
Signs of acute infarction on imaging	2,048 (25.2)	882 (22.1)	373 (26)	323 (29.1)	382 (34)	<0.001
Hyperdense artery sign baseline	4,021 (50)	1,778 (44.9)	758 (53.5)	637 (58)	690 (62.3)	<0.001
Blood glucose (mg/dL)	128.5 (109–160)	127 (108–155)	125 (107–152)	130 (110–162)	135 (114–170)	<0.001
Blood glucose (mg/dL)						<0.001
<128.5	2,077 (50.6)	974 (52.3)	492 (53.9)	339 (48.1)	272 (43.5)	
≥128.55	2,029 (49.4)	890 (47.7)	420 (46.1)	366 (51.9)	353 (56.5)	
Systolic blood pressure (mm Hg)	151 (136–170)	152 (137–170)	150 (135–167)	152 (138–170)	150 (135–170)	0.341
Hypertension	6,274 (73.9)	3,090 (74.7)	1,078 (72.9)	838 (73.9)	828 (72.4)	0.322
Diabetes mellitus	1,971 (23.2)	959 (23.2)	309 (20.9)	293 (25.8)	266 (23.2)	0.034
Hyperlipidemia	2,569 (30.6)	1,204 (29.5)	476 (32.5)	374 (33.2)	349 (30.7)	0.038
Current smoker	958 (13.5)	423 (12.4)	182 (14.7)	121 (12.5)	159 (16)	0.011
Previous stroke	1,047 (12.7)	527 (12.8)	185 (12.5)	128 (11.3)	119 (10.4)	0.131
Previous TIA	431 (5.1)	224 (5.5)	67 (4.6)	63 (5.6)	45 (3.9)	0.130
Atrial fibrillation	2,628 (31.1)	1,272 (30.8)	468 (31.9)	354 (31.4)	336 (29.4)	0.566
Congestive heart failure	1,065 (12.6)	515 (12.5)	200 (13.6)	152 (13.4)	123 (10.8)	0.130
Previous mRS 0	5,310 (64.7)	2,556 (63.1)	993 (67.8)	718 (63.5)	799 (71.1)	<0.001
Antiplatelet treatment	3,419 (40.5)	1,670 (40.4)	603 (40.9)	480 (42.5)	429 (37.4)	0.092
Aspirin treatment	2,846 (33.9)	1,391 (33.8)	490 (33.3)	396 (35.3)	364 (31.9)	0.402
Clopidogrel treatment	621 (7.5)	318 (7.7)	104 (7.1)	78 (6.9)	82 (7.2)	0.725
Oral anticoagulant treatment	669 (8)	310 (7.5)	131 (8.9)	99 (8.8)	86 (7.5)	0.232
Oral antihypertensive treatment	5,838 (70.2)	2,899 (70.2)	1,042 (70.8)	813 (71.9)	771 (67.2)	0.079
Oral antidiabetics	1,459 (17.6)	704 (17.1)	239 (16.3)	241 (21.4)	207 (18.1)	0.004
Statins	2,508 (30.3)	1,215 (29.6)	454 (30.9)	363 (32.2)	339 (29.9)	0.348

Table 1. Continued

Variable	SHS & pSHS (n=8,560)	No CED (n=4,169)	Mild CED (n=1,483)	Moderate CED (n=1,141)	Severe CED (n=1,156)	Overall *P*
Decreased consciousness (NIHSS 1a ≥1)	3,558 (44.2)	1,700 (43.6)	545 (38.7)	481 (43.9)	542 (49.1)	<0.001
EVT with or without prior IVT	1,525 (17.8)	653 (15.7)	338 (22.8)	200 (17.6)	238 (20.6)	<0.001
Decompressive hemicraniectomy	175 (2)	27 (0.6)	14 (0.9)	25 (2.2)	95 (8.2)	<0.001

