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Combined Clinical and Radiological Prognostic Model in Acute Ischemic Stroke

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Abstract

We sought to propose and test the validity of a comprehensive prognostic model in middle cerebral artery-stroke treated with intravenous thrombolysis. A total of 127 consecutive patients (aged 70 ± 12 years; 54% males) were included in this retrospective study. Variables included in our prognostic model were: NIHSS on admission (1-3 points), occurrence of hyperdense middle cerebral artery sign and early ischemic signs on baseline CT (1 point each), NIHSS at 24 hours (0-3 points), posttreatment hemorrhage (1 point), and infarct volume (0-4 points). The score range was 1-13, with higher values suggest unfavorable prognosis. Our prognostic score was correlated with the modified Rankin scale (mRS) at 3 months after stroke [correlation coefficient of 0.62, $P < 0.001$] and can thus help early prediction of the functional outcome. Logistic regression showed that NIHSS at 24 hours and EICs on baseline CT were independent predictor of our prognostic score (adjusted odds ratio of 4.1 and 5). Adopting a cut-off value of prognostic score ≤ 3 for favorable prognosis and ≥ 7 for unfavorable prognosis helped to predict the need for institutionalization and the functional outcome with higher accuracy and predictive values compared with using scores only based on NIHSS.

Key words: acute ischemic stroke, prognostic score, computed tomography, infarct volume, favorable prognosis, cut-off values.

Introduction

Acute ischemic stroke is one of the leading causes of morbidity and mortality (Muller-Nordhorn *et al.,* 2008). Stroke unit treatment and reperfusion with recombinant tissue plasminogen activator (rtPA) are major therapeutic achievements but there is great need for further improvement to reduce individual and socio-economic burden. A valid and simple clinical predictive model could help improve stroke care, e.g. by early instigation of proper rehabilitation measures. A main drawback in clinical stroke research has been the heterogeneity of patient materials. Predictive models, allowing for classification of patient groups would greatly enhance conditions for evaluation of novel stroke unit care strategies. Foreseeing patient outcome may also provide a tool to streamline stroke care.

Several models to predict the functional outcome after stroke have been reported in the literature with variable validity. The six simple variable (SSV) model was developed in the Oxfordshire Community Stroke Project and validated in a hospital based cohort, with the main aim to predict survival free of dependency (modified Rankin Scale < 3) (Counsell *et al.,* 2002). This model includes age, dependency and living alone before the stroke and ability to lift arms off the bed, ability to talk normally and ability to walk independently after the stroke. Another model, based on age and the National Institutes of Health Stroke Scale (NIHSS), was recently proposed (Konig *et al.,* 2008). Brain imaging with computed tomography (CT) and magnetic resonance imaging (MRI) has helped improve diagnosis and outcome prediction. Infarct volume measured by MRI was found to significantly predict outcome after stroke (Saunders *et al.,* 1995). Semiquantitative estimation of infarct extension on CT with the ASPECTS score can predict good functional outcome (Barber *et al.,* 2000). Other studies have combined clinical and radiological variables. CT-features and admission NIHSS showed to be important predictors of survival in hyperacute extensive MCA infarcts (Lam *et al.* 2004). ASPECT score applied to perfusion CT in acute stroke patients showed to predict the clinical outcome of intravenous thrombolysis and was superior to NIHSS, early ischemic changes on baseline

non-enhanced CT and CT-angiography (Kloska *et al.,* 2007). However, Johnston et al showed that NIHSS at 1 week is highly predictive of 3-month outcome in ischemic stroke patients and the addition of infarct volume did not improve the accuracy of the outcome prediction (Johnston *et al.,* 2002). Despite these attempts, there is still a need for a reliable predictive model that can be applied early in the stroke treatment.

Taking into consideration the present controversy about the validity of different models combining the clinical and imaging data, we sought to propose a comprehensive but simple model based on clinical and radiological data available 24 hours after treatment with rtPA. The subsequent aim of the study was to test the validity of our proposed prognostic score.

Methods and Materials

127 consecutive patients with middle cerebral artery (MCA)-stroke treated with intravenous rtPA at the neurology department of our university hospital with specialized stroke unit were identified from the thrombolysis register and included in the retrospective analysis of this study. Mean age was 70 ± 12 years (mean ± SD), median age 73 (range 30-87 years); 54% were males. All patients were examined with a baseline plain CT of the brain on admission and 24 hours after treatment, using a multislice CT (SOMATOM Sensation 16, Siemens AG, Forchheim, Germany) with slice collimation of 0.75 mm and image thickness of 4.5 mm.

