Differences in Outcome and Predictors Between Ischemic and Intracerebral Hemorrhage

The South London Stroke Register

Ajay Bhalla, MD; Yanzhong Wang, PhD; Anthony Rudd, FRCP; Charles D.A. Wolfe, MD, FFPHM

Background and Purpose—Few population-based studies describing functional outcome between ischemic stroke and intracerebral hemorrhage (ICH) in the short- and long-term are available. Knowledge of the natural history and factors associated with poor outcome is important in providing prognostic information and resource allocation.

Methods—Data were collected within the population-based South London Stroke Register between 1995 and 2011. Baseline data were collection of sociodemographic factors, case mix, risk factors before stroke, and acute stroke processes, with outcomes at 7 days, 3 months, 1 year, 5 years, and 10 years after stroke. Logistic regression was used to determine factors associated with poor outcome (dead and dependency: Barthel index <15).

Results—Age and incontinence were associated with poor outcome at 3 months, 1 year, 5 years, and 10 years in ICH, whereas age, incontinence, failed swallow, atrial fibrillation, and diabetes mellitus were associated with poor outcome in ischemic stroke. ICH was more likely to have poorer outcomes at 3 months (odds ratio, 2.2; 95% confidence interval [CI], 1.8–2.8) and 1 year (odds ratio, 2.1; 95% CI, 1.7–2.6) but not at 5 years (odds ratio, 1.1; 95% CI, 0.8–1.4) or 10 years (odd ratio, 0.8; 95% CI, 0.57–1.22); however, the improvement of functional outcome from day 7 to 3 months was significantly greater for ICH (regression coefficient: 1.8; 95% CI, 1.1–2.6; P<0.0001).

Conclusions—ICH has poorer outcomes up to 5 years after stroke. The improvement of functional outcome up to 3 months was significantly greater with ICH. Identification of factors associated with poor outcome may be used for clinical predictions. (Stroke. 2013;44:2174-2181.)

Key Words: infarction • intracerebral hemorrhage • patient outcome • recovery of function
black African, and 13% other ethnic groups. The detailed methods of notification of patients and data collection have been described previously. In brief, patients were identified using multiple sources of notification by specially trained study nurses and field-workers, and all data were collected prospectively. The diagnosis of stroke, using the World Health Organization clinical definition, was verified by a study clinician, and patients were examined within 48 hours of referral to South London Stroke Register where possible. Data collected were checked with the patients’ general practitioner and medical records. Patients with subarachnoid hemorrhage were excluded, as they have a different natural history and care needs to ICH.

**Sociodemography and Case Mix**

Data on sociodemographic characteristics collected at initial assessment include the following: age; sex; self-definition of ethnic origin (1991 Census question) stratified into white, black (Black Caribbean, black African, and black other), and other ethnic group; socioeconomic status (Registrar General’s occupational codes), grouped into manual and nonmanual occupation. Clinical details at the time of maximal impairment were obtained. These included information on motor deficit, swallowing (using the 3-oz water swallow test), speech, and urinary incontinence. The level of consciousness was assessed using the Glasgow Coma Scale (GCS) dichotomized into GCS <13 (impaired consciousness) and GCS ≥13. Activities of daily living before stroke were assessed using the Barthel index and were classified as 0 to 14 (moderate/severe disability) and 15 to 20 (mild disability/independent). Classification of pathological stroke subtype was categorized into ischemic stroke or hemorrhagic stroke (primary and secondary ICH) based on results from at least one of the following: brain imaging (computed tomographic scan or MRI) and postmortem studies.

**Prior Risk Factors**

Prior history of hypertension (general practice or hospital records of high blood pressure >140 mmHg systolic or >90 mmHg diastolic), diabetes mellitus (self-reported), atrial fibrillation (general practice or hospital records), previous transient ischemic attack (self-reported), alcohol drinking status (yes/no), smoking history (current, ex-smoker, never smoked), and previous ischemic heart disease was recorded.

**Effective Interventions After Stroke**

We examined a range of indicators of the processes of care after an acute stroke suggested to be useful proxy measures for the overall quality of stroke care. Patients were classified as (1) not admitted to hospital; (2) admitted to stroke unit; (3) admitted to general medical ward/intensive care; and (4) unknown. Whether patients who were admitted to a stroke unit spent 50% of their hospital admission there was also documented. The provision of a swallow assessment was also described. Data were also collected on the use of antihypertensive agents during the first 3 months of stroke for both subtypes, as well as the use of antplatelet and cholesterol-lowering agents in ischemic stroke during the same time period.