Values are presented as median (interquartile range) or number (%).
SHS, severe hemispheric syndrome; pSHS, persistent severe hemispheric syndrome; CED, cerebral edema; IVT, intravenous thrombolysis; EVT, endovascular treatment; OTT, onset to treatment time; TIA, transient ischemic attack; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

Table 2. Univariate analysis in patients with SHS and pSHS by grade cerebral edema

Variable	CED INFO (n=7,949, 100%)	No or mild CED (n=5,652, 71.1%)	Moderate or severe CED (n=2,297, 28.9%)	Overall *P*
Age (yr)	77 (69–84)	78 (69–84)	76 (66–82)	<0.001
Age (yr)				<0.001
<50	315 (4)	194 (3.4)	121 (5.3)	
50–59	559 (7)	364 (6.4)	195 (8.5)	
60–69	1,264 (15.9)	858 (15.2)	406 (17.7)	
70–79	2,573 (32.4)	1,803 (31.9)	770 (33.5)	
≥80	3,230 (40.7)	2,426 (43)	2,296 (35)	
Male sex	3,690 (46.4)	2,596 (45.9)	1,094 (47.6)	0.169
Acute treatment	6,520 (82)	4,661 (82.5)	1,859 (80.9)	0.243
IVT only	581 (7.3)	399 (7.1)	182 (7.9)	
EVT only	848 (10.7)	592 (10.5)	256 (11.1)	
IVT+EVT				
NIHSS score	21 (18–23)	21 (18–23)	21 (18–23)	0.393
OTT for IVT (min)	150 (113–195)	150 (112–195)	150 (114–195)	0.393
OTT for IVT (min)				0.646
<112	1,800 (24.8)	1,295 (25)	505 (24.1)	
112–149	1,815 (25)	1,277 (247)	538 (25.7)	
150–194	1,880 (25.9)	1,349 (26.1)	531 (25.4)	
≥195	1,768 (24.3)	1,249 (24.2)	519 (24.8)	
Signs of acute infarction on imaging	1,960 (25.6)	1,255 (23.1)	705 (31.6)	<0.001
Hyperdense artery sign baseline	3,863 (51)	2,536 (47.3)	1,327 (60.2)	<0.001
Blood glucose (mg/dL)	128 (109–158)	126 (108–155)	132 (112–164)	<0.001
<128.5	3,672 (51.2)	2,691 (53.1)	981 (46.6)	
≥128.55	3,502 (48.8)	2,379 (46.9)	1,123 (53.4)	
Systolic blood pressure (mm Hg)	151 (136–170)	151 (136–170)	151 (136–170)	0.976
Hypertension	5,834 (73.9)	4,168 (74.2)	1,666 (73.2)	0.325
Diabetes mellitus	1,827 (23.3)	1,268 (22.6)	559 (24.5)	0.065
Hyperlipidemia	2,403 (30.8)	1,680 (30.3)	723 (31.9)	0.147
Current smoker	885 (13.4)	605 (13)	280 (14.3)	0.183
Previous stroke	959 (12.2)	712 (12.7)	247 (10.9)	0.022
Previous TIA	399 (5.1)	291 (5.2)	108 (4.7)	0.389
Atrial fibrillation	2,430 (30.9)	1,749 (31.1)	690 (30.4)	0.511
Congestive heart failure	990 (12.6)	715 (12.8)	275 (12.1)	0.380

