A three-item scale for the early prediction of stroke recovery

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Summary

Background Accurate assessment of prognosis in the first hours of stroke is desirable for best patient management. We aimed to assess whether the extent of ischaemic brain injury on magnetic resonance diffusion-weighted imaging (MR DWI) could provide additional prognostic information to clinical factors.

Methods In a three-phase study we studied 66 patients from a North American teaching hospital who had: MR DWI within 36 h of stroke onset; the National Institutes of Health Stroke Scale (NIHSS) score measured at the time of scanning; and the Barthel Index measured no later than 3 months after stroke. We used logistic regression to derive a predictive model for good recovery. This logistic regression model was applied to an independent series of 63 patients from an Australian teaching hospital, and we then developed a three-item scale for the early prediction of stroke recovery.

Findings Combined measurements of the NIHSS score (p=0·01), time in hours from stroke onset to MR DWI (p=0·02), and the volume of ischaemic brain tissue on MR DWI (p=0·04) gave the best prediction of stroke recovery. The model was externally validated on the Australian sample with 0·77 sensitivity and 0·88 specificity. Three likelihood levels for stroke recovery—low (0–2), medium (3–4), and high (5–7)—were identified on the three-item scale.

Interpretation The combination of clinical and MR DWI factors provided better prediction of stroke recovery than any factor alone, shortly after admission to hospital. This information was incorporated into a three-item scale for clinical use.

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Introduction

For several decades physicians have been searching for methods that will allow early and accurate assessment of prognosis after ischaemic stroke.[1–4] It is established that by 6 months after a stroke about 20–30% of patients have died, 20–30% are moderately to severely disabled, 20–25% have mild to moderate disability, and the remainder are without deficit.[5] However, it is often not clear for some days after stroke onset how patients are likely to fare. Patients with initially similar clinical deficits can improve dramatically or worsen during the first 48–72 h.[6–8] Changes in clinical status might sometimes be related to pathophysiologic events such as early reperfusion,[6,7] haemorrhagic transformation or oedema of the ischaemic lesion,[8] and prognoses can markedly differ between experienced physicians. The need for early and accurate outcome assessment is of increasing relevance in the current climate of financial constraint where there are calls to improve the efficacy of care while maintaining quality. It also seems likely that new but possibly risky stroke therapies will need to be administered within the first hours after stroke[9] and that decisions based upon the relative risks and benefits of treatment could be aided by knowing the likely outlook of the patient. The uncertain outlook in the first days after stroke adds further to the initial distress and anxiety of patients and their families.

Early prediction of stroke outcome might be improved by developing clinical criteria[10] or by using brain imaging data.[7] Advances in brain imaging technology include magnetic resonance diffusion-weighted imaging (MR DWI), which allows detection of focal cerebral ischaemic lesions during the first few hours of stroke.[11] We and others[12,13] have previously reported that the volume of the lesions on DWI correlates with acute clinical severity and stroke outcome. In this study our aim was to assess the prognostic value of imaging data in relation to clinical factors. The results were validated on the independent data from a second series of patients from Australia and we developed a three-item scale for the early prediction of stroke recovery.

Methods

Patients

We included 66 patients who were admitted to the Beth Israel Deaconess Medical Center (Boston, MA, USA) with a diagnosis of acute ischaemic stroke. Patients with transient ischaemic attacks were excluded. We identified all patients from the Stroke MRI Database who had had MR DWI within 48 h of stroke onset, anterior circulation stroke, the National Institutes of Health Stroke Scale (NIHSS) score measured at the time of MR scanning, and the outcome Barthel score[14,15] obtained between 1 and 3 months after stroke. We obtained data for 347 patients consecutively studied with MR DWI from the MRI Stroke Database from 1993 to July, 1998. Patients were excluded for the following reasons: non-ischaemic stroke pathology or transient ischaemic attacks (n=97), posterior circulation stroke (n=46), haemorrhagic stroke (n=22), multiple stroke (n=9), MRI done later than 48 h (n=41), lack of outcome data (n=61), outcome data not recorded between 1 and 3 months (n=4), and missing DWI data (n=1).

Independent patient data was obtained from the Royal Melbourne Hospital in Australia. 63 patients had been consecutively studied with MR DWI between 1996 and 1999 within 24 h of the onset of ischaemic stroke. These patients met entry criteria for the study and were the basis for an external validation study of the model derived from the Beth Israel Deaconess patients.

