SHORT REPORT

Predictors of risk of intracerebral haemorrhage in patients with a history of TIA or minor ischaemic stroke

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We developed a model identifying patients with previous cerebral ischaemia at increased risk of intracerebral haemorrhage (ICH). Based on data from eight cohorts, 107 ICHs were found to have occurred among 12 648 patients. Multivariate Cox regression analysis identified the following predictors: age (≥60 years, hazard ratio (HR) 2.07), blood glucose level (≥7 mmol/l, HR 0.33), systolic blood pressure (≥140 mm Hg, HR 2.17), and antihypertensive drugs (HR 1.53). The highest risk quartile was associated with five times more ICHs than the lowest quartile.

Each year approximately 1 million strokes occur in the European Union, of which approximately 80% are ischaemic strokes, 15% are intracerebral haemorrhages (ICHs), and 5% are subarachnoid haemorrhages. As the risk of stroke after a transient ischaemic attack (TIA) or ischaemic stroke is approximately 12% in the first year, preventive measures, such as anticoagulant or antiplatelet treatment, are indicated. However, antithrombotics may have detrimental adverse effects, the most devastating of which is an ICH; the incidence of this type of bleeding is far higher in patients after cerebral ischaemia (300–3700 per 100 000 per year) than in the general population (20–35 per 100 000 per year). Determining which patients are at increased risk of ICH is important so as to better target antithrombotic treatment in these subjects. In this study a model was developed to identify patients with previous cerebral ischaemia at highest risk of ICH.

METHODS

The Cerebrovascular Cohort Studies Collaboration (CCSC) is a joint undertaking in which individual patient data from cohort studies in patients with a previous episode of cerebral ischaemia are pooled. The current analysis is based on data from eight cohorts in which there was adequate brain imaging after follow up strokes such that haemorrhagic strokes could be reasonably reliably identified (for extra references see supplementary information available at http://jnnp.com/supplemental). Patients with ischaemic stroke or TIA aged 18 years and above and a Rankin grade ≤3 at baseline were studied. Data on presenting events, baseline characteristics, results of baseline investigations including brain and vascular imaging, and all recorded follow up events were obtained. Detailed consideration was given to the definition of each variable used in the original studies. Where definitions were identical, data were merged. When possible, differences in definitions of variables between studies were resolved by reconstructing definitions to achieve comparability. Since only few patients had a follow up longer than 7 years, we only included follow up data collected during the 7 years after inclusion in our analyses.

Symptomatic ICH was the predicted outcome of interest and was based on CT scan or autopsy. All of the studies differentiated between ICHs and subarachnoid haemorrhages or subdural haemorrhages. In none of the studies were cases classified as ICHs without good evidence on brain imaging.

DATA ANALYSIS

Using Cox regression analysis, we assessed as a first step the univariable associations between potential predictors and the occurrence of ICH. It was not feasible to adjust for source of study, because risk of ICH in patients with cerebral ischaemia in the separate studies was low. Therefore, to study the effect of the different trials from which patients originated, we compared the maximum likelihood estimate (MLE) of the model with one of the potential predictors and risk of ICH with the MLE of the model with origin of trial and risk of ICH. If there was no statistically significant difference between these two MLEs, then there was no confounding influence of origin of study.

In a second step we selected candidate predictor variables that were associated with ICH in the univariable analyses (p<0.20). These variables were entered into the multivariate Cox regression analyses using forward stepwise selection to develop a multivariate model. The variables associated with risk of ICH in the multivariable analyses were dichotomised using clinically meaningful cut offs. To adjust for overfitting in the modelling process, we performed bootstrapping to shrink the regression coefficients. We multiplied the shrunk regression coefficients by 10 and rounded them to the nearest integer to calculate a risk score and categorised the score into quartiles. To assess the relative increase in risk of ICH per score category, we performed a Cox regression analysis with score category and risk of ICH. For external validation, we will have to wait until new data are added to the CCSC data set.

RESULTS

A total of 107 ICHs occurred in 53 761 person years; the incidence of ICH was 1.0% in 5 years (95% confidence interval (CI): 0.8 to 1.2) (see web table 1 available at http://jnnp.com/supplemental). The mean follow up was 4.3 years. Comparison of the MLEs of the models showed no confounding by origin of study for the variables associated with ICH in the univariable analyses. Therefore, we concluded that origin of study did not influence the results.

Factors that were associated with ICH in the univariable analyses were age, systolic and diastolic blood pressure, use of antihypertensive drugs, blood glucose level, history of angina, and daily smoking (see web table 2 available at http://jnnp.com/supplemental). In the multivariate Cox regression analyses, age (hazard ratio (HR) 2.07), blood glucose level (≥7 mmol/l, HR 0.33), and systolic blood pressure (≥140 mm Hg, HR 2.17) were associated with increased risk of ICH. Multivariate Cox regression analysis identified the following predictors: age (≥60 years, hazard ratio (HR) 2.07), blood glucose level (≥7 mmol/l, HR 0.33), systolic blood pressure (≥140 mm Hg, HR 2.17), and antihypertensive drugs (HR 1.53). The highest risk quartile was associated with five times more ICHs than the lowest quartile.

