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ORIGINAL COMMUNICATION

The effect of thrombolysis on short-term improvement depends on initial stroke severity

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Abstract A large number of parameters have been identified as predictors of early outcome in patients with acute ischemic stroke. In the present work we analyzed a wide range of demographic, metabolic, physiological, clinical, laboratory and neuroimaging parameters in a large population of consecutive patients with acute ischemic stroke with the aim of identifying independent predictors of the early clinical course. We used prospectively collected data from the Acute Stroke Registry and Analysis of Lausanne. All consecutive patients with ischemic stroke admitted to our stroke unit and/or intensive care unit between 1 January 2003 and 12 December 2008 within 24 h after last-well time were analyzed. Univariate and multivariate analyses were performed to identify significant associations with the National Institute of Health Stroke Scale (NIHSS) score at admission and 24 h later. We also sought any interactions between the identified predictors. Of the 1,730 consecutive patients with acute ischemic stroke who were included in the analysis, 260 (15.0%) were thrombolyzed (mostly intravenously) within the recommended time window. In multivariate analysis, the NIHSS score at 24 h after admission was associated with the NIHSS score at admission ($\beta = 1, p < 0.001$), initial glucose level ($\beta = 0.05, \quad p < 0.002$) and thrombolytic intervention ($\beta = -2.91, p < 0.001$). There was a significant interaction between thrombolysis and the NIHSS score at admission ($p < 0.001$), indicating that the short-term effect of thrombolysis decreases with increasing initial stroke severity. Thrombolytic treatment, lower initial glucose level and lower initial stroke severity predict a favorable early clinical course. The short-term effect of thrombolysis appears mainly in minor and moderate strokes, and decreases with increasing initial stroke severity.

Keywords Stroke severity · Severe strokes · Thrombolysis · Glucose

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Introduction

Several prognostic models have been developed and validated to predict long-term outcome in patients with acute stroke [1–4]. These indices include several variables including age, the National Institute of Health Stroke Scale (NIHSS) score, gender, prior stroke, diabetes mellitus and fever. Such models provide prognostic information that can be provided to the patient and family, and also help clinicians in making decisions regarding treatment and rehabilitation. However, fewer data are available regarding the predictors of the early course following acute stroke [5], and studies have been limited by a small sample size or have involved the analysis of a limited number of variables.

In the present study we analyzed a wide range of demographic, metabolic, physiological, clinical, laboratory and neuroimaging parameters in a large population of patients with acute ischemic stroke with the aim of identifying independent predictors of the early clinical course.

Methods

We used prospectively collected data from the Acute Stroke Registry and Analysis of Lausanne (ASTRAL) [6]. All consecutive patients who were admitted to the stroke unit and/or intensive care unit of our hospital between 1 January 2003 and 12 December 2008 within 24 h of the last-well time with a main diagnosis of acute ischemic stroke were prospectively included. Recurrent strokes were registered as new events if they led to a new admission. Exclusion criteria included transient ischemic attack (TIA), intracerebral hemorrhage, subarachnoidal hemorrhage, cerebral sinus venous thrombosis and late admission (>24 h after stroke onset). Stroke severity at 24 h as measured using the NIHSS score after admission was the main outcome. Acute recanalization treatments were given according to the recommendations of the European Stroke Organization [7]: before the publication of ECASS-III [8], intravenous thrombolysis given within 3 h and within 4.5 h thereafter, and endovascular treatments within 6 h; these patients were considered as treated "within the recommended time window" in the current analysis. Symptomatic intracranial hemorrhage (sICH) within the first 24 h was defined according to the ECASS-II criteria [9]. Stroke etiology was classified according to the TOAST classification [10].

Demographic data (age, gender, ethnicity, insurance), metabolic parameters (glucose, creatinine, cholesterol levels), full blood count, physiological parameters (temperature, heart rate, blood pressure) and the NIHSS score at admission and 24 h after admission were prospectively recorded for each patient. When possible, NIHSS scores were determined by a NIHSS-certified stroke unit physician who was not blinded to the treatment. When the NIHSS scores were determined by a noncertified physician (particularly during night and weekend duties), they were discussed between the assessing and a NIHSS-certified physician the next working day. In intubated patients, NIHSS score determinations were in general performed before intubation, and an effort was made to assess the NIHSS score during a window without sedation. If more than one blood pressure measurement was available at admission or at 24–48 h, the first recording was registered. Moreover, a systematic search was performed for every patient to identify vascular risk factors including arterial hypertension, atrial fibrillation, diabetes mellitus, valvulopathy, coronary artery disease and smoking. Also recorded were prehospital Rankin score (mRS), previous strokes, TIAs or retinal ischemia, as well as prior medication. Finally, silent lesions, leukoaraiosis and early ischemic changes on brain CT scans were recorded as well as arterial stenosis/occlusion, since all patients underwent brain parenchymal (mostly CT) and arterial (mostly CT angiography) imaging. Extra- and/or intracranial stenosis of >50% or occlusion of the arteries supplying the ischemic territory was considered significant.