Informed consent for the use of MRI and clinical data was obtained. The MRI protocols had been approved by the Institutional Review Board at the Beth Israel Deaconess Medical Center (Boston) and the Ethics Committee at the Royal Melbourne Hospital (Australia).

Neuroimaging

MR DWI was carried out at the Beth Israel Deaconess Medical Center as described previously.[12] All studies were done within the first 48 h of stroke on a 1·5 Tesla MR whole body system (Siemens AG, Erlangen, Germany); the Vision system or its prototype. DWI was done by multislice single-shot echoplanar imaging. For the analysis the volume of the brain lesion on the MR DWI scan (DWI lesion volume) was used.[12] DWI lesion volumes had been measured twice by observers unaware of the clinical data, with an interobserver reliability of r>0·95. Patients at the Royal Melbourne Hospital in Melbourne, Victoria had been studied with echoplanar DWI within the first 24 h of stroke on a General Electric Signa 1·5 Tesla scanner using validated volumetric methodology.

Clinical data

We assessed the clinical factors of age at the time of stroke, sex, history of treated hypertension, history of heart disease, the NIHSS score, entry into a drug trial, and time after onset of symptoms to MR scanning.[1–4,16] The NIHSS score is widely used in North America to provide a measure of the severity of neurological dysfunction at the patients' first hospital visit. This score has undergone extensive validation and reliability assessments and consists of 11 graded items measuring multiple aspects of the neurological examination.[10] A score greater than 25 indicates very severe neurological impairment, between 15 and 25 severe impairment, between 5 and 15 mild to moderately severe impairment, and less than 5 mild impairment. All NIHSS scores had been obtained within 1 h of MR scanning. Hypertension was defined as a medical history of treated hypertension. Patients who had raised blood pressure but no history of hypertension at the time of presentation were not classified as hypertensive.[2] Heart disease was defined as cardiac abnormalities based on information obtained from the medical history, clinical examination, and the results of electrocardiogram and echocardiogram recordings. We defined time from stroke onset as time from the onset of symptoms to the start of MR scanning, which was the time at which the NIHSS score was recorded. If a patient woke up with a deficit then the time was backdated to when the patient was last known to be without deficit—nine patients in Boston and nine patients in Australia. We also included whether the patient had been enrolled in trials of putative neuroprotective therapies. When available, data on temperature, blood pressure, and serum glucose at the end of admission were also recorded.[17–18]

Barthel index

The Barthel Index provides a functional assessment of ten activities of daily living.[14] This scale has undergone extensive reliability and validation assessments.[14,15] The maximum score of 100 indicates full independence. A score of 90 and above indicates patients who have near full functional independence and at most need assistance with one or two activities of daily living.[14,15,19] Patients who died were given a score of zero. In the Boston patients the Barthel score had been measured between 1 and 3 months after stroke (in 90% of patients at 3 months). In all of the Australian patients the Barthel score had been recorded at 3 months.

Statistics

Good stroke recovery was defined as a score of 90 or higher on the Barthel index at follow-up.[19] In the first phase of the study, the factors examined were age, sex, history of treated hypertension, history of heart disease, the NIHSS score, entry into a drug trial, time from onset of symptoms to MRI scanning, and DWI lesion volume measurement.[1–4,16] In the univariate analyses, we compared each of these factors for good or poor recovery using Mann-Whitney U statistics or Fisher's exact tests as appropriate. Those factors significantly associated with outcome were then individually categorised, based on optimum discrimination between good and poor stroke recovery using recursive partitioning methods. We derived a multiple logistic regression model for good recovery with both forward and backward variable selection methods. We determined the sensitivity and specificity of the model and assessed goodness of fit with the Hosmer and Lemeshow statistic.

We compared the demographic and outcome details of the Boston and Australian patients in the second phase of the study. The logistic regression model derived from the Boston patients was applied to the Australian patients. Goodness of fit and the sensitivity and specificity of the model for the prediction of stroke recovery were determined. We assessed the calibration of the logistic regression model by establishing the observed proportions of patients recovering across three probability ranges of recovery in the combined test and validation series (129 patients).

