Prediction of Functional Outcome in Patients With Primary Intracerebral Hemorrhage: The FUNC Score

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Background and Purpose—Intracerebral hemorrhage (ICH) is the most fatal and disabling stroke subtype. Widely used tools for prediction of mortality are fundamentally limited in that they do not account for effects of withdrawal of care and are not designed to predict functional recovery. We developed an acute clinical score to predict likelihood of functional independence.

Methods—We prospectively characterized 629 consecutive patients with ICH at hospital presentation. Predictors of functional independence (Glasgow Outcome Score ≥4) at 90 days were used to develop a logistic regression-based risk stratification scale in a random subset of two thirds and validated in the remaining one third of the cohort.

Results—At 90 days, 162 (26%) patients achieved independence. Age, Glasgow Coma Scale, ICH location, volume (all \(P < 0.0001\)), and pre-ICH cognitive impairment (\(P = 0.005\)) were independently associated with Glasgow Outcome Score ≥4. The FUNC score was developed as a sum of individual points (0–11) based on strength of association with outcome. In both the development and validation cohorts, the proportion of patients who achieved Glasgow Outcome Score ≥4 increased steadily with FUNC score. No patient assigned a FUNC score ≤4 achieved functional independence, whereas >80% with a score of 11 did. The predictive accuracy of the FUNC score remained unchanged when restricted to ICH survivors only, consistent with absence of confounding by early withdrawal of care.

Conclusions—FUNC score is a valid clinical assessment tool that identifies patients with ICH who will attain functional independence and thus, can provide guidance in clinical decision-making and patient selection for clinical trials. (Stroke. 2008;39:2304-2309.)

Key Words: intracerebral hemorrhage | outcome | models | statistical
We sought to develop a clinical score, assessed on admission, to predict patients’ likelihood of reaching functional independence should they survive ICH.

Subjects and Methods

We retrospectively analyzed data collected as part of an ongoing single-center prospective longitudinal cohort study of primary ICH.27,28 Patients with ICH with a baseline admission CT scan and data available on functional status at 90 days were considered eligible. At our center, all patients with ICH undergo CT scanning as well as additional imaging studies, including angiography, CT angiography, and MRI. Based on the results of these imaging studies as well as review of baseline clinical data, patients with secondary causes of ICH such as vascular malformation, central nervous system tumor, antecedent trauma or ischemic stroke, vasculitis, excessive anticoagulation (international normalized ratio >3.0), or blood dyscrasia were excluded.

Study subjects were identified by screening hospital admission logs. Patients with ICH, or next of kin, were approached by study personnel during the hospitalization and consent was sought for enrollment into the longitudinal study. For patients in whom consent could not be obtained, medical record information was stored in a database registry. All study procedures were approved by the local Institutional Review Board.

Information on demographics, medical history, and medication use and dosage was collected through interview of consenting subjects by study personnel or supplemented by the medical record review, as previously described.27,28 All CT scans were downloaded directly to a workstation and stored in DICOM format where they were reviewed by study investigators blinded to clinical data. Volume of ICH was calculated as previously described.29 ICH was considered lobar in location if the origin of the hemorrhage appeared to be in the cerebral hemispheres superficial to the deep gray matter structures. Hemorrhages originating in the thalamus and basal ganglia were considered “deep” in location, as previously described.27,28

Clinical variables, including hypertension, diabetes, and coronary artery disease, were defined as previously described.27,28 Glasgow Coma Scale (GCS) was the first one recorded on admission to the Massachusetts General Hospital emergency department. Pre-ICH cognitive impairment was defined as a history of cognitive impairment based on family interview and medical record review supplemented by the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) administered to a proxy/relative about changes in cognitive performance of the patient over the last 10 years.30

Using a telephone interview, Glasgow Outcome Scale was determined at 90 days. “Functional independence” was defined as Glasgow Outcome Scale ≥4.

All variables (age, GCS, gender, hypertension, diabetes, coronary artery disease, warfarin use, intraventricular hemorrhage (IVH), ICH volume, ICH location, pre-ICH cognitive impairment) were categorized and compared using χ² tests. The level of significance was set at 2-sided P<0.05 for all statistical analyses. Those variables known to predict outcome in ICH (age, GCS, IVH, ICH volume, ICH location) and/or those that reached P<0.2 in univariate analysis were considered for multivariable analysis.

A risk stratification scale was developed using logistic regression analysis within a randomly allocated two thirds of the cohort (“model development subset”) and validated in the remaining one third (“model validation subset”) of the patients. Goodness of fit of the predictor model was measured by c-statistic (area under the receiver operating characteristic curve) and reported for both subsets. The nearest integer from the parameter estimates obtained from the multiple logistic regression model was used in assigning the score points for FUNC score. Statistical analyses were performed using SAS version 9.1.3 (SAS Institute, Cary, NC).