This study was approved by the ethics committee of our institution and was therefore performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Statistical analysis

In this retrospective analysis, heart rate, ejection fraction and temperature were analyzed as categorical variables, with the cut-off values at 90 min^{-1}, 30% and 38°C, respectively. Blood pressure was analyzed as a continuous variable. Laboratory values were analyzed as continuous variables and are reported as median (interquartile range, IQR). NIHSS scores at admission and 24 h later were analyzed as continuous variables.

All parameters presented in Table 1 were included in a univariate analysis to identify significant associations with NIHSS score at 24 h after admission. The parameters found to be of statistical significance ($p < 0.05$) were entered in a multivariate robust regression analysis model to search for independent associations. The level of significance was set at 95% ($p = 0.05$).

Results

Between 1 January 2003 and 12 December 2008, 3,165 patients with an acute ischemic stroke were admitted to the stroke unit or intensive care unit. Of these, 1,435 (45.3%) were excluded for the following reasons: intracerebral hemorrhage (166 patients, 5.2%), TIA (577, 18.2%), late admission (623, 19.7%), ocular ischemia (57, 1.8%) and lack of NIHSS score at 24 h (12, 0.4%). Finally, 1,730 patients with acute ischemic stroke were included in our analysis. Interestingly, 41% of patients had a prehospital mRS of ≥1, probably due to the fact that we did not analyze only first-ever strokes, but also recurrences.

Table 1 summarizes the main demographic, clinical, laboratory and imaging data of the patients. The median NIHSS score was 6 (IQR 3–14) at admission and 4 (IQR 2–11) 24 h later. There was no interaction between NIHSS score at admission and the infarct side. Thrombolysis was performed within the recommended time limits in 260 patients (15.0%, of which 0.8% were acute endovascular treatments), of whom 10 (3.8%) had a NIHSS score of 4, none had a score of 3 and 1 (0.4%) had a score of 2. Only one of the nonthrombolyzed patient and 5 (1.9%) of the thrombolyzed patients suffered a sICH. The admission NIHSS score of the patients with sICH was ≥21 in two (33%), 16–21 in two (33%) and 10–15 in two (33%); no

Table 1 Patient characteristics ($n = 1{,}730$)