https://doi.org/10.5853/jos.2022.01956

Table 2. Continued

Variable	CED INFO (n=7,949, 100%)	No or mild CED (n=5,652, 71.1%)	Moderate or severe CED (n=2,297, 28.9%)	Overall *P*
Previous mRS 0	5,066 (65.2)	3,549 (64.3)	1,517 (67.3)	0.012
Antiplatelet treatment	3,182 (40.4)	2,273 (40.6)	909 (40)	0.620
Aspirin treatment	2,641 (33.6)	1,881 (33.7)	760 (33.6)	0.943
Clopidogrel treatment	582 (7.4)	422 (7.5)	160 (7)	0.437
Oral anticoagulant treatment	626 (7.9)	441 (7.9)	185 (8.1)	0.692
Oral antihypertensive treatment	5,525 (70.1)	3,941 (70.3)	1,584 (69.6)	0.491
Oral antidiabetics	1,391 (17.7)	943 (16.9)	448 (19.7)	0.003
Statins	2,371 (30.2)	1,669 (29.9)	702 (31)	0.327
Decreased consciousness (NIHSS 1a ≥1)	3,268 (43.5)	2,245 (42.3)	1,023 (46.5)	0.001
EVT with or without prior IVT	1,429 (18)	991 (17.5)	438 (19.1)	0.108
Decompressive hemicraniectomy	175 (2.2)	41 (0.72)	120 (5.2)	0.001

Values are presented as median (interquartile range) or number (%).
SHS, severe hemispheric syndrome; pSHS, persistent severe hemispheric syndrome; CED, cerebral edema; IVT, intravenous thrombolysis; EVT, endovascular treatment; OTT, onset to treatment time; TIA, transient ischemic attack; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

Table 3. Multivariable model for prediction of moderate and severe CED with RR (Poisson regression, with GEE)

Variable	Moderate to severe CED		
	RR	95% CI	*P*
Age (yr)			
<50	1.00		
50–59	0.89	0.73–1.08	0.230
60–69	0.80	0.67–0.96	0.014
70–79	0.76	0.64–0.90	0.002
≥80	0.66	0.55–0.78	<0.001
Age <50 years	1.56	1.24–1.97	<0.001
Male sex	1.02	0.95–1.10	0.577
Acute infarction on imaging	1.29	1.19–1.39	<0.001
Hyperdense artery sign baseline	1.39	1.29–1.50	<0.001
Blood glucose (>128.5 mg/dL)	1.21	1.12–1.31	<0.001
Previous stroke	0.91	0.81–1.03	0.150
Previous mRS 0	1.01	0.93–1.10	0.852
Oral antidiabetics	1.07	0.97–1.18	0.201
Decreased consciousness (NIHSS 1a ≥1)	1.14	1.06–1.24	0.001

CED, cerebral edema; RR, relative risk; GEE, generalized estimated equation; CI, confidence interval; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

center studies that included broader populations. The strongest predictors for moderate/severe CED development were a younger age and HAS on baseline neuroimaging. These findings have been previously reported.[10,12,15]

Elderly patients who developed large infarctions may have brain atrophy, and this may compensate for CED. HAS on baseline CT is an indirect finding of LVO and it is associated with SHS and LHI.

As previously reported, we also found that a higher blood glucose level at admission was a risk factor for CED development.[10] This consistent association between glucose levels and CED after a large ischemic stroke has been the basis of pre- and clinical research of glibenclamide as a potential treatment for these patients.[16]

The association of recanalization therapies and CED remains unclear. In the line of our findings regarding signs of acute infarction at baseline, a recent meta-analysis has shown that in patients with LHI, EVT, and reperfusion were associated with severe CED only in the group with very large core volume.[17]

Regarding long-term outcomes, the presence of any CED, moderate and severe and severe CED were independently associated with worse functional outcome, with a 60% decrease in the odds of functional independence. Our results regarding the effect of CED in functional outcome and mortality are consistent with a previous study in patients treated with IVT.[9]

Presence of CED was associated with a higher risk of death at 90 days, including in-hospital mortality, and the risk increased from 1.5 to 4 times higher as compared to patients with no CED. Regarding treatment, randomized trials showed that surgical decompression reduced the risk of death, and meta-analyses of these trials showed that surgery also increased the chance of a favorable outcome.[6,18]

Although being a well-known complication of large stroke, the management of CED remains a topic of discussion. The European Stroke Organization has recently published guidelines

Table 4. Effect of CED on long-term prognostic outcomes among patients with SHS & pSHS and available CED information

