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ORIGINAL COMMUNICATION

Predicting functional outcome and survival after acute ischemic stroke

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Abstract *Objective* Disability and mortality represent the most relevant clinical outcome after acute ischemic stroke. However, validated and comprehensive prognostic models for recovery have not been developed. An accurate model including all previously suggested independent outcome predictors could improve the design and analysis of clinical trials. We therefore developed prognostic models for functional dependence and death after 100 days in a large cohort of stroke patients. *Methods* From the German Stroke Database, 1754 prospectively collected records of patients with acute ischemic stroke were used for the development of prognostic models. Intubated patients and patients with low functional status before stroke were excluded. Functional independence was defined as a Barthel Index ≥95 after 100 days. Prognostic factors assessable within 72 hours after admission were identified by a systematic literature review. The final models of binary logistic regression analyses were internally validated and calibrated. *Results* The resulting cross-validated and calibrated models correctly classified more than 80 % of the patients and yielded the following prognostic factors for functional independence: Age, right and left arm paresis at admission, NIH-Stroke Scale at admission, Rankin Scale 48–72 hours later, gender, prior stroke, diabetes, fever, lenticulostriate infarction, neurological complications. The following variables were identified as prognostic factors for death: Age, NIH-Stroke Scale at admission, and fever. *Conclusions* Our work gives an important insight into prognostic factors after acute ischemic stroke and presents predictive models with high prognostic accuracy. Together with a prospective validation study, currently underway, we hence hope to improve the prediction of functional outcome after ischemic stroke.

Key words stroke · cerebral ischemia · prognosis · outcome

Introduction

In view of the diversity in therapeutic goals and the existing varieties in outcome assessment following acute ischemic stroke, recent guidelines acknowledge the importance of considering at least two outcome variables in clinical stroke trials [6]. One is inevitably mortality within the first months after the event. A second clinically meaningful variable can be described as functioning and disability which includes body functions, activities and participation [36]. The assessment of the latter two components can be standardized using outcome scales, of which one of the most commonly applied scales in stroke

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research is the Barthel Index (BI) [6, 19, 27]. Here, a suitable cut-off value can be used to identify patients with a complete recovery, which is a recommended endpoint for clinical trials in stroke research [6]. For an accurate outcome prognosis regarding these endpoints, a systematic model development is required. Although many studies have suggested numerous prognostic factors, little is known about the impact of these variables in a comprehensive prognostic model. Instead, only a few variables have been investigated simultaneously. Furthermore, these variables were not selected systematically. Thus, no prognostic model has been reported to date that considers all previously suggested factors in its development [7]. In addition, existing models have rarely been externally or internally validated. Only a validated comprehensive model, however, allows for accurate prognosis of patients, correct stratification of treatment groups, and prediction of the distribution of endpoint variables in a clinical trial. This in turn can increase the power to detect clinically relevant differences.

The German Stroke Database was initiated by the German Stroke Foundation (Stiftung Deutsche Schlaganfall-Hilfe) in 1998. Within two years, data on all patients with an acute stroke or transient ischemic attack were collected in 23 neurology departments with an acute stroke unit. The data pool contains 9849 patients with various cerebrovascular diagnoses and a variety of clinical variables assessed at admission, during hospital stay, and at follow up intervals of 100 days and 12 months after admission.

To develop prognostic models for complete restitution and mortality 100 days after an acute ischemic stroke, we focused on clinical variables which were obtained within the first 72 hours after admission of a stroke patient. With these models we aimed to identify independent prognostic variables for functional outcome and mortality after ischemic stroke and thereby facilitate an estimate of prognosis and guide future study designs.

Methods

Selection of variables

A systematic literature review for independent prognostic factors for outcome after ischemic stroke was conducted in the following literature databases: Database of Abstracts of Reviews of Effectiveness DARE (URL: http://nhscrd.york.ac.uk/), Cochrane Library (1998, Issue 1) and MEDLINE (URL: http://www.ncbi.nlm.nih.gov/pubmed/). The abstracts of all identified publications on prognostic factors after ischemic stroke were screened for those that met the criteria of evidence-based medicine for prognostic studies [29]. Based on these results and the clinical judgement on the impact of localization of infarction, 38 sets of variables assessable within the first 72 hours after admission were selected for further investigation. This time frame represents a compromise between a valid and accurate assessment of the variables of interest on one hand and an early prognosis on the other.

