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

Magnus Thorén[1], M.D., Elsa Azevedo[2], M.D., Ph.D., Jesse Dawson[3], M.D., Jose A Egido[4,], M.D., M.Phil., Anne Falcou[5], M.D., Ph.D., M.Sc., Gary A Ford[6], FRCP, Staffan Holmin[7], M.D., Ph.D., Robert Mikulik[8], MD, PhD, Jyrki Ollikainen[9], M.D., Nils Wahlgren[1], M.D., Ph.D., Niaz Ahmed[1], M.D., Ph.D.

1. Department of Neurology, Karolinska University Hospital and Department of Clinical Neuroscience, Karolinska Institutet, Sweden

2. Department of Neurology, São João Hospital Center, and Department of Clinical Neurosciences and Mental Health, Faculty of Medicine of University of Porto, Portugal

3. Institute of Cardiovascular and Medical Sciences, College of Medical, Veterinary & Life Sciences, University of Glasgow, United Kingdom

4. Stroke Unit, Neurology Department, Hospital Clínico San Carlos, Madrid, Spain

5. Emergency Department Stroke Unit, Policlinico Umberto I Hospital, "Sapienza" University of Rome, Rome, Italy

6. Acute Stroke Service, Oxford University Hospitals NHS Foundation Trust, and Radcliffe Department of Medicine, Oxford University, United Kingdom

7. Department of Neuroradiology, Karolinska University Hospital and Department of Clinical Neuroscience, Karolinska Institutet

8. International Clinical Research Center and Department of Neurology, St. Anne's University Hospital Brno, and Faculty of Medicine, Masaryk University, Brno, Czech Republic[9].

9. Department of Neurology, Tampere University Hospital, Tampere, Finland

Corresponding Author: Dr Magnus Thorén, MD

Karolinska Stroke Research

Department of Neurology R3:04

Karolinska University Hospital

S-17176 Solna, Sweden

Fax: +46 8 517 737 57

Phone: +46 8 517 736 28

E-mail: magnus.thoren@sll.se

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List of tables and figures

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

Abstract

Background – 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 (IVT).

Methods – We used an image-based classification of CED with three degrees of severity (less severe CED 1 and most severe CED 3) on post-IVT imaging scans. We extracted data from 42187 patients recorded in the SITS-International Register during 2002-2011. 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 9579/42187 patients (22.7%: 12.5% CED 1, 4.9% CED 2, 5.3% CED 3). In patients with CED vs. no CED, the baseline NIH stroke scale (NIHSS) score was higher (17 vs. 10; P<0.001), signs of acute infarct was more common (27.9% vs. 19.2%; P<0.001), hyperdense artery sign was more common (37.6% vs. 14.6%; P<0.001), and blood glucose was higher (6.8 vs. 6.4 mmol/L; P<0.001). Baseline NIHSS, 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 cerebral edema are NIHSS, 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 and/or surgical treatment.

Introduction

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 2nd and 5th day after stroke onset.[4,5] A large and potentially life-threatening infarct of the territory of the middle cerebral artery territory (MCA) is often called a malignant MCA infarct.[1] If treated conservatively, about 50-80% of patients with this condition die.[6-8] Surgical treatment by early decompressive hemicraniectomy (DHC) decreases mortality in selected patients, and DHC 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 MCA infarction were size of infarct, size of perfusion deficit and need for mechanical ventilation.[11] Previous studies in patients treated with IVT found that baseline NIHSS, onset-to-treatment time, hyperdense artery sign (HAS) and early infarct signs on first CT[12] and presence of a large ischemic core at baseline[13] were independent predictors of cerebral edema.

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, an internet-based academic interactive, prospective register 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 2002-2011 were extracted.

Variables

Data collected for this study were baseline characteristics including demographic, risk factors, medications, stroke severity as measured by National Institutes of Health stroke scale (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 CT or MRI brain imaging was carried out between 22 h and 36 h 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 22-36 hours and/or additional post-treatment scans, rated by local investigators. If present, CED was classified into three 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 was partly based on

ECASS-2 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, e.g. effacement of cortical sulci or ventricular compression.[15]

Secondary outcome measures were the proportion of patients with symptomatic intracerebral hemorrhage (SICH), according to three 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 22–36 h post-treatment imaging, combined with a neurological deterioration of 4 points or more on the NIHSS from baseline, or from the lowest NIHSS value between baseline and 24 h, or leading to death.[14] SICH per ECASS 2 was defined as any hemorrhage plus a neurological deterioration of 4 points or more 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 register 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 chi-square 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<.05 was used through 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 two questions: first, whether odds ratios 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<.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 (AUC) by receiver operating characteristic (ROC) analyses and the Hosmer-Lemeshow test.