For the purpose of our prognostic model the following data were collected for every individual patient: (a) NIHSS on admission. (b) Occurrence of hyperdense middle cerebral artery sign (HMCAS) and other early ischemic signs (EIC) on baseline CT. The EICs that were sought for were: loss of insular ribbon, sulcal effacement, obscuration of lentiform nucleus, loss of gray and white matter differentiation in the basal ganglia and focal hypoattenuation. (c) NIHSS 24 hours after treatment with rtPA. (d) Occurrence of cerebral hemorrhage at 24 hours' CT-control. (e) Measurement of infarct volume on CT performed 24 hours after thrombolysis. Volume measurements were performed using the "Volume" application at a Leonardo workstation. (f) Functional outcome at three months according to the modified Rankin Scale (mRS). (g) The patients' accommodation at 3-months follow up was recorded and categorized for the purpose of analysis into: (a) living in own home (either independentlvy or with municipal help), or (b) institutionalized (hospitalized, living nursing home or in rehabilitation units).

Occurrence of EICs and HMCAS were evaluated independently by two neuroradiologists who were blinded to stroke symptoms and the side affected. The functional outcome with mRS at three months was evaluated by a stroke neurologist. The neurologist who did the evaluation was blinded to the occurrence of EIC at the baseline CT and the infarct size on CT 24 hours after treatment. Furthermore, patient outcome was classified as favorable (independence; mRS 0–2) or unfavorable (dependence or death; mRS 3–6).

Table 1.
The here proposed prognostic model. Numbers written in bold represent the maximum score that can be recorded for the given variable.

	Score
1. NIHSS at admission:	
Mild stroke: ≤ 6	1
Moderate stroke: 7-15	2
Severe stroke: ≥ 16	**3**
2. Baseline CT:	
No EICs	0
HMCAS	**1**
Other EICs	**1**
3. NIHSS: 24 hours after treatment:	
NIHSS ≤ 2	0
NIHSS: 3-6	1
NIHSS: 7-15	2
NIHSS: ≥ 16	**3**
4. Bleeding on CT 24 hours after treatment	**1**
5. Infarct volume on CT 24 hours after treatment:	
No infarct	0
< 40 cm3	1
40-79 cm3	2
80-159 cm3	3
≥ 160 cm3	**4**
Maximal score	13

NIHSS = National Institutes of Health Stroke Scale; EICs = Early ischemic changes; HMCAS = Hyperdense middle cerebral artery sign.

Table 1 shows our proposed prognostic model: NIHSS on admission (1–3 points), occurrence of HMCAS and early ischemic signs (EIC) on baseline CT (1 point each), NIHSS at 24 hours (0–3 points),

occurrence of posttreatment hemorrhage (1 point), and infarct volume (0–4 points). Score of one and 13 means favorable and unfavorable prognosis, respectively.

For comparison a prognostic score based only on baseline NIHSS in predicting the functional outcome was calculated for every individual patient. We also tested the validity in our population of a prognostic score based on a cut-off value for the baseline NIHSS: an NIHSS of ≤ 6 predicts favorable outcome and a score of ≥ 7 predicts unfavorable outcome (Adams *et al.,* 1999).

Statistical analysis

Statistical analysis was performed using SPSS version 17. The correlation between our proposed prognostic score and different variables was tested by Spearman's correlation test for continuous variables and by Mann-Whitney U test for categorical variables. Multivariate logistic regression was performed to determine which of the variables were independent predictors of our prognostic model. Analysis of the data obtained from the aforementioned tests helped us to define cut-off values for prognostic scores for favorable and unfavorable functional outcome. Fisher's exact test and/or chi-square probability tests were performed to test the validity of proposing: (a) the prognostic score of ≤ 3 as a cut-off value for favorable prognosis (mRS ≤ 2), and (b) the prognostic score of ≥ 7 as a cut-off value for unfavorable prognosis (mRS 3-6). Statistical significance was set to a P value ≤ 0.05.

Results

The mean value for the prognostic score for the whole study population was 5.4 ± 3.1 (mean ± SD, median = 5), Table 2. Patients with favorable outcome (mRS ≤ 2) constitute 49 % of patient population (n = 62), Table 3. The prognostic scores recorded for the whole study cohort, among patients with favorable functional outcome and among those with unfavorable functional outcome are shown in Table 3 and Figure 1. Spearmans correlation test showed statistically significant correlation between our proposed prognostic score and functional outcome according to mRS (correlation coefficient 0.62; P < 0.001). There was statistically significant correlation between our prognostic score and NIHSS recorded at admission, NIHSS at 24 hours and with the infarct volume on 24 hours CT control (correlation coefficient of 0.82, 0.87, and 0.85 respectively;

Table 2.
The association between the recorded score according to our prognostic model and different categorical variables.