Models varying key CED independent variable	mRS 0–2 at 90 days (n=7,433)			Mortality 90 days (n=7,618)		
	OR	95% CI	*P*	OR	95% CI	*P*
Model 1: Any CED vs. no CED	0.36	0.24–0.53	<0.001	1.58	1.36–1.83	<0.001
Model 2: Severe CED vs. no/mild/moderate CED	0.42	0.23–0.76	0.004	3.94	3.00–5.13	<0.001
Model 3: Moderate & severe CED vs. no/mild CED	0.35	0.23–0.55	<0.001	2.54	2.14–3.02	<0.001

Models were adjusted by age, sex, vascular risk factors (hypertension, diabetes mellitus, hyperlipidemia, current smoker, previous stroke, previous transient ischemic attack, atrial fibrillation, congestive heart failure), previous mRS 0, onset to treatment time, National Institutes of Health Stroke Scale item 1a ≥1 at baseline, acute infarction on imaging, hyperdense artery sign, blood glucose (mg/dL). In this table, as the outcome for mRS 0–2 is functional independence, OR <1 are less likely to achieve functional independence while OR >1 are more likely.
CED, cerebral edema; SHS, severe hemispheric syndrome; pSHS, persistent severe hemispheric syndrome; mRS, modified Rankin Scale; OR, odds ratio; CI, confidence interval.

on the management of space-occupying brain infarction.[19] In this document, surgical decompression is recommended to reduce the risk of death and to increase the chance of a favorable outcome in adult patients aged up to and including 60 years with space-occupying hemispheric infarction who can be treated within 48 hours of stroke onset, and low-quality evidence to support this treatment in older patients. There is continued uncertainty about the benefit and risks of surgical decompression in patients with space-occupying hemispheric infarction if performed after the first 48 hours. However, in a real-world setting, patients who undergo hemicraniectomy present frequently with complications that were underestimated in randomized clinical trials and may worsen the functional outcome, with 80% of survivors completely dependent (mRS 4–5).[20]

Recently, new guidelines on CED management in neurocritical care patients have been published.[21] For acute treatment, they suggest using either hypertonic sodium solutions or mannitol for the initial management of CED in patients with acute ischemic stroke (conditional recommendation, low-quality evidence), although neurological outcomes appear to be not affected. Previous guidelines state that there are insufficient data on the effect of hypothermia, barbiturates, or corticosteroids in the setting of ischemic cerebral swelling.[3] For these reasons, the management of patients with CED is still a challenge for stroke physicians, more clinical research is needed in early detection, prevention, and treatment of CED development.

This study presents some limitations. First, it is an observational study based on retrospective analyses, although data were collected prospectively. Our findings were limited to those who received IVT or EVT treatments and might not be generalizable to those who did not receive either therapy. Moreover, there is a proportion of missing and unknown data in some variables, including some missed cases of fatal CED, that may have influenced the results. Thus, there is a potential bias of patient selection. The associations observed in this study should be viewed as hypotheses-generating and need confirmation in further studies. Finally, another limitation is that we have defined persistent severe neurological deficit according to clinical criteria and not according to radiological findings, as data regarding final infarct volume were not available due to the lack of a centralized reading of the CTs. This could introduce some interobserver variability. However, pooled treatment of moderate/severe versus no/mild edema would tend to reduce this effect. The strengths of this study are the very large international sample size and consistent results with previous single and multicenter studies.

Conclusions

In conclusion, in patients with clinical signs of extensive ischemia, the most important predictors of moderate/severe CED development were young age, high blood glucose, signs of acute infarct, HAS on baseline scans and decreased LOC. The presence of any, moderate/severe, and severe CED were associated with worse functional outcome and a higher risk of death at 3 months, that increases proportionally with the severity of CED.

Supplementary materials

Supplementary materials related to this article can be found online at https://doi.org/10.5853/jos.2022.01956.