Results

In total, 45071 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 22-36 hours (or any extra investigation) was either missing or uncertain. The remaining 42187 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 (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 22-36 hours examination. A minority of patients, 3.5%, had

their edema status changed between the 22-36 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<.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 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 and 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 that receive IVT.

In univariable analysis (Table 2), the following clinical or radiological baseline variables were positively associated (increased risk of edema development) with all three edema types (P<.05) compared to no edema: NIHSS, impaired consciousness, signs of current ischemia on imaging, HAS and blood glucose. Point estimates of odds ratios (OR) in most cases increased with severity of edema. Highest OR was observed for HAS in CED 1 and CED 3 compared to no CED. In addition, history of diabetes mellitus, hypertension, atrial fibrillation and congestive heart failure were positively associated with all three CED types. OR for these associations were modest, below 1.6. Previous stroke and current smoker were negatively associated (lower risk of edema development) with all three types. The following variables had a negative association with only one or two CED types: male gender (CED 1 and CED

3), OTT (CED 1 and CED 2), mean arterial pressure (CED 1), previous TIA (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 ($P<.05$) with all three 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 odds ratios for edema.

Table 3 shows results from the stepwise regression analysis with continuous variables categorized in quartiles. Because few patients had information on previous TIA 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 gender, onset-to-treatment time, 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. OR for other variables ranged between 1 and 2. Previous

stroke had a significantly lower OR for CED 1 and CED 2. ROC analysis resulted in similar AUC:s for all three models, 0.72-0.82, 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 ICD-10, 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 ICD diagnosis in the registry.

The proportions of patients with various definitions of SICH are shown in Figure 1. The frequency of all types of SICH increased by severity of CED and the most severe type of SICH, i.e. SICH per SITS-MOST increased up to 15.9% compared to 0.5% in patients with no edema.

Follow-up with mRS scoring at three months was completed for 33737 patients, i.e. 80% of the study cohort (Figure 2). The proportion of deaths (mRS 6) at follow-up were: 8% (no CED), 18% (CED 1), 39% (CED 2) and 65% (CED 3). The proportion of patients having reached mRS 0-2 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 five 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 in three 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 to 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] Since 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 CT or MRI.[13,19,24-27]

For two 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 blood-brain barrier 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 edema, in our cohort CED 1 and CED 2. This finding remains largely unexplained. However, a loss of brain tissue due to 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 to 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 to 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% to 71%) compared to our study (26% to 32%). Also, frequency of CED 2 and 3 was similar between our and Helsinki cohort (10%). Only limited data is 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 three-level edema imaging grading scheme different from ours, found a 45%, i.e. clearly higher, frequency of any cerebral edema.[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 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 due to larger infarcts since a study indicates that the presence of CED (as measured by MRI) independently predicts worse outcome also in smaller infarcts.[33] The absolute excess mortality at 3 months, compared to 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 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 CT, 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 believe 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 22-36 hours, i.e. early, using data available at baseline. Third, it is an observational study based on retrospective analysis, although data were collected 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 cerebral edema. 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 due to factors not recorded among the baseline variables.

In conclusion, we found that the most important baseline predictors for early cerebral edema 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 and/or BBB damage. Based on these clinical predictors, patients at risk of cerebral edema 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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Figure legends

Figure 1. Distribution of symptomatic intracerebral hemorrage (SICH) among patients with different CED types on imaging at follow-up.