Factor	Boston			Australia		
	Outcome			Outcome		
	Overall (n=66)	Good (n=37)	Poor (n=29)	Overall (n=63)	Good (n=28)	Poor (n=35)
Age (years)	69·6 (14·8)	70·2 (16·6)	68·7 (12·7)	69·9 (10·0)	64·9 (12·5)	73·9 (7·4)
Men	34 (52%)	17 (46%)	17 (59%)	34 (54%)	18 (64%)	16 (46%)
Hypertension	32 (49%)	18 (49%)	14 (48%)	. .	. .	. .
Heart disease	29 (46%)	15 (41%)	14 (48%)	. .	. .	. .
NIHSS score	10·5 (6·6)	8·0 (5·6)	13·7 (6·4)	10·9 (6·9)	5·6 (4·1)	15·1 (5·8)
Time from onset (h)	9·7 (7·0)	11·5 (7·7)	7·5 (5·4)	9·3 (6·6)	10·6 (7·1)	8·2 (6·0)
DWI lesion volume (mL)	21·1 (34·1)	9·1 (14·1)	36·3 (44·8)	30·8 (51·8)	11·9 (15·5)	45·9 (64%)
Drug study	40 (61%)	21 (57%)	19 (66%)	15 (24%)	2 (7%)	13 (37%)
Barthel index	72·0 (33·5)	97·9 (3·8)	39·0 (23·9)	64·6 (38·5)	97·9 (3·5)	38·0 (32·4)

Values are mean (SD) unless otherwise stated.

Table 1: **Comparison of demographics and outcomes between Boston and Australian patients**

Factor	Coefficient (SE)	Odds ratio (95% CI)
Constant	1·99 (1·32)	. .
DWI lesion volume	−1·62 (0·77)	0·20 (0·04–0·90)
NIHSS score	−2·61 (1·13)	0·07 (0·01–0·67)
Time from onset	1·22 (0·46)	3·37 (1·36–8·37)

Table 2: **Logistic regression model of stroke recovery for Boston patients**

In the third phase of the study, a three-item scale for the early prediction of stroke recovery was developed to encompass the information obtained in an easy and quick form to be used at the time of clinical assessment. Points were assigned for the categories of the three factors, using a simple weighting scheme based on our findings. The two categories of DWI lesion volume were assigned 0 or 1 point, the three categories of NIHSS score 0, 2, or 4 points, and the three categories of time 0, 1, or 2 points. The points for each factor were then added up to give a total score for the patient (maximum score of 7). Patients were classified by their total score as having a low likelihood of recovery (total score 0–2), medium (3–4), and high (5–7). The observed percentages and 95% CI of recovered patients across three levels of the three-item scale were determined in the 129 patients in the combined test and validation samples.

Results

Table 1 shows the demographic and outcome details of the Boston and Australian patients. 37 of 66 Boston patients had good recovery from their strokes by 3 months, defined as a Barthel score of 90 or higher. Five patients had died. 12 patients were studied within 3 h of stroke onset, 13 between 3 and 6 h, 26 between 6 and 12 h, and 15 between 12 and 36 h after stroke. In the 63 Australian patients, 28 had good recovery by 3 months (table 1) and eight patients had died. 34 of the Australian patients had been studied within the first 6 h of stroke onset, the remainder within the first 24 h. 21 Australian and 12 Boston patients had an initial NIHSS score of more than 15.

In the univariate analyses in the Boston patients, three factors were significantly associated with good stroke recovery (table 1): DWI lesion volume (p=0·002), NIHSS score (p<0·0001), and time from symptom onset to scanning (p=0·03). Age, sex, history of hypertension, history of heart disease, and participation in a drug trial were not significantly different for patients with good and poor stroke recovery (table 1). The relation of stroke recovery with time from onset to scanning indicated that later studied patients were more likely to recover, even though there was no difference in their initial NIHSS score.

We categorised the three statistically significant factors in the univariate analyses for optimum discrimination between good and poor stroke recovery using recursive partitioning. The categories obtained were: DWI lesion volume=0 (⩽14·1 mL), 1 (>14·1 mL), NIHSS score=0 (⩽3), 1 (4–15), 2 (>15), and time=0 (⩽3 h), 1 (3 <time ⩽6 h), 2 (>6 h). The derived categories were in accordance with those accepted in clinical practice.

In the logistic regression analysis, age, sex, history of hypertension, history of heart disease, and entry into a drug study were eliminated by both forward and backward stepwise variable selection. Inclusion of temperature, serum glucose concentration, and blood pressure provided no additional discriminative information.

Table 2 shows the operational logistic regression model and odds ratios for each of the factors. The significant factors in the model were DWI lesion volume (p=0·04), NIHSS score (p=0·01), and time from symptom onset (p=0·02). Patients with DWI lesion volumes ⩽14·1 mL were five times more likely to recover from their strokes than patients with larger DWI lesion volumes, after adjustment for the other factors.