Disclosure

Niaz Ahmed is the Chairman of SITS International, which receives a grant from Boehringer Ingelheim for the SITS-International Stroke Thrombolysis Register and from Stryker, Covidien,

and Phenox in collaboration with Karolinska Institutet for the SITS-OPEN study. Shih-Yin Chen is an employee of Biogen and owns stock in Biogen. Nicole Tsao was an employee of Biogen at the time of the study and owns stock in Biogen. This study was funded by Biogen. Other authors have no disclosures regarding conflict of interest.

Acknowledgments

SITS is financed directly and indirectly by grants from Karolinska Institutet, Stockholm County Council, the Swedish Heart-Lung Foundation, the Swedish Order of St. John, Friends of Karolinska Institutet, and private donors, as well as from an unrestricted sponsorship from Boehringer-Ingelheim. SITS has previously received grants from the European Union Framework 7, the European Union Public Health Authority, Ferrer International and EVER Pharma. SITS is currently conducting studies supported by Boehringer-Ingelheim and Biogen, as well as in collaboration with Karolinska Institutet, supported by Stryker, Covidien, and Phenox. Niaz Ahmed is supported by grants provided by the Stockholm County Council and the Swedish Heart-Lung Foundation. S Holmin is supported by grants provided by the Söderberg Foundations, the Stockholm County Council, the Erling Persson Foundation, VINNOVA, and HMT. Irene Escudero-Martínez has received a grant from "Fundación Progreso y Salud, Junta de Andalucía" (grant EF-0437-2018). Magnus Thorén has received grants or funding from Stiftelsen Tornspiran, Stiftelsen Sigurd och Elsa Goljes Minne, STROKE-Riksförbundet, Capio forskningsstiftelse, and Karolinska University Hospital.

References

1. Battey TW, Karki M, Singhal AB, Wu O, Sadaghiani S, Campbell BC, et al. Brain edema predicts outcome after nonlacunar ischemic stroke. *Stroke* 2014;45:3643-3648.
2. Huttner HB, Schwab S. Malignant middle cerebral artery infarction: clinical characteristics, treatment strategies, and future perspectives. *Lancet Neurol* 2009;8:949-958.
3. Wijdicks EF, Sheth KN, Carter BS, Greer DM, Kasner SE, Kimberly WT, et al. Recommendations for the management of cerebral and cerebellar infarction with swelling: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2014;45:1222-1238.
4. Torbey MT, Bösel J, Rhoney DH, Rincon F, Staykov D, Amar AP, et al. Evidence-based guidelines for the management of large hemispheric infarction: a statement for health care professionals from the Neurocritical Care Society and the German Society for Neuro-intensive Care and Emergency Medicine. *Neurocrit Care* 2015;22:146-164.
5. Qureshi AI, Suarez JI, Yahia AM, Mohammad Y, Uzun G, Suri MF, et al. Timing of neurologic deterioration in massive middle cerebral artery infarction: a multicenter review. *Crit Care Med* 2003;31:272-277.
6. Vahedi K, Hofmeijer J, Juettler E, Vicaut E, George B, Algra A, et al. Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomised controlled trials. *Lancet Neurol* 2007;6:215-222.
7. Wartenberg KE. Malignant middle cerebral artery infarction. *Curr Opin Crit Care* 2012;18:152-163.
8. Hofmeijer J, Algra A, Kappelle LJ, van der Worp HB. Predictors of life-threatening brain edema in middle cerebral artery infarction. *Cerebrovasc Dis* 2008;25:176-184.
9. Strbian D, Meretoja A, Putaala J, Kaste M, Tatlisumak T; Helsinki Stroke Thrombolysis Registry Group. Cerebral edema in acute ischemic stroke patients treated with intravenous thrombolysis. *Int J Stroke* 2013;8:529-534.
10. Thorén M, Azevedo E, Dawson J, Egido JA, Falcou A, Ford GA, et al. Predictors for cerebral edema in acute ischemic stroke treated with intravenous thrombolysis. *Stroke* 2017;48:2464-2471.
11. Wahlgren N, Ahmed N, Dávalos A, Ford GA, Grond M, Hacke W, et al. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. *Lancet* 2007;369:275-282.
12. Thorén M, Dixit A, Escudero-Martínez I, Gdovinová Z, Klecka L, Rand VM, et al. Effect of recanalization on cerebral edema in ischemic stroke treated with thrombolysis and/or endovascular therapy. *Stroke* 2020;51:216-223.
13. Larrue V, von Kummer RR, Müller A, Bluhmki E. Risk factors for severe hemorrhagic transformation in ischemic stroke patients treated with recombinant tissue plasminogen activator: a secondary analysis of the European-Australasian Acute Stroke Study (ECASS II). *Stroke* 2001;32:438-441.
14. Li J, Zhang P, Wu S, Wang Y, Zhou J, Yi X, et al. Stroke-related complications in large hemisphere infarction: incidence and influence on unfavorable outcome. *Ther Adv Neurol Disord* 2019;12:1756286419873264.
15. Du M, Huang X, Li S, Xu L, Yan B, Zhang Y, et al. A nomogram model to predict malignant cerebral edema in ischemic stroke patients treated with endovascular thrombectomy: an observational study. *Neuropsychiatr Dis Treat* 2020;16:2913-2920.
16. Simard JM, Sheth KN, Kimberly WT, Stern BJ, del Zoppo GJ,