We refrained from considering specific treatment methods as possible predictors because no specific effective treatment is commonly applied to a considerable number of patients. Additionally, our aim was to provide models suitable for stratification in clinical trials. By including treatment methods like thrombolysis, we would have measured clinical judgement rather than treatment effect. In clinical trials, however, this judgement is unavailable for stratification because of randomized allocation to treatment. Detailed information on the selection process and the final list of variables is available from the web site (http://www.uni-essen.de/neurologie/stroke/). The variables included in the final models (see Results) are described in Table 1.

The BI 100 days after an acute ischemic stroke was chosen as the first dependent variable. It evaluates individual abilities in feeding, dressing, mobility (walking on a level surface and ascending/descending stairs), and personal hygiene (grooming, toileting, bathing, and control of bodily functions) on a total score from 0 (total functional dependence) to 100 (total functional independence). It can be assessed by interview with the patient or a next-of-kin or (para-)medical personnel. Based on the International Classification of Functioning, Disability and Health (ICF) [36], the BI measures functioning and disability in mobility and self care. It adequately reflects functional consequences for daily activities that are immediately important to the patient. Therefore, the BI can be considered an outcome that is clinically relevant to the patient [32]. Mortality after 100 days was chosen as the second outcome variable and represents the worst possible outcome.

Data assessment

Data were collected prospectively within the German Stroke Database of the Stiftung Deutsche Schlaganfall-Hilfe in 23 neurology departments in 1998 and 1999. All participating hospitals had an acute stroke unit and, in most cases, also a neurological intensive care unit. They serve catchment areas of 100,000–1 million inhabitants and are the main care providers for stroke patients in these regions. Cranial CT (95.8 %) or MRI (35 %), extra- and transcranial Doppler sonography or angiography of brain supplying arteries (including CT or MR angiography), ECG or ECG monitoring, basic blood tests and additional laboratory investigations were performed in all patients. Two thirds of all patients were examined by transthoracic or transesophageal echocardiography. Aspects of data safety of the Stroke Database were considered to be clarified by the responsible data protection officer. All patients gave informed consent if their personal data were to be transferred to the data management center.

Table 1 Clinical variables in the prognostic models

- Age at event (in years)
- Gender
- Prior stroke: history of prior stroke
- Diabetes mellitus: history of elevated blood glucose at two independent readings or elevated HbA1c at admission or antidiabetic medication
- Baseline neurologic impairments at admission as rated on the National Institute of Health Stroke Scale with single items (best motor right and left arm) and overall score
- Overall functional impairments as rated on the Modified Rankin Scale 48–72 hours after admission
- Lenticulostriate arteries infarction: as evidenced on cerebral imaging
- Fever > 38 °C: aural temperature rise to > 38 °C within 72 hours after admission
- Neurological complications: within 72 hours after admission, including recurrent cerebral ischemia (Def: rapid onset focal neurological deterioration with exclusion of parenchymal hemorrhage on cerebral imaging in case of persisting deficits), symptomatic parenchymal bleeding (Def: symptomatic and asymptomatic secondary parenchymal bleeding diagnosed on cerebral imaging or autopsy), and epileptic seizure

Data were collected in accordance to an extensive manual and included the variables that had been identified in our review of the literature or, in the case of infarct localization, had been chosen by clinical judgement. The outcome was assessed at 80 to 150 (median 96) days after admission and included mortality and functional independence as rated on the BI. All data were collected on standardized questionnaires by the treating neurologists. The scores were quantified by local investigators who were familiar with the National Institute of Health Stroke Scale (NIH-SS) from other clinical trials or the NIH-SS training video. Likewise, the findings of cerebral imaging and the TOAST-classification were scored in the documenting hospital according to a standardized protocol [10].

After a final consistency check with the source data at site, questionnaires were sent to the data management centers at the University of Essen and the Stiftung Deutsche Schlaganfall-Hilfe, Gütersloh. They were rechecked by two physicians for completeness and plausibility and entered in duplicate into the database by trained personnel. Missing or implausible data were queried to the treating neurologist. Data quality was furthermore ensured by monthly reports and clinical site visits.