Combinations of the three significant factors from the logistic regression provided 18 descriptive categories of stroke patients. Of these 18 categories, no Boston patients were observed in five (table 3). As an example, there were no patients observed in the category of DWI lesion volume=0, NIHSS score=0, and time from onset to scanning=0 (ie, DWI lesion volume ⩽14·1 mL, NIHSS score ⩽3, and time from onset ⩽3 h; table 3). Patients fitting that category may have had transient ischaemic attacks and would have been excluded from the study. In the category associated with DWI lesion volume=0, NIHSS score=1, and time from onset to scanning=2 (ie, DWI lesion volume ⩽14·1 mL, NIHSS score 4–15, and time from onset later than 6 h) the model gave a probability of 0·86 for recovery. 19 (90%) of the 21 Boston patients in that category were noted to recover (table 3). The sensitivity of the model for the prediction of good recovery was 0·77 and the specificity was 0·71 with an overall probability of being correct of 0·74. The Hosmer and Lemeshow statistic indicated that the fit of the model to the data was good (p=0·24). In an analysis of

Factors				Boston		Australia	
DWI lesion volume	NIHSS score	Time from onset	Probability of stroke recovery (logistic model)	Number of patients	Number with recovery	Number of patients	Number with recovery
0	0	2	0·998	6	6	5	5
0	0	1	0·961	2	2	4	3
1	0	2	0·943	0	. .	1	1
0	0	0	0·881	0	. .	0	. .
0	1	2	0·860	21	19	8	5
1	0	1	0·831	0	. .	0	. .
0	1	1	0·646	7	2	9	4
1	0	0	0·593	0	. .	1	1
1	1	2	0·549	6	3	7	5
0	1	0	0·350	4	3	1	1
0	2	2	0·311	0	. .	0	. .
1	1	1	0·265	2	1	3	1
0	2	1	0·118	1	0	2	1
1	1	0	0·097	5	0	3	1
1	2	2	0·087	8	1	8	0
0	2	0	0·038	1	0	2	0
1	2	1	0·026	1	0	6	0
1	2	0	0·008	2	0	3	0

Table 3: **Illustration of the logistic regression model for the original Boston patients and its application to Australian patients for the allotted categories**

Factor	Assigned points
DWI lesion volume (mL)	
⩽14·1	1
>14·1	0
NIHSS score	
⩽3	4
4–15	2
>15	0
Time from onset (h)	
⩽3	0
3< time⩽6	1
>6	2
Total score (sum of assigned points)	0–7

To use the scale the clinician should identify the NIHSS score, time from onset, and DWI lesion volume for each patient. These values are matched to the corresponding assigned points shown in the table and are summed to give a total score. The total scores range from 0 to 7.

Table 4: **A three-item scale for the prediction of stroke recovery shortly after admission**

Probability of recovery (logistic model)	Average predicted % recovered (logistic model)	Number of recovered patients/ total	Observed % recovered (95% CI)	Three-item scale total score
0·008–0·118	7%	3/42	7% (0–15)	0–2 (low)
0·265–0·646	46%	21/40	53% (37–68)	3–4 (medium)
0·831–0·998	91%	41/47	87% (77–97)	5–7 (high)

Table 5: **Observed % of patients with stroke recovery across three probability ranges of the logistic regression model and three levels of the three-item scale**

the predictive value of the NIHSS score alone, the sensitivity was 0·69 with a specificity of 0·60, with an overall probability of being correct of 0·65.

All factors in the Australian patients were similar to those of the Boston patients with the exception of the number of patients who had participated in a drug study (table 1). Application of the derived logistic regression model to the Australian patients provided data for 15 of 18 combinations of factors (table 3). The sensitivity of the logistic regression model applied to the Australian data was 0·77 and the specificity was 0·88, with an overall accuracy of 0·82. The Hosmer and Lemeshow statistic indicated that the fit of the logistic model to the Australian data was good (p=0·76).

We have developed a three-item scale for the early prediction of stroke recovery which will be quick and easy to use at the time of clinical assessment (table 4).

In the combined series (n=129) the observed percentages of patients with stroke recovery across three total score levels of the three-item scale, and three probability ranges from the logistic regression based model were determined (table 5). The same patient results were seen across the three levels of the three-item scale and the three probability ranges in the logistic regression model. In the Boston patients the proportions of patients showing recovery for the three levels of the scale were 1 (6%) of 17 with a total score=0–2, 9 (47%) of 19 with a total score=3–4, and 27 (93%) of 29 with a total score=5–7. In the Australian patients the values were 2 (8%) of 25, 12 (57%) of 21, and 14 (78%) of 18, respectively.