Jacobson S, et al. Glibenclamide in cerebral ischemia and stroke. *Neurocrit Care* 2014;20:319-333.
17. Ng FC, Yassi N, Sharma G, Brown SB, Goyal M, Majoie CBLM, et al. Cerebral edema in patients with large hemispheric infarct undergoing reperfusion treatment: a HERMES Meta-Analysis. *Stroke* 2021;52:3450-3458.
18. Reinink H, Jüttler E, Hacke W, Hofmeijer J, Vicaut E, Vahedi K, et al. Surgical decompression for space-occupying hemispheric infarction: a systematic review and individual patient meta-analysis of randomized clinical trials. *JAMA Neurol* 2021;78:208-216.
19. van der Worp HB, Hofmeijer J, Jüttler E, Lal A, Michel P, Santalucia P, et al. European Stroke Organisation (ESO) guidelines on the management of space-occupying brain infarction. *Eur Stroke J* 2021;6:XC-CX.
20. Pledl HW, Hoyer C, Rausch J, Ebert AD, Seiz M, Arp M, et al. Decompressive hemicraniectomy in malignant middle cerebral artery infarction: the 'Real World' Beyond Studies. *Eur Neurol* 2016;76:48-56.
21. Cook AM, Morgan Jones G, Hawryluk GW, Mailloux P, McLaughlin D, Papangelou A, et al. Guidelines for the acute treatment of cerebral edema in neurocritical care patients. *Neurocrit Care* 2020;32:647-666.

https://doi.org/10.5853/jos.2022.01956

Supplementary Table 1. Baseline characteristics of SHS, pSHS, SHS & pSHS, and no SHS nor pSHS populations