Results

Patient Characteristics and Model Development

There were 795 consecutive ICH admissions with symptom onset between January 1, 1998, and August 31, 2005. Baseline CT scan was not performed or was missing in 46 of 795 (6%), and other data on demographics or medical history was missing in 19 of 795 subjects (3%), leaving 730 subjects with complete baseline information. Of these, 90-day outcome status was available for 629 of 730 (86%) patients. Those subjects without follow-up information had similar baseline characteristics as subjects with follow-up information, except for a lower likelihood of having lobar ICH location (P=0.02).

There were 223 of 629 (53%) who were urgently transferred from community hospital emergency departments to the Massachusetts General Hospital emergency department, whereas the remaining 195 of 629 (47%) arrived directly to the emergency department (“nontransfer”).

There were 345 of 629 (55%) patients who survived to 90 days and, of these, 162 of 345 (47%) achieved functional independence. For model development, two thirds of the total cohort (N=418 of 629) were randomly selected stratified by Glasgow Outcome Scale score, leaving one third (N=211 of 629) of subjects for validation (Table 1).

In the model development stage, age, admission GCS, ICH volume, presence of IVH, warfarin use, and history of
pre-ICH cognitive impairment were significantly associated with functional independence (all with \( P < 0.01 \)) in the univariate analysis. ICH location, a known clinical predictor of outcomes in ICH, was also a candidate for multivariable analysis with a borderline probability value (\( P = 0.19 \)).

After multivariable logistic regression analysis, clinical variables on admission independently associated with functional independence were age, GCS, ICH volume, ICH location, and pre-ICH cognitive impairment (Table 2), but not warfarin use (OR, 1.0; 95% CI, 0.5 to 2.0) or IVH (OR, 0.8; 95% CI, 0.4 to 1.4). The c-statistic for this model was 0.88. This model was subsequently tested in the validation subset (\( N = 211 \)) and showed a c-statistic of 0.82.

**The FUNC Score**

The FUNC score, a functional outcome risk stratification scale, was developed from logistic regression analysis of the model development subset (\( N = 418 \)). Based on strength of association with the log odds of the outcome, independent predictor variables were weighted to develop the FUNC score as a sum of individual points (Table 3). The score ranged from 0 to 11 with a score of 11 indicating strong likelihood of functional independence. GCS scores (≤8 and ≥9) and ICH volume (<30 cm³, 30 to 60 cm³, and >60 cm³) were divided into the most clinically meaningful categories to facilitate the score’s usefulness. ICH location categories received point values based on their graded strength of association with outcome. Based on the age distribution of the cohort, categories of age <70, 70 to 79, and ≥80 years were derived and graded point values assigned accordingly.

In the model development subset, more than 85% (12 of 14) of patients with a score of 11 reached functional independence at 90 days. On the contrary, only 2 of 48 (4%) patients with a score of 5 achieved independence. In fact, there were no patients with a FUNC score of ≤4 who reached functional independence (\( n = 0 \) of 93). A similar trend was observed when the FUNC score was applied to the validation subset, in which patients demonstrated no chance of achieving functional independence at 90 days if their score was ≤4 and, conversely, at least a 75% chance of independence with a FUNC score of 11 (Table 4).

To eliminate the potential bias introduced by early withdrawal of care in patients with ICH, we applied the FUNC score to those 345 of 629 (55%) patients who survived to 90 days.
days. In this “Survivors only” cohort, the FUNC score predicted functional independence at 90 days with similar reliability. Of 19 patients who survived ICH and had FUNC score of 11, 18 (95%) achieved Glasgow Outcome Scale ≥4 as compared with none of the patients who had FUNC scores ≤4.

FUNC score predicted functional independence equally well regardless of whether patients had been transferred from a referring hospital emergency department (c-statistic 0.88). There were no patients in either the “transfer” or “nontransfer” subset who achieved functional independence at 90 days with FUNC score of ≤4, whereas the proportion of patients who achieved functional independence in these respective subsets per FUNC score category did not differ. Furthermore, FUNC score’s ability to predict functional outcome at 90 days remained unchanged regardless of whether patients underwent a surgical intervention during their hospitalization (c-statistic 0.87).

To maximize clinical usefulness of the FUNC score, we grouped FUNC score values to define clinically meaningful outcome prediction categories by proportion of the patients who achieve functional independence at 90 days as follows: 0 to 4% = 0%; 5 to 7 = 1% to 20%; 8 to 21% to 60%; 9 to 10 = 61% to 80%; and 11 = 81% to 100%. These categories were incorporated into a clinical outcome prediction tool, “FUNC Score Prediction Tool” (http://www.massgeneral.org/stoptstroke/funcCalculator.aspx), which was designed to facilitate ICH patient assessment by: (1) assigning a FUNC score on admission; and (2) early prognosis of functional outcome based on the data (“percent functionally independent at 90 days”) from both the entire cohort as well as ICH survivors only (Figure).