Prognostic score			
	Mean ±SD	Median	P-value
Whole study population	5.4 ± 3.1	5	
HMCAS			
Patients with HMCAS	8 ± 2.7	8	
Patients with no HMCAS	4.1 ± 2.5	3.5	< 0.001
Other EICs			
Patients with EICs	7.1 ± 3.2	8	
Patients with no EICS	5 ± 3	5	0.003
Bleeding			
Patients with bleeding	8.3 ± 3.2	8.5	
Patients with no bleeding	5 ± 2.9	5	< 0.001
Functional outcome			
Patients with unfavorable outcome (mRS=3–6)	7.4 ± 2.8	8	
Patients with favorable outcome (mRS ≤ 2)	3.3 ± 1.8	3	< 0.001

HMCAS = Hyperdense middle cerebral artery sign

Table 3.
The prognostic scores recorded for the whole study cohort, in patients with favorable functional outcome and in those with unfavorable functional outcome.

Functional outcome			
Score	Unfavorable	Favorable	Total
1	1 (9 %)	10 (91 %)	11
2	2 (14 %)	12 (86 %)	14
3	2 (11 %)	16 (89 %)	18
4	5 (38 %)	8 (62 %)	13
5	10 (53%)	9 (47%)	19
6	7 (58 %)	5 (42 %)	12
7	4 (80 %)	1 (20 %)	5
8	9 (100 %)	0	9
9	7 (88 %)	1 (12 %)	8
10	7 (100 %)	0	7
11	6 (100 %)	0	6
12	5 (100 %)	0	5
	65 (51 %)	62 (49 %)	127

Unfavorable outcome (dependence, mRS = 3–6)
Favorable outcome. (independence, mRS ≤ 2)

Fig. 1

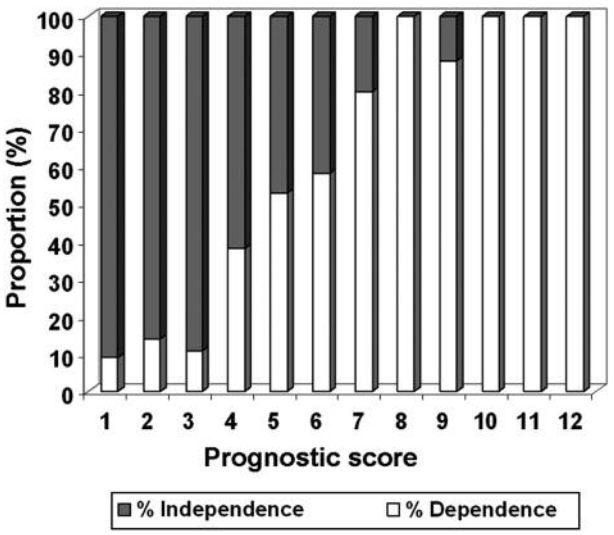

FIG. 1. —The correlation between the recorded prognostic score and the functional outcome according to modified Rankin Scale (mRS). Spearman's correlation coefficient 0.62, P < 0.001.

P < 0.001). Age was not significantly correlated with our prognostic criteria (correlation coefficient of 0.09; P = 0.29). Males recorded higher scores than females (Mean value ± SD was 6.1 ± 3.4 years for males and 4.5 ± 2.5 years, respectively for females, P = 0.07). Our proposed prognostic score showed statistically significant association with HMCAS (P < 0.001), EICs (P < 0.003) on baseline CT, and occurrence of bleeding after treatment with rtPA (P < 0.001), Table 2. Logistic regression showed that NIHSS at 24 hour (P = 0.04 and adjusted odds ratio of 4.1), and EICs on baseline CT (P = 0.03 and adjusted odds ratio of 5) were independent predictors of our proposed prognostic score.

Based on our finding of the significant correlation between our prognostic score and the functional outcome according to mRS (Table 2, Fig. 1), we adopted a prognostic score of ≤ 3 and ≥ 7 as a cut-off value for favorable and unfavourable prognosis, respectively. Adopting these cut-off values: (a) 38

Table 4.