Variable	Any SHS (NIHSS >15 baseline) (n=20,485)	Any pSHS (NIHSS >15 at 24 hours) (n=11,077)	Both SHS and pSHS (n=8,560)	No SHS nor pSHS (n=41,810)
Age (yr)	73.5±12.9	74.7±12.2	75±12.2	69±13.7
	76 (67–83)	68 (58–77)	77 (68–84)	71 (61–79)
Female sex	10,629 (51.9)	5,781 (52.2)	4,594 (53.7)	18,100 (43.3)
Acute treatment				
IVT	16,168 (78.9)	9,112 (82.3)	7,035 (82.2)	38,771 (92.7)
EVT	1,643 (8)	801 (7.2)	622 (7.3)	1,161 (2.8)
IVT+EVT	2,674 (13.1)	1,164 (10.5)	903 (10.5)	1,878 (4.5)
Hypertension	14,220 (69.4)	8,120 (73.3)	6,274 (73.9)	27,426 (65.9)
Diabetes	4,076 (19.9)	2,647 (23.9)	1,971 (23.2)	8,426 (20.2)
Hyperlipidemia	5,995 (29.3)	3,365 (30.4)	2,569 (30.6)	12,508 (30.2)
Smoker	4,423 (21.6)	2,328 (21)	958 (13.5)	7,226 (17.3)
Previous stroke	2,502 (12.2)	1,380 (12.5)	1,047 (12.7)	5,095 (12.2)
Previous TIA	1,012 (4.9)	577 (5.2)	431 (5.1)	2,780 (6.7)
Atrial fibrillation	5,916 (28.9)	3,250 (29.3)	2,628 (31.1)	6,617 (15.9)
Congestive heart failure	2,310 (11.3)	1,367 (12.3)	1,065 (12.6)	2,956 (7.1)
Previous mRS 0	13,275 (64.8)	6,999 (65.9)	5,310 (64.7)	31,724 (77.9)
Antiplatelet	7,912 (38.6)	4,429 (40)	3,419 (40.5)	15,434 (37.2)
Aspirin	6,070 (29.6)	3,434 (31)	2,846 (33.9)	12,929 (30.9)
Clopidogrel	1,395 (6.8)	791 (7.1)	621 (7.5)	2,886 (6.9)
Oral anticoagulation	1,674 (8.2)	844 (7.6)	669 (8)	1,793 (4.3)
Antihypertensive	13,333 (65.1)	7,522 (67.9)	5,838 (70.2)	25,300 (61.4)
Antidiabetics	3,013 (14.7)	1,963 (17.7)	1,459 (17.6)	6,574 (16)
Statins	5,978 (29.2)	3,285 (29.7)	2,508 (30.3)	12,018 (29.2)
OTT (min)				
IVT	140 (105–185)	150 (114–195)	150 (112–194)	154 (115–205)
EVT	220 (155–324)	245 (175–366.5)	240 (190–310.5)	240 (168.5–370)
NIHSS baseline	20 (17–22)	19 (16–22)	21 (18–23)	7 (5–15)
NIHSS 1a ≥1	7,585 (40.2)	3,908 (37.8)	3,558 (44.2)	2,808 (7.3)
SBP baseline (mm Hg)	150 (133–167)	152 (137–170)	151 (136–170)	152 (138–170)
DBP baseline (mm Hg)	80 (70–90)	80 (71–90)	80 (70–90)	81 (75–90)
Glucose baseline (mg)	125 (106–152)	128 (109–161)	128.5 (109–160)	118 (102–143)
Cholesterol baseline (mg)	172 (145–200)	173 (146–201)	172 (145–200)	180 (151–210)
Current infarct baseline	4,360 (21.3)	2,524 (23.4)	2,048 (25.2)	4,061 (10.2)
Hyperdense artery sign baseline	8,928 (43.6)	4,802 (44.5)	4,021 (50)	5,966 (15.1)
Side (CTA occlusion)	6,060	2,921	2,330	5,352
Left	3,580 (59.1)	1,804 (61.8)	1,538 (66)	2,247 (42)
Right	2,440 (40.3)	1,090 (37.3)	773 (33.1)	3,083 (57.6)
Both	40 (0.6)	27 (0.8)	20 (0.9)	22 (0.4)

Values are presented as mean±standard deviation, median (interquartile range), or number (%).
SHS, severe hemispheric syndrome; pSHS, persistent severe hemispheric syndrome; NIHSS, National Institutes of Health Stroke Scale; IVT, intravenous thrombolysis; EVT, endovascular treatment; TIA, transient ischemic attack; mRS, modified Rankin Scale; OTT, onset to treatment time; SBP, systolic blood pressure; DBP, diastolic blood pressure; CTA, computed tomography angiography.

