Developing predictive models of excellent and devastating outcome after stroke

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Abstract

Background: models to predict functional status post-stroke have utility in balancing groups in randomised trials, for outcome comparison between stroke centres and may assist in outcome prediction. This study aimed to develop models of both excellent [modified Rankin score (mRS) 0–1] and devastating outcomes (mRS of 5–6).

Methods: patients admitted with ischaemic or haemorrhagic stroke in 2001–02 to the Halifax Infirmary, Canada, were enrolled. Sixteen clinical variables from the first neurological assessment and six radiological variables from the acute CT scan were used to the model outcome at 6 months.

Results: five hundred and thirty-eight stroke patients were enrolled. Thirty per cent had an excellent outcome and 30% had a devastating outcome. Three models of the excellent outcome were developed [area under the receiver operator curve (AUC) 0.866–0.882] including the variables age, pre-stroke functional status, stroke severity, ability to lift both arms, walk independently, normal verbal Glasgow Coma Scale and leukoaraiosis. Predictive models of the devastating outcome (AUC of 0.859–0.874) included additional variables living alone pre-stroke and total anterior circulation stroke. The simplest models of both outcomes were externally validated (AUC of 0.856–0.885).
Developing predictive stroke outcome models

Introduction

Functional status following stroke has been used as a primary outcome in stroke research, most commonly using the modified Rankin score (mRS). This describes outcome in terms of symptoms, disability, dependence and mortality [1]. Models of outcome may be useful for balancing treatment groups in randomised trials, comparing outcomes between stroke centres and prognostication in clinical practice. Many studies use an outcome of independent survival (mRS of 0–2) or disability-free survival (mRS of 0–1). However, studies of hemicraniectomy for malignant stroke and a therapeutic trial in haemorrhagic stroke have used outcomes of survival with mild dependence (mRS of 0–3) and a devastating outcome (mRS of 5–6), respectively [2, 3]. The utility of simple clinical variables in predicting independent survival (mRS of 0–2) post-stroke has previously been confirmed [4, 5]. The aim of this study was to identify predictive variables and models of excellent (mRS of 0–1) and devastating outcomes (mRS of 5–6), and where possible to externally validate any model.

Methods

Study population

Patients admitted consecutively with a diagnosis of stroke between 2001 and 2002 at the Halifax Infirmary were enrolled in the Stroke Outcomes Study (SOS) as previously described [4]. All patients underwent cranial imaging urgently on arrival in the emergency department. Information was collected from the first clinical assessment on admission by the on-call neurology team (see below). Patients were followed up by telephone interview 6 months post-stroke and assessed using the mRS [1]. Images from each patient’s first CT scan were analysed using the Consortium for the Investigation of Vascular Impairment of Cognition (CIVIC) scale [4, 6].

Predictor variables

The modelling included the following variables derived from the first medical assessment: age, gender, stroke severity score (SSS) [7], stroke subtype [either intraparenchymal haemorrhage as determined by CT or MRI, or Oxfordshire Community Stroke Project (OCSP) [8] subtype for ischaemic stroke], atrial fibrillation on the ECG, previous TIA or stroke, pre-stroke functional status, use of tissue-plasminogen activator (tPA), time from symptom recognition to presentation, stroke localisation, stroke on waking, living alone pre-stroke, normal verbal component of the Glasgow Coma Scale (GCS) [9], able to lift both arms off the bed, and to walk without assistance of another person. Six radiological variables were included: any abnormality, any focal abnormality, number of focal lesions, acute infarction, acute infarction or haemorrhage, and leukoaraiosis score [4]. The majority of these variables were binary; age, SSS, leukoaraiosis score, pre-stroke functional status and number of focal lesions were coded as continuous variables, and stroke subtype and localisation as categorical variables.

Statistical techniques for generating the models

The data are presented as mean ± SD unless otherwise stated. Comparisons between groups were made using the Chi-square test, Student’s t-test and the Mann-Whitney test where appropriate with significance of $P < 0.05$. To formulate models predictive of an excellent or a devastating outcome, univariate analysis was performed comparing patients with and without these outcomes in the training data set (SOS). Significant variables ($P < 0.05$) were subjected to multivariate logistic regression analysis. A stepwise selection procedure was applied; the probability for entry of a variable was 0.01 and 0.1 for removal. Three models were produced per outcome by entering either (i) all clinical variables, (ii) all clinical variables excluding SSS, since SSS is more complex than individual variables, and (iii) including all radiological and clinical variables. For each model, the statistical assumptions of linearity (for age) were verified [10, 11]. A pooled interaction test [10] was used to explore interactions between age, sex and other model predictor variables.

Validation of models

Bootstrap techniques [12] with re-sampling 500 times were used to internally validate all models. External validation used the OCSP ($n = 530$) [8] data set, a community-based incidence study. The OCSP database did not provide SSS or CIVIC variables. Therefore, not all models could be externally tested. Model discrimination was assessed using the area under a receiver operating characteristic curve (AUC) [13]. The best model was defined as the model with the statistically significant largest AUC [13, 14] using analyses of variance or, if no model was statistically superior, the model with the simplest variables. The confidence intervals

Conclusion: this study demonstrates new externally validated predictive models of both excellent and devastating outcomes. Leukoaraiosis was the only independent radiological predictor of both outcomes. Living alone pre-stroke predicted devastating outcome post-stroke.