If the patient or his relatives/caregivers did not consent in submission of his personal data, the participating center forwarded only anonymous data to the data management center and performed upon bimonthly request the follow up interview at site. Otherwise, the follow up was performed by trained telephone interviewers at the University of Essen or the Stiftung Deutsche Schlaganfall-Hilfe who were not strictly blinded to the baseline variables. If the patient could not be reached via telephone or via his treating physician, a follow up letter was sent. If still no information on the patient outcome could be obtained, a query at the citizen registry was made to check for current address or death.

In order to assure high data quality, only patients from those centers were considered that had included more than 90 % and followed up more than 80 % of their patients. Of these, all patients were included who additionally met the following criteria: No serious functional impairment (Rankin Scale < 4) before the event to ensure that patients were functionally independent to a certain degree [6], admission within 24 hours after stroke, not intubated during the first 72 hours to allow for a valid assessment of all relevant variables, survival in the first three days, and follow up between 80 and 150 days after admission or death until follow up. Case records with missing data were excluded from the analyses.

Patients

In 1998 and 1999, 6412 patients with ischemic stroke were included in the database. According to the criteria established by the National Survey of Stroke, ischemic stroke was defined as a focal neurological deficit of presumably vascular origin lasting > 24 hours and excluding primary hemorrhage on initial cerebral imaging [34]. Seven centers (Minden, München-Harlaching (only 1998), Essen, Benjamin Franklin Berlin, München-Großhadern (only 1998), Frechen and Leipzig) met the specified quality criteria, registering a total of 3203 patients. Reasons given for not including a patient were forgetfulness of the treating physicians, loss of questionnaires, early transfers to other hospitals, misdiagnoses, or lack of time. Of the 3203 registered patients, only patients with a Rankin Scale < 4 prior to the event (3078), only patients admitted within 24 hours after the onset of the stroke symptoms (2383), those who were not intubated during the first 72 hours (2259), and those who survived the first three days (2245) were included. Of the remaining patients, 17 refused to participate in the follow up interview, 280 were reached only outside 80–150 days after admission, 194 were lost to follow up, and 1754 patients were interviewed between 80 and 150 days after admission or were found to have died by the time of the interview. As the follow up of patients was not complete, it cannot be ruled out that the included patients are biased towards those with characteristics which facilitate a follow up after 80 to 150 days. In total, 1754 patients met all inclusion and no exclusion criteria, and their data were used in the analyses (Fig. 1).