Supplementary Table 2. Clinical and radiological outcomes of the SHS, pSHS, SHS & pSHS, and no SHS nor pSHS populations

Variable	Any SHS (NIHSS >15 baseline) (n=20,485)	Any pSHS (NIHSS >15 at 24 hours) (n=11,077)	Both SHS and pSHS (n=8,560)	No SHS nor pSHS (n=41,810)
NIHSS 24 hours	8 (15–21)	20 (18–24)	21 (18–24)	3 (1–6)
CED 24 hours imaging	17,905	10,371	7,949	36,559
Any CED	5,801 (32.4)	4,735 (45.7)	3,780 (47.6)	2,670 (7.3)
CED 1 mild	2,707 (15.1)	1,797 (17.3)	1,483 (18.7)	2,085 (5.7)
CED 2 moderate	1,587 (8.9)	1,428 (13.8)	1,141 (14.4)	398 (1.1)
CED 3 severe	1,507 (8.4)	1,510 (14.6)	1,156 (14.5)	187 (0.5)
No CED	11,457 (64)	5,258 (50.7)	4,169 (52.4)	33,889 (92.7)
Uncertain	647 (3.6)	378 (3.6)		
PH2/rPH2/SAH 24 hours	1,238/18,577 (6.7)	1,292/10,729 (12)	794/8,257 (9.6)	887/40,263 (2.2)
PH2 24 hours	795/18,574 (4.3)	903/10,676 (8.5)	550/8,255 (6.7)	368/40,263 (0.9)
SICH mSITS-MOST 24 hours	598/18,491 (3.2)	935/10,677 (8.8)	468/8,257 (5.7)	185/40,263 (0.5)
SICH ECASS-II 24 hours	1,006/17,356 (5.8)	1,654/10,609 (15.6)	867/8,244 (10.5)	552/40,242 (1.3)
Worse or death 24 hours	4,226/19,790 (21.4)	5,175/11,075 (46.7)	3,016/8,560 (35.2)	2,962/41,810 (7.1)
NIHSS day 7	11 (4–18)	18 (14–22)	18 (14–22)	2 (0–4)
mRS 0–2 day 7	2,689/15,801 (17)	117/9,346 (1.3)	74/7,433 (1)	19,394/30,700 (63.2)
mRS 0–3 day 7	4,556/15,801 (28.8)	427/9,346 (4.6)	325/7,433 (4.5)	24,235/30,700 (78.9)
Stroke etiology	15,226	8,621	6,462	22,038
Cardioembolism	8,763 (57.6)	4,690 (54.4)	3,769 (55.6)	10,669 (48.4)
Large artery	6,463 (42.4)	3,931 (45.6)	3,008 (44.4)	11,369 (51.6)
mRS 0–2 at 90 days	4,622/17,808 (26)	532/9,857 (5.4)	374 (4.9)	26,806/36,648 (71.9)
mRS 0–3 at 90 days	7,048/17,808 (39.6)	1,489/9,857 (15.1)	1,111 (14.6)	30,826/36,648 (82.9)
Mortality at 24 hours	2,675/19,562 (13.7)	2,298/11,048 (20.7)	1,715 (20.1)	403/41,593 (1)
Mortality at 90 days	5,887/17,871 (32.9)	4,836/9,864 (49)	3,728 (48.9)	1,980/36,702 (5.4)

Values are presented as median (interquartile range) or number/total number (%).
SHS, severe hemispheric syndrome; pSHS, persistent severe hemispheric syndrome; NIHSS, National Institutes of Health Stroke Scale; CED, cerebral edema; PH2, parenchymal hemorrhage type 2; rPH2, remote parenchymal hemorrhage type 2; SAH, subarachnoid hemorrhage; SICH, symptomatic intracranial hemorrhage; mSITS-MOST, modified version of the Safe Implementation of Thrombolysis in Stroke Monitoring Study; ECASS-II, European-Australian Cooperative Acute Stroke Study 2; mRS, modified Rankin Scale.

https://doi.org/10.5853/jos.2022.01956