Characteristic	Value
Demographics	
Age (years)	72 (60–81)
Female gender	766 (44.3%)
Last-well time to admission time (min)	
Known-onset stroke	137 (87–198)
Unknown-onset stroke	753 (496–980)
Laboratory measurements (within 24 h of stroke onset)	
Hemoglobin (g/l)	140 (129–151)
White blood cell count ($\times 10^3$/l)	8.1 (6.5–10.7)
Platelet count ($\times 10^3$/l)	225.0 (186–273)
Glucose (mmol/l)	6.5 (5.7–7.9)
Creatinine (mmol/l)	90 (75–107)
Total cholesterol (mmol/l)	5.4 (4.6–6.5)
Vital signs/Clinical examination (at admission)	
Temperature (°C)	36.4 (36.0–36.8)
Heart rate (min^{-1})	77.5 (67.7–90.0)
Systolic blood pressure (mmHg)	158 (140–178)
Diastolic blood pressure (mmHg)	89 (80–100)
NIHSS score ≤4	705 (40.6%)
NIHSS score >22	115 (6.6%)
Site of infarction	
Right	717 (41.5%)
Left	836 (48.3%)
Bilateral	163 (9.4%)
Undetermined	14 (0.8%)
Arterial territory affected	
Anterior circulation	1,074 (62.1%)
Vertebrobasilar circulation	502 (29%)
Both territories	21 (1.2%)
Undetermined	133 (7.7%)
Medical history/Previous treatment	
Hypertension	1,151 (66.5%)
Atrial fibrillation	438 (25.3%)
Diabetes mellitus	233 (13.5%)
Newly diagnosed diabetes mellitus	30 (1.7%)
Prosthetic valve/mechanical/biological	58/45/13 (3.4%)
Coronary artery disease	262 (15.1%)
Smoking	411 (23.8%)
Previous stroke(s)/TIA(s)	462 (26.7%)
Antiplatelet treatment	655 (37.8%)
Antihypertensive agents	932 (53.7%)
Oral hypoglycemic agents	137 (7.9%)
Insulin	60 (3.5%)
Anticoagulant	171 (9.9%)
Lipid-lowering drugs	393 (22.7%)
Prestroke Rankin score 0	1,020 (59.0%)
Thrombolysis within recommended time limits	
Intravenous	246 (14.2%)
Intraarterial	14 (0.8%)
Symptomatic hemorrhagic transformation	5 (1.9%)
Imaging study findings	
Silent lesions on brain CT scan	380 (22.0%)
Acute ischemic lesions on brain CT scan at admission	531 (30.7%)
Leukoaraiosis	360 (20.8%)
Significant pathology on arterial imaging	668 (38.6%)
Stroke subtypes	
Atherosclerotic (>50% stenosis)	218 (12.6%)
Possibly atherosclerotic (<50% stenosis)	252 (14.6%)
Cardioembolic	501 (29.0%)
Dissection	83 (4.8%)
Lacunar/microangiopathy	260 (15.0%)
Other/rare	68 (3.9%)
Multiple/coexisting	84 (4.9%)
Unknown	190 (11.0%)
Patent foramen ovale	67 (3.9%)

Categorical variables are presented as *n* (%). Continuous variables are presented as median (interquartile range).

patient with an admission NIHSS score ≤4 suffered a sICH.

In the univariate analysis, 16 variables showed a significant association with the NIHSS score at 24 h after admission (Table 2). However, only initial stroke severity ($\beta = 1$, $p < 0.001$), glucose level ($\beta = 0.05$, $p = 0.002$) and thrombolytic intervention ($\beta = -2.91$, $p < 0.001$) remained significant in the multivariate analysis. A significant interaction ($p < 0.001$) was identified between the admission NIHSS score and intervention (Fig. 1). This interaction was no longer statistically significant for NIHSS scores of >21. This interaction remained significant after excluding patients (a) with a low NIHSS score (≤4), (b) treated with intraarterial thrombolysis, and (c) with a sICH. We also sought to determine whether this interaction remained when the end-point was a favorable functional outcome at 3 and 12 months (as represented by a mRS ≤2); however, this was not the case, since thrombolysis was no longer a significant predictor of outcome.

Discussion

Initial stroke severity, thrombolytic treatment and glucose levels were correlated with the early neurological course as measured by the NIHSS score at 24 h after admission. In particular, thrombolytic intervention improved the early clinical course in patients with minor and moderate strokes,

Table 2 Uni- and multivariate analysis of predictors of NIHSS score at 24 h after admission

Variable	Univariate analysis		Multivariate analysis	
	β	p value	β	p value
NIHSS score at admission	1	<0.001	1	<0.001
NIHSS score at 4–6 h	1	<0.001		
Temperature	2.67	0.001		
Heart rate	1.47	<0.001		
Glucose	0.27	<0.001	0.05	0.002
C-reactive protein	0.11	<0.001		
White cell count	0.54	<0.001		
Hemoglobin	−0.29	0.001		
Red cell distribution width	0.24	0.01		
Age	0.03	<0.001		
Gender (female)	−0.92	0.001		
Prehospital Rankin score	1.03	<0.001		
Atrial fibrillation	1.74	<0.001		
Intervention	4.21	<0.001	−2.91	<0.001
Acute ischemic lesion on CT/MRI at admission	5.77	<0.001		
Significant arterial pathology	5.27	<0.001		

All parameters were assessed at admission. Only significant values are presented.