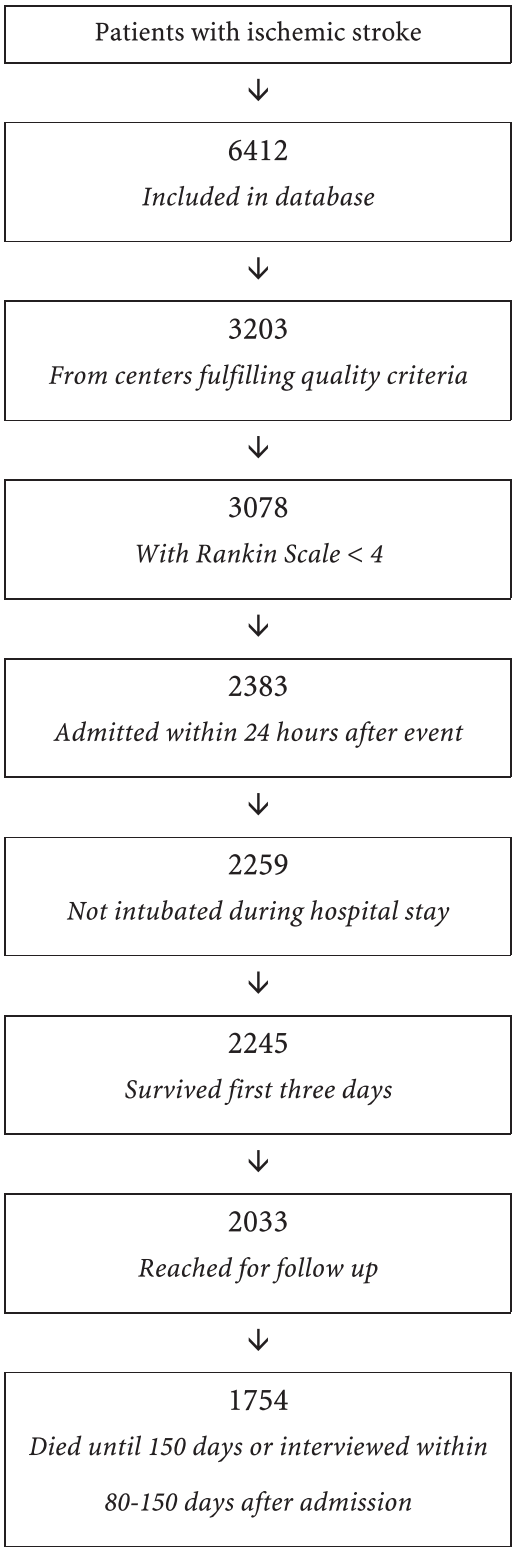

Fig. 1 Flow diagram of patients included in the analyses.

Statistics

We developed two binomial logistic regression models for the prediction of complete restitution (defined as BI ≥95) and mortality:

Model I predicts complete functional restitution versus incomplete restitution or mortality.
Model II predicts mortality versus survival.

Descriptive statistics were obtained for all 38 sets of variables and the recruiting center. With a frequency of less than 4% in one of the alternative categories, four binary variables were excluded (localization of the infarct in the anterior cerebral artery, borderline middle/posterior cerebral arteries, borderline anterior/ middle cerebral arteries, and long perforating arteries). Another four single variables were eliminated because of substantive correlations with other variables and less predictive value or reliability than the respective correlated variable (NIH motor left leg, motor right leg, commands, and packyears of smoking). To model the relationship between continuous variables (age and body mass index) and outcome, fractional polynomials were used on a randomly selected 25% of the total sample [28]. For age, the best fit was obtained including only the linear term. No significant gain was achieved by including body mass index; this variable was therefore excluded. The ordinal variables NIH-SS total score and Rankin Scale were treated as linear variables in the regression models. We used this method because a linear fit is regarded as the natural approach when expecting a monotone effect of the ordinal covariate [2]. In addition, we applied fractional polynomials on randomly selected 25% of the total sample to model the relationship between these two scores and the outcome. For both variables, the best fit was obtained including only the linear term. In addition, no significant center effect was observed prior to multivariate model building upon use of logistic regression with dummy-coded center variables (likelihood ratio test $p > 0.1$).

The remaining 41 variables were fitted into logistic regression models via forward, backward and stepwise selection. For model I, the number of events per variable (EPV) was > 20. Nevertheless, variables were retained only if their resulting p-value was ≤0.005 [3]. For model II, due to the low EPV = 5 [3], all variables with p-values > 0.001 were excluded. From models with all variables that resulted from any of the selection procedures, any variable with $p > 0.005$ (model I) or $p > 0.001$ (model II) was eliminated stepwise. To the remaining set of variables, every previously eliminated variable was again added and kept in the model if it fulfilled the same criteria. Finally, all two-way interactions of the resulting variables were investigated and kept if $p \leq 0.005$ (model I) or $p \leq 0.001$ (model II) and if for categorical variables each cell contained at least 4% of observations.

For the final models, parameter estimates with standard errors, odds ratios and asymptotic 95% confidence intervals for all variables were calculated. In addition, the proportion of explained variance R^2 is given for each model [20]. Leave-one-out cross-validation was used to estimate the shrinkage factor γ in both models [33]. For both models, the Receiver Operator Characteristic (ROC) plotting specificity against sensitivity is presented. The threshold for classification using the logistic distribution function was set so that the predicted proportion of events was equal to the observed. Finally, the calibrated percentage of correctly classified patients is presented [33].

Results

Of the 1754 patients, 59.2% were men. Mean age of patients was 68.1 years (SD 12.7). After 100 days, 1025 patients (58.4%) had completely recovered (BI ≥95), 563 patients (32.1%) had incompletely recovered (BI < 95), and 166 patients (9.5%) had died. This low mortality can be attributed to the exclusion of patients requiring intubation or who died within three days after admission. In addition to the inclusion in the Stroke Database, 94 patients (5.3%) had participated in clinical trials. 104 patients (6.1%) had received systemic thrombolysis. The distribution of further clinical variables that are included in the final models is shown in Table 2. Detailed descriptive statistics on all variables can be found on the web site.

