A prospective study of 166 cases using multivariate analysis

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Using death and functional status as end points, we prospectively analyzed the outcome 6 months after spontaneous intracerebral hemorrhage in 166 patients admitted to an acute-care stroke unit on the first day of their stroke. Seventy-one patients (43%) died, 69 (42%) had a satisfactory outcome, and 26 (16%) had a poor functional outcome. Early (30-day) survival was correlated with morphologic parameters on the initial computed tomogram (hemorrhage size, midline shift, and intraventricular spread of the hemorrhage), while later (6-month) survival was correlated with age. Using logistic regression, we found five independent predictors of satisfactory outcome at 6 months: age, hemorrhage size, intraventricular spread of the hemorrhage, limb paresis, and communication disorders. Of these, age was the most important predictor by far. (Stroke 1991;22:1-6)

After computed tomography (CT) was introduced, intracerebral hemorrhage (ICH) was diagnosed more frequently and with greater accuracy. To develop therapeutic strategies for patients with ICH, one needs to be able to predict their evolution, particularly during the very acute stage (≤24 hours after stroke onset). The aim of this work was to determine based on initial clinical and CT findings the prognostic factors in ICH patients.

On admission of a patient with severe ICH, the paramount concern is whether he will survive the episode. As a result of the more frequent diagnosis of small hematomas, the overall acute mortality of ICH has declined to approximately 30%. Studies have focused on early survival after ICH and on the identification of its prognostic factors. However, prognosis after the acute stage has seldom been evaluated. The first part of our study was designed to determine predictors of survival in ICH patients during both the acute and the later stages. In patients who survive the acute stage, the prediction of functional outcome is of great importance but remains difficult because of methodologic problems including sample selection bias, timing of the initial assessment, criteria for measuring outcome, and the role of confounding factors. The second part of our study was aimed at defining the factors that determine the probability of favorable functional outcome in patients who survive the acute stage of ICH.

Subjects and Methods

Data were collected on consecutive patients with supratentorial spontaneous ICH admitted to the acute-care stroke unit of the Pellegrin Hospital, which serves primarily the urban community of Bordeaux (population approximately 700,000). The inclusion criteria were 1) admission ≤24 hours after stroke onset; 2) CT demonstration of an ICH with or without intraventricular spread of the hemorrhage; and 3) absence of an external cause for the stroke such as head injury, anticoagulant therapy, or a definite intracranial source of hemorrhage that could necessitate surgery (i.e., aneurysm, arteriovenous malformation, or tumor). Over 3 years, 166 patients were included. Their initial assessment, by neurologic examination and CT, was performed ≤6 hours after admission. Each patient was then followed up for a minimum of 6 months.

Among the several baseline variables that were recorded, we selected the following as those most likely to be relevant to prognosis according to the literature: 1) age, 2) sex, 3) hemorrhage side (left or right), 4) hemorrhage location (putamen, thalamus, or lobe), 5) hemorrhage size (maximum percentage of the hemispheric surface area; see below), 6) midline shift displacement on CT scan of >5 mm,
7) intraventricular spread of the hemorrhage, 8) initial level of consciousness (normal, drowsy [lump ing obnubilation and stupor], or comatose), 9) limb paresis (upper, lower, or both limbs; complete paresis, useless movements, useful movements, or normal motion), 10) oral comprehension (absent, incomplete, or normal), and 11) oral expression (impossible, incomplete, or normal). Language function and limb paresis of comatose patients were assessed at the lowest grades (i.e., complete paresis, absent oral comprehension, and impossible oral expression). The size of the ICH on a CT scan was estimated by measuring the longest axis of the region of increased attenuation and its greatest width at 90° to this axis.9

The product of these two dimensions was then divided by the area of the total hemispheric surface and expressed as a percentage. The patients were divided into three classes by hemorrhage size: <10%, 10–30%, and >30% of the hemispheric surface area. Blood pressure at admission was not taken into account because it is often markedly elevated during the first 1–2 days after any severe stroke.