**Outcome Measures**

Outcome as measured by the Barthel index was categorized into good (Barthel index ≥15) and poor (death or dependency: Barthel index 0–14). These were assessed 7 days, 3 months, 1 year, 5 years, and 10 years after stroke.

**Statistical Methods**

Data were available from January 1, 1995, and we were able to obtain complete records up to December 31, 2011. We included all index cases (first-ever stroke excluding subarachnoid hemorrhage) up to December 31, 2010, and incorporated follow-up until December 31, 2011. Survival time was from date of stroke to date of death, confirmed by the Office for National Statistics. Patients with no record of death were censored on December 31, 2011.

Continuous variables are summarized as mean (SD) and categorical data as count (percentage). Student t test and Wilcoxon signed-rank test were used to test differences in continuous variables where appropriate, and the χ2 test was used for proportions. The prognostic value of sociodemographic/socioeconomic factors, case mix, effective intervention, and prior stroke risk factors for 3-month, 1-year, 5-year, and 10-year outcome was examined using multivariate logistic regression, separately for patients with ischemic stroke and ICH. Improvement in Barthel index ≤3 months was compared between patients with ischemic stroke and hemorrhagic stroke using the Wilcoxon signed-rank test, and it was further investigated by using multivariate linear regression adjusted for prognostic variables. Sensitivity analyses were performed to assess possible effects of missing data by comparing the observed and complete case analyses with missing data analyses using various imputation methods, where missing data for survivors were imputed at all time points using a best- and then worst-case scenario for binary outcomes. Loss to follow-up rates varied by time point (after accounting for deaths): 3 months (24%), 1 year (17.9%), 2 years (29.1%, but data not collected in 1998/1999), 3 years (18.9%), 4 years (16.8%), 5 years (18.5%), 6 years (15.4%), 7 years (14.2%), 8 years (12.3%), 9 years (12.6%), and 10 years (11.7%). All tests were 2-tailed, and P<0.05 was considered statistically significant. Odds ratios (OR) and regression coefficients with 95% confidence interval (CI) for prognostic factors were calculated in multivariate logistic and linear regression models.

All statistical analyses were performed with statistical software R, version 2.11.1.

**Results**

Overall, 3730 stroke patients were registered between January 1995 and December 2011, of which 3177 patients (85.2%) had ischemic stroke and 553 patients (14.8%) had ICH. Table 1 describes the sociodemographic characteristics and acute care process measures of the study population. The percentage of patients in both ICH and ischemic stroke declined throughout each 3-year cohort (P=0.003). Patients with ICH were more likely to be younger (P<0.001) and men (P=0.04) compared with ischemic stroke. There was a higher percentage of patients of white origin in ischemic stroke and higher percentage of black African in ICH (P<0.001). Manual workers were more frequently observed in ischemic stroke compared with ICH (P<0.001).

Patients with ischemic stroke were more likely to have previous ischemic heart disease (P=0.0004), atrial fibrillation (P<0.0001), previous transient ischemic attack (P<0.0001), diabetes mellitus (P<0.0001), and be current smokers (P<0.0001) than ICH. Patients with ICH had more severe clinical impairments for stroke (incontinence, GCS <13, failed swallow) compared with ischemic stroke (P<0.001), but were more likely to be less disabled before stroke (Barthel index <15; P=0.05). Patients with ischemic stroke were more likely to be managed in the community at stroke outset compared with ICH. However, for patients admitted to hospital, patients with ischemic stroke were more likely to be managed in a stroke unit and spend >50% of their length of stay there compared with ICH (P<0.0001). The swallow test (P<0.0001), as well as brain imaging (P=0.01), was more likely to be assessed in patients with ischemic stroke. MRI rates across each 3-year cohort were as follows: 1995–1998 (13%), 1999–2002 (11.7%), 2003–2006 (24%), and 2007–2010 (67%); P<0.0001.
Table 2 shows the factors associated with poor outcome at 1, 5, and 10 years for both ischemic stroke and ICH after adjusting for case mix. At 1 year, increasing age for both groups was significantly associated with poor outcome. Clinical impairments for stroke, such as urinary incontinence and being disabled at day 7, were significantly associated with poor outcomes in both groups. However, GCS <13, failed swallow, being women, and disabled before stroke were only significantly associated with poor outcome in ischemic stroke. Antihypertensive agents were significantly associated with a good outcome in ischemic stroke patients only. Patients from both groups who were managed in a stroke unit were less likely to have a poor outcome, but this did not reach statistical significance. However, nonadmission to hospital was associated with better outcome in ischemic stroke patients only. Patients with atrial fibrillation and diabetes mellitus were more likely to have poor outcomes in ischemic stroke than in ICH. When the model was run at 3-month outcome data (full data