To predict complete restitution in functional outcome versus incomplete restitution or mortality (BI ≥95 vs. BI < 95 or death) model I was developed. The final model included the 11 variables shown in Table 3. An increased risk of not attaining complete recovery was found in older patients, in patients with more severe right arm weakness on admission, in patients with more severe left arm weakness on admission, a more severe level of neurological impairments on admission (NIH-SS total score), more severe functional impairment (Rankin Scale) 48–72 hours after admission, female gender, history of stroke, diabetes mellitus, fever > 38 °C, stroke localization in the lenticulostriate territory, and neurological complications. The ROC for this model is shown in Fig. 2. Upon use of the threshold 0.437, 80.7% of all patients could be correctly classified. Details of the classification correctness in each group are given in Table 4. The final model explained $R^2 = 55.4\%$ of the complete variation. A shrinkage factor of $\gamma = 0.97$ was obtained. Model II predicts mortality versus survival and includes three variables (Table 5). The risk of dying within the first 100 days after a stroke in our sample was higher in patients with higher age, greater neurological impairments at admission (NIH-SS total score), and fever > 38 °C within 72 hours after admission. Fig. 3 gives the ROC for model II. A total of 90.4% of patients were classified correctly when using the threshold 0.289; details are presented in Table 6. The proportion of variance explained by this model was $R^2 = 40.9\%$, and the shrinkage factor was estimated to be $\gamma = 0.99$.

Table 2 Characteristics of the clinical variables in 1754 patients with ischemic stroke

Categorical variables	Frequency (%)	Continuous variables	Mean (SD)
Prior diabetes mellitus	24.9	NIH motor left arm	0.63 (1.17)
Prior stroke	20.1	NIH motor right arm	0.66 (1.16)
Fever > 38 °C	12.5	NIH total score	6.89 (6.24)
Lenticulostriate arteries infarction	10.7	Rankin scale after 48–72 hours	3.06 (1.42)
Neurological complications	4.2		

SD Standard deviation; *NIH* National Institute of Health Stroke Scale at admission

Table 3 Results of the logistic regression model I to predict incomplete functional restitution or mortality versus complete restitution (BI < 95 or dead vs. BI = 95)

Variable	β	S. E.	Odds ratio	95% CI
Intercept	−8.390	0.509		
Neurological complications	1.294	0.332	3.647	1.901–6.996
Fever > 38 °C	1.08	0.23	2.963	1.859–4.722
Lenticulostriate arteries infarction	0.751	0.216	2.120	1.389–3.235
Diabetes mellitus	0.640	0.151	1.896	1.410–2.550
Prior stroke	0.523	0.160	1.688	1.232–2.312
Female gender	0.383	0.138	1.467	1.119–1.924
Age (difference of 1 year)	0.066	0.006	1.068	1.055–1.082
Rankin scale (difference of 1 scale score)	0.542	0.070	1.719	1.498–1.973
Right arm weakness (difference of 1 scale score)	0.395	0.089	1.485	1.247–1.767
Left arm weakness (difference of 1 scale score)	0.485	0.103	1.625	1.328–1.988
NIH-SS total score at admission (difference of 1 scale score)	0.073	0.024	1.076	1.027–1.128

β regression coefficient; *S. E.* standard error; *CI* confidence interval; *NIH-SS* National Institute of Health Stroke Scale

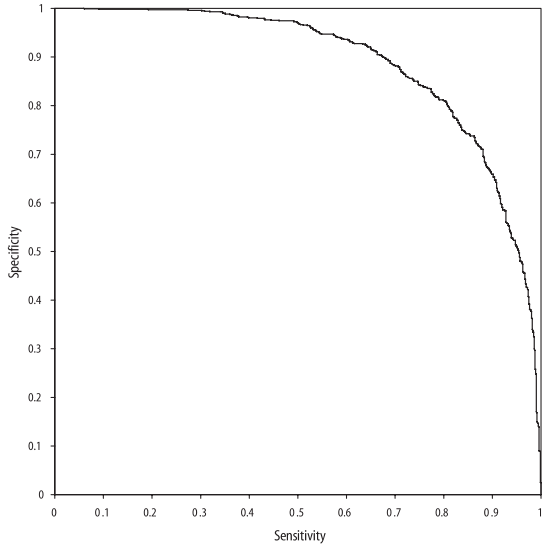

Fig. 2 Receiver Operator Characteristic for model I.