Patient outcome was studied prospectively with a clinical follow-up of at least 6 months. The Glasgow Outcome Scale as described for head injuries10 was used. This scale classifies patients into one of five mutually exclusive categories defined as 1) good recovery (capable of returning to the former level of function even with a minor deficit), 2) moderately disabled (independent but objectively or subjectively disabled), 3) severely disabled (dependent on others for the activities of daily living but capable of social interaction), 4) vegetative state (no social or relational interaction), and 5) dead.

Univariate analysis was first performed to correlate the patients' outcome and each potential prognostic factor using the χ² test. Then, logistic regression analysis was used to estimate the probability of a given outcome in an individual patient as a function of that patient’s prognostic factors. Outcome was expressed as: 1) alive at 30 days versus dead by 30 days, 2) alive at 6 months versus dead by 6 months, or 3) satisfactory outcome at 6 months (good recovery or moderately disabled) versus unsatisfactory outcome at 6 months (severely disabled, vegetative state, or dead). With adjustment techniques a new problem arises, that of “multicolinearity”: when two test variables are strongly colinear, i.e., vary together in a parallel fashion (in the same direction and with similar magnitudes), the effect on the response variable can be explained by either test variable, which results in a reduction of power when analyzing the contribution of each. Thus, when shifting from univariate to multivariate analysis (as in a multiple regression model), the apparent influence of such multicollinear test variables can be greatly reduced or even disappear. To prevent multicolinearity between some obviously related test variables, we used a tree-structured logistic (TSL) analysis.11 This analysis involves grouping related test variables into factors, which are then analyzed before the individual test variables. The advantage over more classical procedures (e.g., a step-down procedure) is that TSL analysis does not eliminate the independent contribution of each related test variable in a factor.

Finally, survival curves were constructed according to age groups using the life table method.

Results

Among the 166 patients, 113 (68%) were male and 53 (32%) were female (sex ratio 2.1). Age ranged between 34 and 82 (mean 61) years, 110 (66%) of the patients being 50–70 years old. The mortality rate at 6 months was 43% (71), with 51 deaths (31%) occurring during the first month following ICH.

Univariate analysis (Table 1) found age (p<0.001), hemorrhage size (p<0.001), midline shift (p<0.0001), intraventricular spread of the hemorrhage (p<0.0001), and initial level of consciousness (p<0.01) to be inversely correlated with 6-month survival. Limb paresis (p<0.003), oral comprehension (p<0.0001), and oral expression (p<0.001) were also highly significant predictors, but because their scoring was dependent on the initial level of consciousness and because they are also correlated with hemorrhage size, they were not included in the multivariate analysis to avoid multicolinearity.

According to the results of univariate analysis and the literature2-7,8 seven potential prognostic factors (age, hemorrhage size, initial level of consciousness, intraventricular spread of the hemorrhage, hemorrhage location, hemorrhage side, and midline shift) were selected for multivariate analysis by logistic regression. The results are presented in Table 2. With classical logistic regression, intraventricular spread of the hemorrhage (p=0.001) was the only independent predictor of 30-day mortality. However, there is a high likelihood of multicolinearity between hemorrhage size, initial level of consciousness, and midline shift (all of which are correlated, as shown for example by Volpin et al.12) Among our 49 patients with no midline shift and a normal initial level of consciousness, 43 (88%) had a hemorrhage size of <10%, while none of the 21 comatose patients with a midline shift had a hemorrhage that small. As a matter of fact, with classical logistic regression these three factors did not appear to be significantly related to 30-day survival. To avoid this limitation, we lumped hemorrhage size, midline shift, and initial level of consciousness into one factor for TSL analysis. This combined variable, called “mass effect,” was then a powerful predictor (χ²=16.2, p=0.001) of 30-day survival. The 6-month mortality was correlated with four baseline variables, particularly with age (p=0.0002) and hemorrhage size (p=0.04), intraventricular spread of the hemorrhage (p=0.045), and mass effect (p=0.04). Hemorrhage side and hemorrhage location were not significantly correlated with survival at either 30 days or 6 months.