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

Tables

Variable	N	No CED n=32608	Any CED n=9579	P
Age, years, median (IQR)	42169	70 (60–77)	70 (60–77)	.65 *
Male gender, %	42187	57.5	56.1	.01 †
OTT, min, median (IQR)	41543	147 (117–175)	145 (117–170)	<.001 *
NIHSS score, median (IQR)	41595	10 (6–15)	17 (13–20)	<.001 *
NIHSS item 1a ≥1, %	41591	16.6	34.2	<.001 †
Infarct signs on imaging, %	39482	19.2	27.9	<.001 †
Hyperdense artery sign, %	39294	14.6	37.6	<.001 †
Blood glucose, mmol/l, median (IQR)	39777	6.44 (5.60–7.80)	6.8 (5.83–8.30)	<.001 *
Mean arterial pressure, mmHg, median (IQR)	41304	106 (97–115)	105 (95–114)	<.001 *
Previous stroke, %	41566	13.7	11.3	<.001 †
Previous TIA, %	7354	8.2	5.5	<.001 †
Current smoker, %	38878	23.1	20.7	<.001 †
Diabetes mellitus, %	41576	16.6	19.6	<.001 †
Hypertension, %	41426	62.9	66.1	<.001 †
Hyperlipidemia, %	38295	34.3	35.9	.005 †
Atrial fibrillation, %	41222	23.2	30.5	<.001 †
Congestive heart failure, %	41292	8.1	10.7	<.001 †
Any antiplatelet treatment, %	41614	36.2	36.1	.99 †
Statin treatment, %	7356	28.5	25.7	.03 †
Oral anticoagulant treatment, %	41932	2.36	3.06	<.001 †

Table 1. Baseline variables in patients without and with edema.

* ANOVA
† Pearson chi-square test

Variable	CED 1		CED 2		CED 3	
	OR	95% CI	OR	95% CI	OR	95% CI
Age	1.00/10 years	0.98–1.02	1.06/10 years	1.02–1.10	0.97/10 years	0.94–1.00
Male gender	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, mmHg, median (IQR)	0.93/10 mmHg	0.91–0.95	0.99/10 mmHg	0.95–1.02	1.03/10 mmHg	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

Table 2. Univariable associations between baseline variables and CED types. Reference: CED 0

Variable	CED 1*			CED 2†			CED 3‡		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Age				0.99	0.99–1.00	.001			
Male gender	1.10	1.02–1.18	.013						
OTT, min									
117–145	1.10	1.00–1.22	.063						
146–174	1.15	1.04–1.28	.006						
≥175	1.10	0.99–1.22	.075						
NIHSS score									
7–11	1.85	1.61–2.13	<.001	2.83	2.09–3.84	<.001	2.10	1.52–2.90	<.001
12–16	3.75	3.27–4.29	<.001	7.86	5.87–10.51	<.001	8.11	6.02–10.91	<.001
≥17	5.64	4.92–6.46	<.001	15.41	11.55–20.56	<.001	16.50	12.3–22.11	<.001
NIHSS item 1a ≥1	1.11	1.02–1.21	.019	1.36	1.22–1.53	<.001	1.58	1.42–1.76	<.001
Infarct signs on imaging	1.27	1.17–1.39	<.001	1.31	1.15–1.48	<.001	1.52	1.35–1.70	<.001
Hyperdense artery sign	2.09	1.92–2.26	<.001	2.13	1.90–2.39	<.001	2.51	2.25–2.79	<.001
Blood glucose, mmol/l									
5.67–6.53	1.07	0.96–1.19	.233	0.97	0.83–1.13	.715	1.08	0.92–1.27	.319
6.54–7.89	1.21	1.09–1.34	<.001	1.05	0.95–1.29	.209	1.30	1.11–1.51	.001
≥7.90	1.35	1.22–1.50	<.001	1.22	1.08–1.48	.004	1.93	1.67–2.24	<.001
Previous stroke	0.81	0.72–0.90	<.001	0.84	0.71–0.99	.034			
Diabetes mellitus				1.23	1.06–1.42	.005			
Hypertension				1.19	1.06–1.42	.005			
Hyperlipidemia	1.11	1.03–1.19	.007						
Atrial fibrillation	1.12	1.03–1.21	.006	1.21	1.07–1.36	.002			
Congestive heart failure				1.23	1.04–1.46	.014			

Table 3. Final multivariable models for prediction of CED types. Reference: CED 0. For continuous variables, odds ratio reference (OR 1.00) is the lowest quartile.

* Model AUC=0.72. Hosmer-Lemeshow P=.19.
† Model AUC=0.79 . Hosmer-Lemeshow P=.59.
‡ Model AUC=0.82 . Hosmer-Lemeshow P=.02.