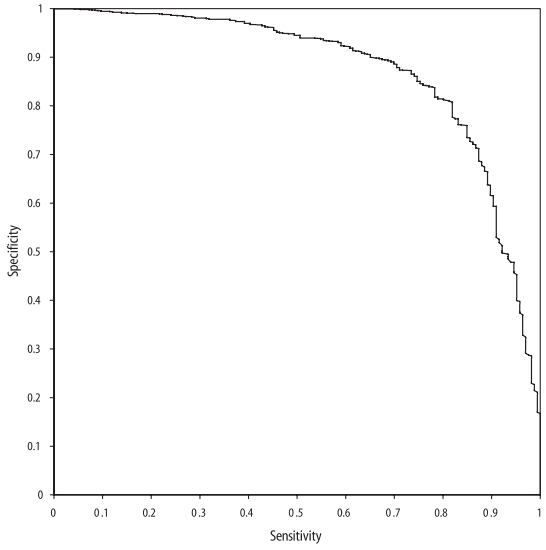

Fig. 3 Receiver Operator Characteristic for model II.

Table 4 Classification of patients in model I using 0.437 as threshold

		Observed frequency (%)		
		BI < 95	BI = 95	Total
Predicted frequency (%)	BI < 95	554 (0.318)	168 (0.096)	722 (0.414)
	BI ≥ 95	168 (0.096)	853 (0.489)	1021 (0.586)
	Total	722 (0.414)	1021 (0.586)	1743

Table 6 Classification of patients in model II using 0.289 as threshold

		Observed frequency (%)		
		Mortality	Survival	Total
Predicted frequency (%)	Mortality	82 (0.047)	84 (0.048)	166 (0.095)
	Survival	84 (0.048)	1500 (0.857)	1584 (0.905)
	Total	166 (0.095)	1584 (0.905)	1743

Table 5 Results of the logistic regression model II to predict mortality versus survival

Variable	β	S. E.	Odds ratio	95% CI
Intercept	−9.370	0.783		
Fever > 38 °C	1.317	0.209	3.732	2.479–5.617
Age (difference of 1 year)	0.076	0.010	1.079	1.058–1.100
NIH-SS total score at admission (difference of 1 scale score)	0.133	0.013	1.142	1.113–1.172

β regression coefficient; *S. E.* standard error; *CI* confidence interval; *NIH-SS* National Institute of Health Stroke Scale

Discussion

Our analysis develops comprehensive and internally validated models predicting functional outcome and mortality after stroke. In accordance with current guidelines [6], we focused on complete recovery and mortality 100 days after an acute stroke as endpoints of primary interest. As advocated by the principles for evidence-based medicine [29], we performed a systematic literature search to identify predictors that had been suggested previously. Thus, we were able to consider all these factors simultaneously which is the only means to estimate their relative influence on outcome variables. In addition, we applied cross-validation methods to internally validate our resulting models. Through this, we were able to develop convincing models with a high prognostic accuracy. This is of special importance because all variables included are available within the first 72 hours after stroke. Although the prediction could probably be improved by including variables that are assessed later, the practical value would be limited as the prediction cannot be given as early. At the other extreme, it might be interesting to develop additional models taking into account only variables that are assessable within the first 6 hours. This in turn limits the number of variables available in clinical routine and requires more stringent inclusion criteria to account for differing delays between event and admission. These models are currently being developed.

Furthermore, our resulting models are based on a very large data set. These data from a multicenter, hospital-based database are most likely representative of all patients hospitalized for acute ischemic stroke in German stroke units. This statement coincides with the results of the univariate analyses which revealed no center effect.

We have demonstrated that the selection of prognostic factors depends on the chosen outcome, as different prognostic factors emerged when predicting functional independence or mortality, respectively. No relevant interaction effects with additional predictive value were detected. In agreement with previous studies [4, 11, 13, 14, 17, 18, 22–24, 30], our data confirmed an independent prognostic role of increasing *age* on both functional dependence and death. Although no information on "do not resuscitate" status was collected, it seems unlikely that this could account for the whole predictive value of age on mortality. Rather, elderly patients had a higher risk of subsequent complications and thereby lower chances to recover from their stroke.