At 6 months there were 95 survivors (57%). Among them, 41 (25% of all patients) had a good
recovery, 28 (17%) were moderately disabled, 25 (15%) were severely disabled, and one (1%) was in a vegetative state. For the prediction of satisfactory outcome at 6 months we selected nine potential prognostic factors: age, sex, hemorrhage side, hemorrhage location, hemorrhage size, intraventricular spread of the hemorrhage, limb paresis, oral comprehension, and oral expression (Table 3). A satisfactory outcome at 6 months was inversely correlated with age (p=0.00015) and less so with hemorrhage size (p=0.04), intraventricular spread of the hemorrhage (p=0.04), and limb paresis (p=0.02). Taking into account the probable multicollinearity between oral comprehension and oral expression, we used TSL analysis with a combined variable called "communication disorder," which was
Table 2. Predictors of Mortality at 30 Days and 6 Months After Intracerebral Hemorrhage in 166 Patients by Logistic Regression

<table>
<thead>
<tr>
<th>Variable</th>
<th>30-day OR (95% CI)</th>
<th>30-day p</th>
<th>6-month OR (95% CI)</th>
<th>6-month p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (10-year groups)</td>
<td>1.2 (0.8–2)</td>
<td>0.35</td>
<td>11.8 (3.1–41.1)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Hemorrhage location</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Putamen vs. lobe</td>
<td>0.9 (0.3–2.6)</td>
<td>0.8</td>
<td>4.1 (0.6–29.2)</td>
<td>0.16</td>
</tr>
<tr>
<td>Thalamus vs. lobe</td>
<td>0.6 (0.1–2.6)</td>
<td>0.51</td>
<td>0.7 (0.07–7.7)</td>
<td>0.81</td>
</tr>
<tr>
<td>Hemorrhage size (each class)</td>
<td>1.6 (0.9–2.9)</td>
<td>0.14</td>
<td>3 (1–8.7)</td>
<td>0.04</td>
</tr>
<tr>
<td>Midline shift (present vs. absent)</td>
<td>2.7 (0.9–8.4)</td>
<td>0.09</td>
<td>1.9 (0.3–12.1)</td>
<td>0.51</td>
</tr>
<tr>
<td>Intraventricular hemorrhage (present vs. absent)</td>
<td>5.3 (2–14.3)</td>
<td>0.001</td>
<td>5.9 (1–33.3)</td>
<td>0.045</td>
</tr>
<tr>
<td>Initial level of consciousness (each grade)</td>
<td>1.5 (0.8–2.9)</td>
<td>0.25</td>
<td>0.7 (0.2–2.2)</td>
<td>0.54</td>
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<tr>
<td>Combined variable “mass effect”</td>
<td>...</td>
<td>0.001</td>
<td>...</td>
<td>0.04</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval.

Table 3. Predictors of Satisfactory Outcome at 6 Months After Intracerebral Hemorrhage in 166 Patients by Logistic Regression

<table>
<thead>
<tr>
<th>Variable</th>
<th>30-day OR (95% CI)</th>
<th>30-day p</th>
<th>6-month OR (95% CI)</th>
<th>6-month p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (10-year groups)</td>
<td>2.6 (1.6–4.4)</td>
<td>0.00015</td>
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<td></td>
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<tr>
<td>Sex (male vs. female)</td>
<td>1.5 (0.6–4.1)</td>
<td>0.39</td>
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<tr>
<td>Hemorrhage side (left vs. right)</td>
<td>1.5 (0.5–4.1)</td>
<td>0.44</td>
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<tr>
<td>Hemorrhage location</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Putamen vs. lobe</td>
<td>1.3 (0.3–5.4)</td>
<td>0.68</td>
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<tr>
<td>Thalamus vs. lobe</td>
<td>0.7 (0.1–3.8)</td>
<td>0.65</td>
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<tr>
<td>Hemorrhage size (each class)</td>
<td>1.7 (1–2.9)</td>
<td>0.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraventricular hemorrhage (present vs. absent)</td>
<td>3.0 (1–8.4)</td>
<td>0.04</td>
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<td></td>
</tr>
<tr>
<td>Limb paresis (each grade)</td>
<td>2.0 (1.1–3.4)</td>
<td>0.02</td>
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<tr>
<td>Oral comprehension (each grade)</td>
<td>2.0 (0.8–5.6)</td>
<td>0.17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral expression (each grade)</td>
<td>1.1 (0.5–2.3)</td>
<td>0.86</td>
<td></td>
<td></td>
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<tr>
<td>Combined variable “communication disorder”</td>
<td>...</td>
<td>...</td>
<td></td>
<td>0.04</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval.