The test of validity of adopting cut-off values for our proposed prognostic score to predict the favorable and the unfavorable prognosis and the form of living after stroke. The table shows also the test of validity of using only baseline NIHSS with a cut-off value of ≤ 6 for favorable prognosis (Adams *et al*., 1999).

Studied variable	Prognostic score	Prognostic score	P-value	Odds ratio	Sensitivity	Specificity	PPV	NPV
Our prognostic score ≤ 3 as cut-off for favorable prognosis:								
	≤ 3	4-13						
mRS ≤ 2	38 (88 %)	24 (29 %)						
mRS 3-6	5 (12 %)	60 (71 %)	<0.001	19.1 (6.8–52.3)	0.61 (0.54–0.66)	0.92 (0.86–0.97)	0.89 (0.78-0.95)	0.71 (0.66–0.75)
Our prognostic score ≥ 7 as cut-off for unfavorable prognosis:								
	≤ 6	≥ 7						
mRS ≤ 2	60 (97 %)	2 (5 %)						
mRS 3-6	27 (3%)	38 (95%)	<0.001	42.2 (10.4-168)	0.97 (0.90-0.99)	0.59 (0.52-0.61)	0.69 (0.64-0.71)	0.95 (0.85-0.99)
Baseline NIHSS of ≤ 6 as cut-off value for favorable prognosis (Adams et al., 1999):								
	HINSS ≤ 6	NIHSS ≥ 7						
mRS ≤ 2	21 (81%)	41 (41%)						
mRS 3-6	5 (19%)	60 (59%)	<0.001	6.1 (2.2-17)	0.34 (0.27-0.38)	0.92 (0.86-0.96)	0.81 (0.64-0.91)	0.59 (0.55-0.62)
Our prognostic score ≤ 3 as cut-off value to predict the form of living after stroke								
	≤ 3	≥ 7						
Home	34 (79%)	21 (53%)						
Institution	9 (21%)	19 (47%)	0.02	3.4 (1.32-8.81)	0.62 (0.54-0.68	0.68 (0.53-0.80)	0.79 (0.69-0.87)	0.48 (0.37-0.56)

mRS = Modified Rankin Scale; PPV = positive predictive value; NPV = Negative predictive value; Institution = Institutionalized patients; Favorable outcome = mRS ≤ 2; Unfavorable outcome = mRS 3-6. Numbers between parentheses in column 5-9 represent 95% confidence interval (95% CI).

out of 43 patients (88 % accuracy) with a score of ≤ 3 had favorable prognosis defined as mRS ≤ 2 ($P < 0.001$, odds ratio 19.1, and sensitivity 0.61), Table 4. (b) 38 out of 40 patients (95% accuracy) with a score of ≥ 7 had unfavorable outcome defined as mRS 3-6 ($P < 0.001$, odds ratio 42.2, and sensitivity 0.97), Table 4. Corresponding values for NIHSS ≤ 6 as cut-off value for favorable prognosis (Adams *et al.,* 1999) showed 81% accuracy, odds ratio of 6.1 and sensitivity 0.34, Table 4.

At 3-months' follow-up: (1) All patients but one patient with prognostic score one lived in their own home without need of external help. (2) Out of 14 patients who scored two: 12 patients lived in their own home without need of external help, one lived in own home with municipal help, and one was hospitalized for pulmonary embolism. (3) Out of 18 patients who scored three: 11 patients lived in their own home without need of external help, five lived in their own home with municipal help, and two were hospitalized for new stroke and renal failure. (4) Out of 5 patients who scored 12: three were dead, one lived in nursing home, and one lived in own home with extensive municipal help. Almost 80% of patients who scored ≤ 3 were living at their own home ($P = 0.02$, odds ratio 3.4, and sensitivity 0.62) Table 4.