Keywords: stroke, outcome, modelling, leukoaraiosis, elderly

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of AUCs and the observed probability of an outcome were calculated with bootstrapping. All analyses were conducted using the SAS software, Version 9.2 (SAS Institute, Inc., Cary, NC, USA) (Supplementary data are available in Age and Ageing online).

Results
A total of 538 ischaemic and haemorrhagic stroke patients were enrolled [4], of whom 30% had an excellent outcome (mRS of 0–1) and 30% had a devastating outcome (mRS
of 5–6) at 6 months (Table 1). Univariate analysis identified several significant predictive variables (Table 1).

Model development

Excellent outcome

Three models of the excellent outcome were developed (Table 2). Multivariate analysis using all clinical variables produced model I including age, pre-stroke functional status, ability to lift both arms and SSS (AUC of 0.879). Excluding SSS produced model II including three variables from model I but SSS was replaced with ability to walk independently and normal verbal GCS (AUC of 0.866). Including radiological variables produced model III with four variables (AUC of 0.882): pre-stroke functional status, ability to lift both arms, SSS and leukoaraiosis score. Dichotomising pre-stroke functional status as an mRS < 2 versus >1 did not produce any superior model or new predictor variables. There was no statistical difference in model performance between models I–III (P = 0.107, Supplementary data available in Age and Ageing online, Figure S1a, Appendix).

Devastating outcome

Modelling devastating outcome using all clinical variables produced model IV with five variables: age, pre-stroke functional status, normal verbal GCS, total anterior circulation stroke (TACS) and SSS (AUC of 0.861, Table 2). Excluding SSS produced model V with age, pre-stroke functional status, normal verbal GCS, TACS and ability to lift both arms (AUC of 0.859). Inclusion of radiological variables produced model VI (AUC of 0.874) with the same variables as model IV but also living alone pre-stroke, but no independent radiological variables. Dichotomising pre-stroke functional status (mRS = 5 vs. mRS ≤ 4) produced a further model (VIa, AUC of 0.861), including age, TACS, normal verbal GCS, SSS and leukoaraiosis score. There was no statistical difference in model performance comparing models IV–VIa (P = 0.084, Table 2, Supplementary data available in Age and Ageing online, Figure S1b, Appendix 1). The coefficients for models I–VIa are shown in Supplementary data available in Age and Ageing online Table S3, Appendix 1).

External validation

Only models II and V could be externally tested in the OCSP data set (AUC of 0.856 and 0.885, Supplementary data available in Age and Ageing online, Figures S2 and S3, Appendix 1) as it contained the same variables.

Discussion

This study developed models of excellent and devastating outcome post-stroke. Models II and V showed good external validity and used the simplest and smallest number of variables; age, pre-stroke functional status, ability to walk independently and lift both arms, normal verbal GCS, and in addition TACS for devastating outcome. Model II is similar to two previous models of independent survival [4, 5], suggesting these specific predictor variables are robust predictors of both independent (mRS of 0–2) and disability-free survival (mRS of 0–1). The similarity in models of these outcomes may be because the clinical difference between mRS 0–2 versus mRS 0–1 is marginal. For example, the treatment effect size with tPA for ischaemic stroke is similar whether outcomes of mRS 0–1 or 0–2 are examined [15]. Also the modified Rankin scale has poorest inter-rater reliability at values of 1 and 2 [16].

For all models of the devastating outcome both TACS and an abnormal verbal GCS were important independent predictors. The leukoaraiosis score was the only independent predictive radiological variable of both outcomes (models III and VIa), replacing age in model II and pre-stroke functional status in model VI. While there may be confounding between these three variables, previous studies identified leukoaraiosis as an independent predictor of poor outcome after ischaemic [4, 17, 18] and haemorrhagic stroke [19], and a predictor of infarct growth and cognitive impairment [17, 18].

Previous studies have differed on whether living alone pre-stroke influences independent survival [4, 5]. Living alone was an independent predictor in only one model (devastating outcome model VI) suggesting that this was a false-positive finding; however, living alone may be a marker of social isolation, which is associated with increased mortality [20].

This study has some limitations. We assumed that the SOS data set was large enough to demonstrate statistical differences between models. We could not attempt external validation of all models because some variables were unavailable in external data sets. Although our cohort was assembled a decade ago, our findings are likely still applicable because acute stroke care in Nova Scotia has not changed substantially since 2001–02. For example, our use of intravenous alteplase increased only slightly from 6.2% of ischaemic stroke patients in SOS to 8% in 2008–09 [21]. Novel therapies (e.g. clot retrieval) may influence outcome prediction models, but such therapies are not currently widespread. As the OCSP data set predates stroke units and thrombolysis, revalidating our models in more modern cohorts would be desirable. Despite these shortcomings, our study demonstrates the utility of simple clinical variables in outcome prediction in the acute setting. In conclusion, this study demonstrates two new externally validated predictive models of the excellent and devastating outcome after stroke using easily collected variables.
Supplementary data

Supplementary data mentioned in the text is available to subscribers in *Age and Ageing* online.

Key points

- This study describes models of a devastating outcome and disable-free survival after stroke.
- Simple clinical variables produce good models of both outcomes, which are non-inferior to more complex models.
- The degree of leukoaraiosis on the acute CT scan has predictive value for both outcomes.
- Living alone pre-stroke appears to predict a higher likelihood of a devastating outcome.

Conflicts of interest

None declared.

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References