<table>
<thead>
<tr>
<th>Risk factors before stroke</th>
<th>Ischemic (n=3177)</th>
<th>ICH (n=553)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>2001 (63%)</td>
<td>322 (58.2%)</td>
<td>0.2</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>352 (11.1%)</td>
<td>32 (5.8%)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>551 (17.3%)</td>
<td>54 (9.8%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Previous TIA</td>
<td>416 (13.1%)</td>
<td>40 (7.2%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>627 (19.7%)</td>
<td>67 (12.1%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Current smoker</td>
<td>998 (31.4%)</td>
<td>153 (27.7%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Consumes alcohol</td>
<td>1663 (52.3%)</td>
<td>273 (49.4%)</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

Summary statistics are mean (SD) or count (%) as appropriate. ICH indicates intracerebral hemorrhage; and TIA, transient ischemic attack.
The direction of ORs for associated factors was unchanged apart from black African patients with ICH (OR, 0.37; 95% CI, 0.09–0.97) who were statistically less likely to have poor outcomes compared with ischemic stroke (OR, 1.6; 95% CI, 0.68–2.45). When the model was run at 5-year outcome data, increasing age and a failed swallow were significantly associated with poor outcome in both groups, whereas being women and from a manual socioeconomic occupation were significantly associated with poor outcome with ICH only. Spending >50% time on stroke unit was significantly less likely to be associated with poor outcome in ischemic stroke, but diabetes mellitus, current smoking status, and having atrial fibrillation were associated with poor outcome in this group. When the model was run at 10-year outcome data,
increasing age and urinary incontinence were significantly associated with poor outcome in both groups, whereas having a GCS <13 and diabetes mellitus were significantly associated with poor outcome in ischemic stroke only.

Figure 1 shows the distribution of poor outcomes (death and dependency: Barthel index <15) and good outcomes (Barthel index ≥15) across all time points. Poor outcomes were evident at all time points for ICH ≤5 years after adjusting for case mix: 7 days (OR, 3.3; 95% CI, 2.6–4.2), 3 months (OR, 2.2; 95% CI, 1.8–2.8), 1 year (OR, 2.1; 95% CI, 1.7–2.6), 5 years (OR, 1.1; 95% CI: 0.8–1.4), and 10 years (OR, 0.8; 95% CI, 0.57–1.22). Figure 2 shows the proportion of patients with a good outcome who have survived across all time points between both groups. The mean improvement of Barthel index from 7 days up to 3 months was higher in ICH (5.81) compared with ischemic stroke (2.58; *P* <0.0001). Multivariate linear regression showed that the regression coefficient for the association between stroke subtype and improvement of Barthel index from 7 days to 3 months after stroke after adjusting for case mix was 1.8 (95% CI, 1.1–2.6; *P* <0.0001; Table 3). In sensitivity analyses, when best- and worst-case imputation methods were applied, although overall rates were altered, the trends over time closely followed those in the observed and complete case analyses.

**Discussion**

The main finding from this study is that improvement of functional outcome ≤3 months was significantly greater with ICH compared with ischemic stroke. Previous studies have described differences in functional outcomes between ICH and ischemic stroke with contrasting results. However, none of these studies have been population based. This is the first study to provide unbiased estimates of prognosis and long-term functional outcome in a large, well-defined population comparing first-in-a-lifetime ischemic stroke and ICH.