Discussion

We report that the combination of clinical and MR DWI variables allowed more reliable early prediction of stroke recovery than any single factor alone. The results were validated in an independent series of patients and showed high sensitivity and specificity. Our results show that a new technology, in this case MR DWI, can potentially add to early clinical management both in terms of improved diagnostic accuracy and improved efficiency.

Potential uses for our results include early decision-making on aggressiveness of care, and discharge planning and rehabilitation, which is of particular relevance in the current health-care climate where there are extreme pressures to shorten length of stay, limit the number of tests, and commence discharge planning soon after the patient's admission. For example, in most hospitals discharge plans are formulated at or after the third day of the admission. The identification of patients with likely recovery might allow discharge planning as early as the first day. In the setting of trials of new acute stroke therapies it might also be valuable to try and predict those with stroke recovery. Patients who are likely to recover could be stratified or even excluded from some drug trials. Our findings could potentially be applied in the emerging field of telemedicine.

Our findings could be further refined with a larger patient sample and a higher proportion of patients with very severe strokes. Further validation and reliability assessment of the three-item scale will require testing on an external sample of patients. Although the sample size is small for recursive partitioning methodology, the resultant categories are very similar to those based on clinical experience and used in other studies.[9,19,20] The incorporation of further pathophysiological information, such as perfusion data (only available for about half the patients) and brain site (cortical or subcortical) and side should be investigated, along with other clinical factors such as temperature, serum glucose, or blood pressure.[17,18] An interesting time-dependence of the results was shown, in both the univariate and logistic regression analyses. One explanation for this finding could be that the most severely impaired patients were studied at the earliest time points, although there was no significant association between admission NIHSS score and time. Alternatively, this time-dependence might be explained by pathophysiologic events such as early reperfusion[6,7] or oedema of the ischaemic lesion, which can lead to marked changes in clinical status in the first 24 h.[8] A patient who has survived for 24 h after stroke could have a higher probability of survival (or a good outcome) than a patient at 2 h after stroke. The potential confounding effects of treatment with putative neuroprotective agents was examined in the analyses but not confirmed, supporting the findings of recent clinical trials.

In both series of patients, we did not record several combinations of DWI lesion volume, NIHSS score, and time from onset, probably because these are unusual in practice—eg, a large DWI lesion volume and a low NIHSS score. Patients with transient ischaemic attacks were excluded, which could account for the low numbers of patients recorded with low NIHSS scores and small DWI lesion volumes.

We have shown that imaging predictors used in combination with neurological predictors were more accurate in predicting outcome than any clinical or imaging factor used alone.[6,7,21] Clinical data, in particular the severity of neurological deficit as measured by the NIHSS score provided powerful prognostic information and formed the major component of the prediction algorithm. This finding lends support to previous reports that NIHSS score is a powerful predictor of outcome, particularly at high and low scores but with less certainty in the middle range.[20] It would be worthwhile to investigate the accuracy of the scale using other stroke classification scales such as the Oxford Stroke Classification, the Canadian Neurological Scale, or the Rankin scale.[22–24] Imaging variables have been reported to provide independent prognostic information at 10 days using computed tomography,[21] and at 24 to 48 h using serial cerebral perfusion studies,[6,7] but not as early as 3–6 h after onset. Although early computed tomography signs can be difficulty to detect, a correlation between the extent of early computed tomography signs in acute ischaemic stroke and clinical outcome had been reported.[25] If these results are confirmed we could incorporate computed tomography measurements in an attempt to make the prediction rule much more widely available for clinical use.

Contributors

In the first phase of the study, Brian Silver and Claudia Chaves were responsible for data collection and helped with study analyses and manuscript revision. Alison Baird, Sok-Ja Janket, and Quentin Eichbaum were responsible for study design, statistical analyses, and co-wrote the manuscript. Robert Edelman and Steven Warach assisted with MRI data

acquisition and analyses, and revision of the manuscript. Louis Caplan helped with study design and manuscript revision. In the second phase of the study, David Darby, Mark Parsons, P Alan Barber, and Stephen Davis participated in data collection of the validation patient series and manuscript revision. In the third phase of the study, James Dambrosia provided new statistical expertise and co-wrote the revised manuscript with Alison Baird.

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