Discussion

One prerequisite in any prognostic study is the systematic inclusion of all patients with the disease under consideration because a predictive model is applicable only to the population from which it is derived. For ICH patients selection bias could be especially harmful if secondary admissions in a specialized ward were included, because this would mean the prior exclusion of all patients dying during primary management elsewhere. To minimize such bias, we included among our consecutive ICH patients admitted on the first day after the onset of stroke only those referred primarily to the acute-care stroke unit. Therefore, we can assume that only patients from our primary catchment area who died at home or during transfer to the hospital were excluded from the present sample.

Some studies used the degree of improvement in functional status as the outcome measure; others used functional status at discharge or at set times after stroke. Because predictors for each of these outcomes may differ, comparisons among studies are difficult. Since the length of hospital stay varies enormously both among hospitals and among patients in a given hospital, the measurement of functional status at discharge can result in faulty conclusions. To avoid these difficulties, we measured functional status 6 months after the stroke, regardless of where the patient was at that time (i.e., hospital, home, or rehabilitation center).

The 51 deaths (31% mortality) occurring during the first month following ICH in this series is comparable to that in other recent studies: Douglas and Haerer1 reported a mortality rate of 40% in 1982, Helweg-Larsen et al2 27% in 1984, Steiner et al3 26% in 1984, Dixon et al4 33% in 1985, and Tuhrim et al5 34% in 1988. These figures are strikingly similar if one considers the differences in time of assessment (at discharge from the hospital in most cases) and the inclusion of posterior fossa hemorrhage in some series.6 The remaining 12% of deaths occurring between 1 and 6 months after stroke, much greater than that of an age-matched normal population,7 is also compatible with that of other studies with longer follow-ups: Helweg-Larsen et al8 found a late mortality rate of 18% at a median follow-up of 4.5 years and Douglas and Haerer9 17% at an average follow-up of 2.5 years.

With multivariate analysis, the severity of hemorrhage as judged by the initial CT findings was highly correlated with the mortality rate. Survival at 1 month seems to depend mostly on the intraventricular spread of the hemorrhage. This factor was found to be a predictor of mortality in some recent studies;2,6,18–21 but was not taken into account in others.8 Intraventricular spread of the hemorrhage was found to be a bad prognostic sign only in patients with ganglionic-thalamic hematomas1 and a sign of worse...
prognosis in those with thalamic than putaminal hemorrhage, but these studies used univariate analysis, which does not eliminate the role of possible confounding factors. Therefore, the question of the true influence of the intraventricular component of cerebral hemorrhage was still unsettled, in that intraventricular spread may have been only an indicator of the extent of bleeding in general or it might have been an epiphenomenon of the more ominous thalamic hemorrhages. With adequate statistical methods, we demonstrated that intraventricular spread of the hemorrhage is a factor of mortality per se, while neither putaminal nor thalamic localization of the intraparenchymatous hemorrhage had any influence on mortality (Table 2).

Hemorrhage size, midline shift, and the initial level of consciousness are known to be important prognostic factors and were very powerful predictors of survival at 6 months in our univariate analysis (Table 1), but on first look at our multivariate analysis (Table 2) none was an independent predictor. A likely explanation is that midline shift and the initial level of consciousness are strongly multicolinear with hemorrhage size so that they no longer appear in a multivariate analysis. After lumping these three factors as the combined variable mass effect, that combined variable became a very significant predictor of mortality during the acute stage is directly related to hemorrhage size so that they no longer appear in a multivariate analysis. After lumping these three factors as the combined variable mass effect, that combined variable became a very significant predictor of 30-day survival (Table 2). By doing so, our results in fact agree with those of other studies on early ICH survival. The initial level of consciousness was always found to be a predictor of mortality. Other studies used the Glasgow Coma Scale to assess level of consciousness, but we found a similar correlation with a simple grading of the level of consciousness as normal, drowsy, or comatose. Hemorrhage size had value in predicting mortality in most recent studies, but direct comparisons with our and older studies are difficult because of different methods of measurement. Some authors used the maximum diameter in centimeters, whereas others used simple or computerized volume measurements, finding a lethal total volume of 50–100 ml and a lethal ventricular volume of 20 ml.