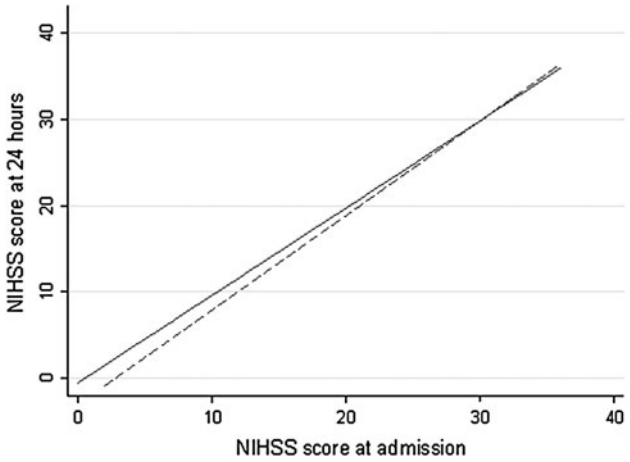

Fig. 1 Relationship between admission NIHSS score and 24-h NIHSS score at a fixed level of acute glucose (*dashed line* intervention patients, *continuous line* nonthrombolyzed patients)

but its effect decreased with increasing initial stroke severity.

Currently, the upper NIHSS score for intravenous thrombolysis as set by the European Medicines Agency is 25 [11], whereas the US Food and Drug Administration states that the risks of treating acute ischemic stroke with alteplase may be increased in patients with a severe neurological deficit (NIHSS score >22) and should be weighed against the anticipated benefits [12]. The rationale for this recommendation is based on the fact that the safety and efficacy of thrombolysis in patients with severe stroke have not been tested in randomized controlled trials, since such patients are usually excluded from thrombolysis trials. Our findings from a stroke center which currently does not have an upper exclusion limit for severe strokes, show that the effect of thrombolysis decreases with increasing initial stroke severity. Recently, an analysis of the Virtual International Stroke Trials Archive (VISTA) has shown that the significant association of outcome with thrombolysis is lost if the baseline NIHSS score is ≥24, which the authors attributed to small sample size and wide confidence intervals [13]. Also, a high baseline NIHSS score was an independent predictor of poor outcome in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) [14]. A subgroup analysis of the ECASS-III trial [15] and a pooled analysis of the ATLANTIS, ECASS and NINDS rTPA trials [16] did not provide strong evidence to support exclusion of patients from treatment based on their initial NIHSS score for any onset-to-treatment interval; however, patients with a very severe stroke were under-represented in these trials, therefore limiting the amount of data from patients with a high NIHSS score. Further studies are warranted to provide more reliable conclusions.

In a recent analysis of the same dataset, we showed that hyper- and hypoglycemia after stroke is deleterious in acute ischemic stroke. We found a J-shaped association between glucose and the 24-h and 12-month outcome [17]. The negative effect of hyperglycemia on short-term outcome may be due to accelerated penumbra loss from high glucose values [18, 19] and underlines the need to pay particular attention to proper glucose management in acute stroke. We failed to identify an association between initial blood pressure and outcome. Previous studies have yielded controversial results about the effect of blood pressure on stroke severity and outcome [20]. Accordingly, it is still

unclear whether its active treatment influences stroke outcome, which is reflected by the level of recommendation in the European Stroke Organisation and American Heart Association/American Stroke Association guidelines on stroke management [7, 21]. Several other well-known predictors of early and late outcome, such as age, chronic and early ischemic changes on neuroimaging, prehospital disability, admission temperature, white cell count and stroke mechanism were not confirmed in our sample; the likely explanation is that most of these parameters were predictors of the baseline NIHSS score in our population (data not shown), which in turn predicted the NIHSS score at 24 h after admission better than these factors themselves. Also, we failed to identify an association between thrombolysis and outcome. We suggest that this may have been due to the moderately small sample size of the study.

The strengths of our study include the large sample size and the wide variety of analyzed parameters, including demographic, clinical, metabolic, physiological, laboratory and neuroimaging variables. In contrast, this study had certain limitations. Firstly, we did not measure initial and final infarct volume, which could have provided a deeper insight into the pathophysiological basis of the reported associations. Secondly, arterial status, recanalization and stroke localization were not included in the current analysis. Thirdly, few of our patients received acute endovascular treatments, limiting the possibility of detecting an effect of different recanalization treatments. Finally, this was an observational retrospective study and patients were not randomized to treatment.

In conclusion, initial stroke severity, thrombolytic treatment, and initial glucose values predict the early clinical course over 24 h. Thrombolytic intervention improved early clinical progression in patients with minor and moderate stroke, but its effect decreased with increasing initial stroke severity. According to these results, treatment modalities other than standard intravenous thrombolysis need to be explored in patients with severe stroke.

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