Although the underlying factors governing early recovery are complex and multifactorial, there are some hypothesized mechanisms that may explain the differences in faster recovery in patients with ICH. Hematoma formation and vasogenic edema may only displace tissue within the white matter, whereas neuronal cells undergoing ischemic injury after hypoperfusion will undergo direct cellular metabolic injury. As vasogenic edema and hematoma resolve after ICH, the tissue may restore its function and hence facilitate early subsequent recovery compared with ischemic stroke. In this study, a greater improvement of functional outcome in ICH was seen, despite lower rates of stroke unit admission, compared with ischemic stroke, despite the evidence of benefits for stroke unit care for patients with ICH. This finding may be driven by previous reports indicating that patient’s access to stroke rehabilitation facilities may be triaged on the basis of their functional or neurological status at days 5 to 7 after stroke. In this study, patients with ICH were more likely to have lower Barthel index scores at day 7 than ischemic stroke. In addition to this, both groups had similar lengths of stay, implying similar duration of inpatient rehabilitation time. Although stroke unit care in this study was more likely to be associated with good outcome at both 3 and 12 months in both groups, this was not statistically significant. However, stroke unit care was strongly associated with good outcome for ischemic stroke at 5 years. It is, therefore, possible that the increased improvement of functional status observed in ICH may have been, in part, as a result of spontaneous neurological processes, such as neuronal reorganization, restitution, and disinhibition, rather than the direct impact of evidence-based interventions.

Although there were differences in outcome ≤3 months after stroke, the proportion of good outcome from 3 months to 10 years remained relatively constant between both groups. Poor outcome, however, was significantly higher in ICH compared with ischemic stroke across all time points ≤5 years after adjusting for case mix but particularly in the first 7 days, and this was likely to be driven by hematoma expansion, vasogenic edema formation, and intraventricular hemorrhage, leading to raised intracranial hemorrhage. After 5 years,
there were no differences in poor outcome, and this may reflect a survival effect with ICH patients who survive beyond 5 years being fitter than patients with ischemic stroke.20 This is the first population study to describe differences in functional outcome in the longer term in both stroke subtypes beyond 1 year and thus highlights the need for ongoing assessment and rehabilitation services for many years after stroke, particularly with ICH. Previous studies1,2,14,21 have confirmed higher case fatality rates with ICH, mainly driven by stroke severity; however, a study by Andersen et al21 demonstrated higher case fatality rates in ICH compared with ischemic stroke only ≤3 months after stroke, independent of stroke severity, implying worse outcome was associated with the hemorrhagic nature of the lesion.

The risk factor and case mix profiles were different among both groups, with ICH being associated with younger age, higher rates of black Caribbean and African ethnicity, more severe clinical impairments for stroke, lower rates of ischemic heart disease, atrial fibrillation, diabetes mellitus, and smoking status. The proportion of ischemic stroke to ICH appeared greater in the later years compared with the earlier years, which may have been driven by the increased uptake of MRI scanning correctly classifying hemorrhagic infarction as infarction rather than ICH.

However, both groups shared similar prognostic factors associated with poor outcome at 3 and 12 months, which included increasing age, clinical impairments for stroke severity, and prestroke disability and poststroke disability at 7 days. Atrial fibrillation and diabetes mellitus were strong predictors of poor outcome in ischemic stroke only at all time points ≤10 years. This may influence recurrent stroke, but is also an opportunity to reduce the burden of recurrent stroke through secondary prevention. There were no significant differences in prior history of hypertension between both groups and, surprisingly, nor was this associated with poor outcome.22 This may have been driven by the possible explanation that those patients with severe stroke have the lowest blood pressures23; however, antihypertensive agent use seemed to have an associated protection against poor outcome ≤1 year in ischemic stroke patients only.

In this study, there was a significant advantage for black African patients in ICH achieving a good outcome at 3 months, but not at 12 months, compared with white patients. This has been described in previous analyses in the South London Stroke Register, suggesting a survival advantage over white patients not explained by age, risk factor profile, stroke severity, or access to stroke unit.24 Genetic, nutrition, and environment factors may play a role in explaining these differences, particularly

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**Table 3. Regression Coefficients for the Association Between Stroke Subtypes and Improvement of Barthel Index From 7 Days to 3 Months After Stroke (Multiply Adjusted)**