**Discussion**

We developed and validated an acute clinical scale, the FUNC score, to identify at hospital admission those patients with primary ICH who are likely to recover functional independence. This simple tool is easy to use at the bedside, requiring information only from the initial patient evaluation and CT scan to complete. The FUNC score was similarly effective in identifying those patients who achieve functional independence at 90 days among the entire cohort as well as among the ICH survivors alone, suggesting that its predictive accuracy is substantially unaffected by withdrawal of care.

Developed and validated in an unselected consecutive cohort of patients with ICH, the FUNC score is widely generalizable compared, for example, with prior published prediction scores, which were developed in a cohort of patients with ICH that excluded both comatose and intubated patients. The contributors to the FUNC score are easily and routinely measured in clinical practice, including on hospital admission. In addition to age, GCS, ICH volume, and ICH location, which have been used reliably by prior investigators, we identified pre-ICH cognitive impairment as an independent predictor of functional independence at 90 days. This variable can be simply and reliably determined using a basic set of questions asking informants to compare the subject’s ability to perform a list of daily cognitive tasks involving memory, praxis, calculation, or reasoning with his or her baseline 10 years before the index event. In this format, cognitive impairment is defined as the presence of deficits in memory or other cognitive domains sufficient to interfere with activities of daily living. The role of pre-existing cognitive dysfunction in outcome from ICH is not unexpected because of the powerful role that premorbid functional status may play in rehabilitation after stroke. Furthermore, because ICH is a disease of the elderly, cognitive dysfunction can be expected to be relatively common among affected patients. In fact, there is
reason to believe that patients with ICH may carry an even greater burden of cognitive impairment than equally aged individuals without ICH. The common vascular pathologies that underlie ICH such as cerebral amyloid angiopathy and hypertensive vasculopathy, both on their own, contribute to vascular cognitive decline, whereas Alzheimer disease itself may accompany cerebral amyloid angiopathy.

We did not identify IVH as an independent predictor of functional independence at 90 days. Once adjusted for other variables, the effect of IVH on functional outcome lost its statistical significance in both the entire cohort as well as when restricted to the ICH survivors only. IVH was strongly correlated with GCS, ICH volume, and ICH location; thus, once controlled for these factors, IVH no longer remained significant. Given that IVH was a significant predictor in multiple prior assessment tools, we re-evaluated our model by entering IVH as a predictor variable. After this modification, IVH showed a modest effect on functional outcome but continued to lack significance (OR, 0.8; 95% CI, 0.4 to 1.4) in the model development subset. Furthermore, entering IVH into our model did not improve its goodness of fit (c-statistic = 0.88).

Because patients with ICH are so often neurologically devastated on presentation, withdrawal of care by the physician–family team is common and, when it is tracked, becomes the most potent predictor of death in ICH. Although this practice clearly can alleviate patient and family suffering, it risks becoming a self-fulfilling prophecy. Furthermore, because withdrawal of care is so widely practiced and inconsistently accounted for in cohort studies of ICH outcome, it is often impossible to eliminate its effect on mortality. Thus, one of the limitations that might have hindered applicability of prior prediction tools is that they most likely were developed and validated in cohorts in whom withdrawal of care was not incorporated into the analyses.

We controlled for the effect of withdrawal of care on patient outcomes by applying the FUNC score exclusively to ICH survivors within our cohort. We assumed that because these patients survived to 90 days, they most likely avoided mortality as a result of early care limitations or withdrawal of care, which was shown to double the hazard of death and lead to mortality in up to 77% of patients with primary ICH. Whether our cohort of ICH survivors is subject to other underestimated bias remains unclear. Nevertheless, the FUNC score reliably predicted functional independence in this group of patients, which allows us to conclude that, on admission, one can use the FUNC score rule to predict the likelihood of patient’s functional independence provided that the patient survives to 90 days. Conversely, one could prognosticate that despite surviving to 90 days, those patients whose FUNC score is ≤4 will have no chance of reaching functional independence. When used in this context, the FUNC score could become a practical and reliable clinical instrument, applied a priori, for the multidisciplinary team of physicians to enable goal-of-care discussions with families as well as triage medical management based on calculated prognosis.

By offering prediction of functional outcome, rather than mortality, the FUNC score can be useful for patients, family members, and decision-makers whose primary concern is not the likelihood of survival, but rather the likelihood of survival with recovery of function. Such a decision tool may also have applicability to the design and conduct of clinical trials in ICH.

Summary

The FUNC score is a valid clinical assessment tool (http://www.massgeneral.org/stopstroke/funcCalculator.aspx), which can be used to identify those patients with ICH who will attain long-term functional independence. FUNC score predictions of independence are essentially unchanged when restricted to 90-day ICH survivors, suggesting that the score is not substantially affected by early withdrawal of care. This acute outcome prediction scale provides essential guidance for physicians and families who are confronted with decision-making about direction of care for their patients and selection strategy for clinical trials.

Disclosures

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