Initial severity of stroke has been shown to be a predictor of functional outcome in many studies [1, 11, 13, 16, 18, 21, 22, 30]. In addition, the following neurological deficits have been described as independent predictors: level of consciousness, orientation, limb paresis, trunc ataxia, and dysphagia [4, 8, 11, 17, 25, 31]. In our analyses, the total NIH-SS score at admission was a prognostic factor for functional dependence or death in model I and mortality in model II. Right and left arm weakness together with the Rankin Scale 48 to 72 hours later emerged as additional prognostic factors for functional dependence or death in model I.

Female gender was found to be a predictor for functional independence (model I) but not for mortality (model II). This finding reflects a possible association of female gender with missing social support and the occurrence of post stroke depression. These factors have been shown to influence functional outcome in longitudinal studies and to be more frequent in female stroke patients [9, 12, 17]. However, these variables are not assessable within the tight time frame of 72 hours after a stroke and have thus not been considered in our analyses. Therefore, female gender is likely to be a surrogate variable for several epidemiological factors which have not been detailed as yet.

Prior stroke has been proposed as a predictor for functional dependence [13, 15, 17]. Correspondingly, it was retained in our model I predicting functional dependence or death. In contrast, it revealed no prognostic impact on mortality in model II. Upon exclusion of patients with severe prior functional deficits, it thus seems to be an independent predictor for functional outcome. We refrained from considering a retrospective estimation of prior functional independence on the Rankin Scale [5] because this was already an inclusion criteron.

In accordance with prior studies, *diabetes mellitus* was found to be a prognostic variable for functional dependence or death in model I [4, 13, 14, 22]. This could be due to greater preexisting comorbidity of diabetic patients as well as to greater neuronal damage of ischemic tissue in hyperglycemia.

Fever of more than 38 °C within three days after stroke was among the most important predictors for functional dependence or death in model I as well as for mortality in model II [4, 12, 35]. This effect could partly be explained by a negative impact on neuronal survival in the ischemic penumbra. Furthermore, fever may be associated with the primary extent of neuronal damage itself.

The localization of stroke as categorized by vascular territories has so far not been investigated as a predictor for functional outcome. In our analyses, infarctions in the *lenticulostriate arteries* supply territory proved to be an independent predictor for functional dependence or death in model I. Because this finding was independent of initial stroke severity, it could possibly reflect the clinical experience of greater reorganization potential in cortical than in subcortical infarctions.

The occurrence of recurrent stroke, parenchymal hemorrhage, and epileptic seizures could not be analysed separately because of the relatively low frequency of

each complication. Therefore, if any of these events occurred, the patient was scored to suffer from a *neurological complication*. The identification of combined neurological complications as a prognostic factor for functional dependence or death in model I is therefore not surprising from a clinical point of view; it reflects the impact of serious adverse events in clinical trials. Categories in the *TOAST classification* of ischemic stroke did not prove to be independent predictors for functional dependence or death in model I or for mortality in model II as previously suggested [1].

Prior to the statistical analysis, we decided to refrain from considering specific treatment methods as possible predictors. Firstly, treatment decisions in our sample were based on clinical judgment which would differ in the context of a clinical trial. Secondly, we surmised that no specific effective treatment is commonly applied to a considerable number of patients. Our data showed, however, that 6.1 % of all patients received thrombolysis within the first 72 hours. Nevertheless, if thrombolysis was added to the resulting models as a possible predictor, it did not meet our significance criteria as an independent predictive variable.

The developed models predict functional independence and mortality 100 days after stroke very accurately. Our analyses form the first step in determining the impact of prognostic factors on functional outcome and mortality. We expect the stability of model I (complete functional restitution) to be high because we used a stringent selection criterion ($p < 0.005$) together with a high EPV (> 20). This is substantiated by a shrinkage factor close to 1 ($\gamma = 0.97$). However, the EPV = 5 of model II (survival) was lower than recommended for prognostic factor studies. Therefore, we employed an even more stringent selection criterion ($p < 0.001$). This resulted in a prognostic model containing only four variables. All of these had previously been suggested as prognostic factors for survival after ischemic stroke. The adequacy of our strategy is further substantiated by a shrinkage factor almost equal to 1 ($\gamma = 0.99$).

Nevertheless, the models need to be externally validated in an independent sample of patients. For this purpose, a prospective validation study is currently underway that aims at confirming the developed prediction models. The resulting validated and comprehensive prognostic models can be helpful to correct for case-mix variations in non-randomized cohorts of patients and provide a valuable tool in the design and comparison of randomized controlled trials.

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