Discussion

With our prognostic model, functional outcome could be predicted as early as 24 hours after treatment with rtPA in 83 patients (65 % of study population; 43 scored ≤ 3, and 40 scored ≥ 7) with high accuracy and predictive values. The remaining 44 patients (35%) with prognostic score of 4-6 had a 50% chance of favorable prognosis, Table 3. Post-hoc analysis showed that the mean value of infarct volume of patients with score of 4-6 was 20.3 cm^3 compared with 10.4 cm^3 in patients with score ≤ 3 and 123.8 cm^3 in patients with score ≥ 7. Retrospective review of the CT images (24 hours after treatment) with regard to the site of the ischemic injury showed that the patients with score of 4-6 who had unfavorable outcome (n = 22) sustained infarctions involving the following functionally strategic structures: internal capsule (n = 10), corona radiata (n = 8), and areas adjacent to central sulcus (n = 4). Thus, further analyses of CTs that belonged to patients who scored 4-6 helped to explain their unfavorable outcome (mRS > 2). We believe that CTs of patients with borderline prognostic score (4-6) should be scrutinized regarding the site of the ischemic injury. Inability to predict the outcome in this group of patients is the main shortcoming of our proposed prognostic model. However, such a shortcoming also occurs in scores that take into consideration the site of the injury. About 25% of patients with a score of 8 on ASPECT (Barber *et al.,* 2000) were dependent despite the fact that the score of 8 was considered within limits for favorable prognosis (ASPECTS > 7). The same applies to prognostic model based only on infarct volumetry. In one study (Saunders *et al.,* 1995) infarct volume of 35.7 ± 29.7 cm^3 was found to be associated with independency while in our study 22 patients with unfavorable prognosis (dependency) who scored 4-6 had a mean value for infarct volume of 20.3 cm^3. In a prognostic model based only on the allotment of NIHSS ≤ 6 and ≥ 7 as predictors for favorable or unfavorable outcome, respectively (Table 4), 101 patients (80% of study cohort) scored NIHSS ≥ 7. These patients had approximately 40% chance of favorable prognosis and 60% chance of unfavorable prognosis. This type of allotment can be applied to a study cohort but is barely suitable for predicting the prognosis in individual patients, while our proposed prognostic model enabled to predict the outcome in at least 2/3 of the patient cohort with high accuracy.

Most of the reported prognostic models based on clinical data use NIHSS as predictor for the functional outcome whereas models using radiological data use predictors as EICs, infarct volume, ASPECTS scale and/or cerebral blood volume on perfusion CT as outcome predictors. Different outcome scales have been used as reference for functional outcome; the most widely used is mRS. Perfusion CT is not available in all stroke centres whereas plain CT is still the standard imaging modality in the initial work-up of acute ischemic stroke. HMCAS has been extensively studied and showed to be associated with bad functional outcome (Manelfe *et al.,* 1999; Abul-Kasim *et al.,* 2009; Kharitonova *et al.,* 2009). Large infarct volume and bleeding showed to be associated with poor functional outcome (Abul-Kasim *et al.,* 2009). Thus, our proposed prognostic score includes most of the widely studied variables which previously were proven to be predictors of the functional outcome, namely NIHSS on admission, EICs and HMCAS on initial CT as well as NIHSS, infarct volume and occurrence of bleeding within 24 hours after treatment.

Another issue that has been a matter of debate when designing a prognostic model is the time point to predict the functional outcome. Woldag *et al*. concluded that parameters for predicting outcome should not be assessed before day 7 after stroke (Woldag *et al.,* 2006). In other studies, prediction of the functional outcome was based on predictors

recorded 3 days (Brouns, *et al.,* 2009) and as early as 6 hours (Konig *et al.,* 2008), respectively, after stroke. We chose using predictors that are recorded at 24 hours in order to provide an early prediction of the functional outcome and facilitate the planning of the post-stroke work. The clinical relevance of improving early stroke management is emphasized by studies showing that immediate stroke unit care is preferable to treatment on a generalized ward (Stroke Unit Trialists' Collaboration, 2007). A valid model should also be able to predict the chances of managing to live independently in own home, the need for adapting the existing accommodation, the extent of the required rehabilitation, and/or the need of institutionalization. This might reduce the time and the cost of stroke by allowing early instigation of suitable rehabilitation measures. Although our prognostic model has been proved to be valid and feasible in our patient cohort, it needs to be externally validated if this model to be widely applied in clinical practice.

Conclusions

The here proposed prognostic model (minimum score of 1 and maximum score of 13) is valid and correlates well with functional outcome measured as mRS at three months and can thus help early prediction of the functional outcome in patients with middle cerebral artery stroke.

The suggested cut-off value for favorable functional outcome with a score of ≤ 3 and for unfavorable functional outcome with a score of ≥ 7, enabled predicting the functional outcome with a high degree of accuracy and high predictive values in 2/3 of the patient cohort. Combined with determination of infarct site in borderline scores (score 4-6), the functional outcome can be predicted in the remaining 1/3 of patients. Although our proposed prognostic model includes four different variables (NIHSS, EICs, Post-treatment bleeding and infarct volume) it may be considered as simple but comprehensive, using easily available data as early as 24 hours following stroke onset, which may facilitate early poststroke care and planning.

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