Abbreviations: CCSC, Cerebrovascular Cohort Studies Collaboration; CI, confidence interval; ICH, intracerebral haemorrhage; MLE, maximum likelihood estimate; TIA, transient ischaemic attack
Table 1  Multivariate Cox regression model

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>95% CI</th>
<th>Shrunken regression coefficients</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥60 years</td>
<td>2.07</td>
<td>1.27 to 3.38</td>
<td>0.64</td>
<td>6</td>
</tr>
<tr>
<td>Age &lt;60 years</td>
<td>1.00</td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Blood glucose level ≥7 mmol/l</td>
<td>0.33</td>
<td>0.14 to 0.74</td>
<td>-0.99</td>
<td>-10</td>
</tr>
<tr>
<td>Blood glucose level &lt;7 mmol/l</td>
<td>1.00</td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Systolic blood pressure ≥140 mm Hg</td>
<td>2.17</td>
<td>1.23 to 3.83</td>
<td>0.67</td>
<td>7</td>
</tr>
<tr>
<td>Systolic blood pressure &lt;140 mm Hg</td>
<td>1.00</td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Use of antihypertensive drugs Yes</td>
<td>1.53</td>
<td>1.05 to 2.25</td>
<td>0.37</td>
<td>4</td>
</tr>
<tr>
<td>Use of antihypertensive drugs No</td>
<td>1.00</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

CI, confidence interval; HR, hazard ratio.

glucose level (HR 0.33), systolic blood pressure (HR 2.17), and use of antihypertensive drugs (HR 1.53) appeared to be independent predictors of ICH (table 1). After bootstrapping, the regression coefficients were shrunk by 14% to adjust for overfitting. From the shrunken regression coefficients we calculated a risk score, which ranged from −10 to 17 in individual patients. We categorised the patients into risk quartiles (Q) of the total population: −10 to 4 (Q1), 6 to 10 (Q2), 11 to 13 (Q3), and 17 (Q4). The 5 year rate of ICH was 0.4% for Q1, 0.6% for Q2, 1.3% for Q3, and 2.0% for Q4. The Kaplan-Meier curves are shown in fig 1. Patients in Q4 were five times more likely to suffer an ICH than those in Q1 (HR 5.17, 95% CI: 2.49 to 10.7).

**DISCUSSION**

Independent predictors of ICH were age, blood glucose level, systolic blood pressure, and use of antihypertensive drugs. With this model it was possible to select a group at higher risk of ICH (HR 5.17). However, the absolute risk of ICH in these patients is still low. Although we consider this not to be clinically insignificant, patients in the highest risk stratum would not be good candidates for the more aggressive forms of antithrombotic treatment, that is, oral anticoagulation or combination antiplatelet treatment.

In the Cerebrovascular Cohort Study Collaboration we have individual patient data available from the cohort studies in patients with a previous episode of cerebral ischaemia. This is an advantage because it allowed us to identify predictors of ICH in these patients, which has not been previously attempted. Individual patient data also allow the inclusion in the analyses of a variety of patient characteristics that might be powerful predictors. However, we could include only variables measured in all studies. Therefore, we could not, for example, include alcohol intake as a predictor of ICH risk. We did not include antithrombotic drugs in the analyses, because almost all patients in the CCSC cohort received antithrombotic drugs. Therefore, the model is applicable to patients on antithrombotic drugs. Moreover, the definition of baseline characteristics may have been slightly different between the studies. Furthermore, CT scanning was rather late in many of the cohorts so we will have missed some ICHs, both at baseline and in defining outcome strokes.

In this study, we evaluated prognostic factors for ICH in patients with a previous TIA or stroke. Since to our knowledge there are no previous reports in similar patients, we compared the prognostic factors that we identified in our study with the risk factors for ICH in the general population. In the current study, we identified systolic blood pressure and use of antihypertensive drugs and age as prognostic factors of ICH in patients with a previous TIA or stroke. This is in accordance with the finding that hypertension is a strong risk factor for ICH. Furthermore, age was found to be a risk factor for ICH in the general population. Finally, we identified blood glucose level as an independent predictor; patients with higher blood glucose levels had a lower risk of ICH. This association remained the same after exclusion of patients who were treated for diabetes. This was an unexpected finding. The underlying mechanism of this association is uncertain and deserves further study, although prognostic factors do not necessarily have a causal association with the outcome.

In conclusion, although it is possible to select a subgroup of patients who are at increased risk of ICH, it remains very difficult to identify individual patients with a high absolute risk of ICH. Whether the current prediction rule is valid and helps in decisions on antithrombotic treatment strategies needs to be determined in further decision-analytical studies in which this prediction rule is used to estimate risk of ICH and where this risk is weighed against the risk of a recurrent TIA or minor ischaemic stroke.

**ACKNOWLEDGEMENTS**

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**ELECTRONIC-DATABASE INFORMATION**

The supplementary information mentioned in the text is available at http://jnnp.com/supplemental.

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REFERENCES