Late mortality was evaluated in fewer studies. Helweg-Larsen et al did not analyze late mortality according to risk factors, whereas for Douglas and Haerer late mortality increased with size of the hematoma and ventricular rupture. With multivariate analysis we found only three factors (age and, to a much lesser degree, hemorrhage size and ventricular spread of the hemorrhage) to predict 6-month survival. For that outcome measure, use of the combined variable mass effect no longer increased the power of the analysis (Table 2). A likely explanation is that, because the vast majority of comatose patients with midline shift die within 1 month, they are not available for later observations, whereas many patients without these features survive, whatever the size of their hematoma. With those restrictions in mind, it remains that the larger the hemorrhage (wherever the location), the poorer the prognosis. A hemorrhage representing 30% of the hemispheric surface area seems to be pivotal since no patient at or above this threshold survived 6 months (Table 1).

Therefore, predictors of early survival were not the same as those of late survival. The 30-day survival was correlated mainly with severity of the anatomic lesions on CT scan, while the 6-month survival was correlated mainly with the patient’s age (Figure 1). In short, the probability of mortality in ICH patients seems to be independent of age until 4 weeks after onset, but it greatly increases with age afterward. The 6-month survival rate was 72% for patients aged <60 years, 55% for those aged 60–69 years, and only 43% in those aged >69 years. One explanation is that mortality during the acute stage is directly related to hemorrhage severity but afterward is more related to general and decubitus complications, which increase with age.

Even though it was originally designed for head trauma, we chose the Glasgow Outcome Scale to measure functional outcome at 6 months because it is a simple, valid, and reliable instrument. This also allowed comparison with other studies. Our ICH patients had a high mortality rate, but survivors had a reasonably good functional outcome on average. In fact, among survivors at 6 months, 72% were fully independent in the activities of daily living. This observation of a satisfactory outcome of ICH at 6 months is in agreement with other studies. Helweg-Larsen et al found that only 17% of ICH survivors had debilitating sequelae, with no influence of the size of the hematoma but with a poorer prognosis in patients with ganglionic-thalamic hematomas. For Douglas and Haerer, 92% of the survivors were ambulatory at follow-up after an average of 2.5 years. Using the same classification of outcome as the present study, Dixon et al found a satisfactory outcome in 60% and Nath et al in 62% of their patients surviving an ICH.

Multivariate analysis showed that functional outcome is mostly related to the clinical and CT findings.
on the initial evaluation. The risk of unsatisfactory outcome increases with age, lesion size, intraventricular spread of the hemorrhage, limb paresis, and communication disorders (Table 3). The differences with previous studies could be due to their much smaller sample sizes and to differences in methodology. For example, there is some controversy as to the importance of age as a prognostic factor, all other factors being equal. However, because previous series were retrospective and used univariate analysis, they could not actually resolve this issue. Nevertheless, it was somewhat surprising that age was so much more powerful an adverse factor than lesion size or intraventricular spread of the hemorrhage and motor or communication deficits, respectively. Perhaps it would be worthwhile to do another study with the same factors considered at the time of discharge, when acute mortality has already occurred and functional prognosis has become the main concern. However, the correlations that we observed can be used to answer some management questions during the acute stage. First, CT findings by themselves can help predict which patients are at high risk of short-term mortality and may require intensive treatment. Second, in survivors of the acute stage, age is by far the most important determinant of both later deaths and functional recovery. This may mean that every effort should be made to salvage younger patients during the acute stage since their possibility of later recovery seems to be high regardless of other parameters. Because the intraventricular spread of the hemorrhage is a major independent predictor of both early and late mortality, it may be advisable to test formally the usefulness of early ventricular drainage in those circumstances. The fact that shunting did not improve short-term (at discharge) outcome in a small retrospective study on 47 patients of whom only nine were shunted at an unspecified date may be due in part to the lack of adjustment for the other variables in that study. Taking into account the other factors identified in the literature and in our study (in particular, age and the size of the parenchymal component of the hemorrhage) may help to optimize the design of a sound prospective trial on this important question.

Acknowledgments

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References

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