<table>
<thead>
<tr>
<th></th>
<th>Regression Coefficient (Multiply Adjusted)*</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 5 y)</td>
<td>−0.23</td>
<td>−0.32</td>
<td>−0.13</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female (vs male)</td>
<td>−0.66</td>
<td>−1.15</td>
<td>−0.17</td>
<td>0.008</td>
</tr>
<tr>
<td>ICH (vs ischemic stroke)</td>
<td>1.8</td>
<td>1.1</td>
<td>2.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>GCS &lt;13 (vs ≥13)</td>
<td>0.86</td>
<td>0.086</td>
<td>1.64</td>
<td>0.03</td>
</tr>
<tr>
<td>Incontinence of urine (vs normal)</td>
<td>2.95</td>
<td>2.37</td>
<td>3.53</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; GCS, Glasgow Coma Scale; and ICH, intracerebral hemorrhage.

*Adjusted for sociodemographic/socioeconomic factors, case mix (severe clinical impairments for stroke), effective interventions (stroke unit, nonadmission, swallow assessment, antiplatelet, antihypertensive, and cholesterol-lowering agents), and prior stroke risk factors.
in first-generation black migrants.\textsuperscript{25} Variation in different causes of ICH, such as hypertensive microaneurysm disease causing deep hemorrhage and amyloid angiopathy causing lobar hemorrhage between white and black populations, may also explain differences in outcomes observed.\textsuperscript{26}

Manual socioeconomic occupation was observed more frequently in ischemic stroke than in ICH, and those patients who were classified as being economically inactive were more likely to be associated with poor outcome at 1 year in both groups. These findings may be related to poorer access and engagement with rehabilitation services in this socioeconomic group.

There are strengths and limitations to this study. The data were derived from a multiethnic population–based register, including both hospitalized and nonadmitted stroke patients whose recovery patterns have not been previously compared. Data have been collected by applying standardized protocols using multiple notification sources ensuring near case ascertainment. This has the advantage of studying a large unbiased sample size (>3,500 patients) with ≥10 years of follow-up data, allowing adequate statistical power to determine differences in functional outcome in both subtypes.

We were unable to differentiate between the different types of hemorrhage (deep and lobar) or hematoma volume, which may play a part in explaining different outcomes because brain imaging was performed as part of the clinical routine rather than a rigorous study protocol. The loss to follow-up rates, once deaths are accounted for, in this study are <20% at each time point except at 3 months and 2 years. One might have expected the highest follow-up rate at 3 months; however, a proportion of patients are registered retrospectively for whom 3-month assessment is not possible. This loss to follow-up may introduce bias, yet estimates from analyses of the patients with complete data did not differ significantly from those presented here. Loss to follow-up may be an issue in certain sociodemographic groups, although we have not been able to identify such groups in this analysis. The healthier participants and those from higher socioeconomic groups may be more likely to participate in research follow-up. In addition, in other cohort and stroke register studies, loss to follow-up rates are not often presented.\textsuperscript{5} Regarding effective secondary prevention interventions, we were not able to analyze data on anticoagulation use because of missing variables, and we were not able to collect data routinely on carotid endarterectomy or neurosurgical procedures for ICH.

We were not able to measure the disability measures on a more frequent basis during the first 3 months, which may have provided more information on the pattern of recovery. As a result of the ceiling effects of the Barthel index, other areas of functioning may need to be assessed in the longer term to determine differences between both groups. Case mix adjustment may also not have been complete. Although we adjusted for GCS, urinary incontinence, and prior and post (7 days) Barthel index, there still could be some residual confounding factors, which might be further reduced by using more detailed measures of case mix. However, we have measured and adjusted for validated case mix variables which have been shown to be predictive for poor outcome in other population studies.\textsuperscript{2,8,27}

These findings have several implications. The initial premise that patients with ICH have poorer recovery compared with patients with ischemic stroke due to stroke severity has been challenged in this study. Having knowledge of recovery patterns of different subtypes can help allocate rehabilitation resources effectively to patients who may benefit. The reasons why more than half of the patients with ICH, for example, were not managed on stroke units need further exploration. The difference in poor long-term outcome for both subtypes lends support to developing longer-term management strategies that reduce significant outcome particularly in ICH. Second, the different trajectories in recovery lend support in generating hypotheses to identify pathophysiological processes that can be targets for treatments (such as reduction in vasogenic edema in ICH). Third, by identifying independent factors associated with poor outcome, these can be used as predictors for prognostic purposes.

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Disclosures

None.

References


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