Intracerebral hemorrhage at young age: long-term prognosis

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Background and purpose: Intracerebral hemorrhage (ICH) is a devastating disorder associated with dismal outcomes. The long-term mortality and functional outcome of ICH in young patients was studied – areas so far poorly investigated.

Methods: A follow-up study was performed on a cohort of patients. Clinical and imaging data on ICH patients aged 16–49 were retrospectively obtained and linked with a nationwide cause-of-death register. The modified Rankin Scale (mRS) was evaluated for 30-day survivors at a visit 9.7 (7.0–12.0) years after ICH onset. Independent factors associated with mortality and unfavorable functional outcome (mRS 2–5) were sought by multivariate analysis.

Results: Amongst the 268 1-month survivors, 1-year survival was 98.1% [95% confidence interval (CI) 96.2%–100%], 5-year survival 93.2% (89.3%–97.1%) and 10-year survival 88.8% (84.9%–92.7%). After adjustment for age and intraventricular hematoma extension, male sex [odds ratio (OR) 3.36, 95% CI 1.28–8.80] and diabetes (OR 2.64, 1.01–6.89) were associated with increased mortality. Unfavorable functional outcome emerged in 49%. After adjustment for confounders, age (OR 1.09 per 1 year, 95% CI 1.03–1.15), initial stroke severity (1.17 per one National Institutes of Health Stroke Scale score point, 1.08–1.27) and intraventricular hemorrhage (3.26, 1.11–9.55) were associated with unfavorable functional outcome.

Conclusions: Of every 10 survivors of acute phase ICH at a young age, one died within 10 years after onset, male sex and diabetes being associated with increased mortality. Half the survivors did not achieve a favorable functional outcome, which was predicted by increasing age, initial stroke severity and intraventricular hemorrhage.

Introduction

Of all strokes, non-traumatic intracerebral hemorrhage (ICH) comprises 10%–20%. Its underlying causes are numerous [1,2]. According to meta-analysis, the overall incidence of ICH is 25 cases per 100 000 annually [3], and its incidence is higher amongst the elderly, showing no decrease during recent decades. ICH has higher early mortality, with a greater proportion of the survivors left with functional impairment in comparison to those with ischemic stroke [1,4,5]. Treatment in the acute phase is largely supportive, with the aim of preventing and treating associated complications and limiting further brain injury [6]. With regard to long-term outcome, another meta-analysis reported a 5-year mortality of 71% in a general ICH patient population [7]. According to another study, survivors independent at 12 months amounted to only 22% [8].

Intracerebral hemorrhage in young adults can be particularly devastating, due to the loss of active years of life, resulting in significant human tragedy and socioeconomic consequences by long sick leaves, early retirement and long-term institutional care. Surprisingly few data exist on long-term mortality rates and long-term functional outcomes of young-onset ICH, however. The few studies including young adult ICH patients have provided mortality rates between 8%.
and 34% [9–11]. A more recent study including 91 ICH survivors aged 18–50 reported a 10-year mortality of 10.3% [12], and in that cohort poor functional outcome, defined as modified Rankin Scale (mRS) >2, was evident in 49% [13].

Our objective was to define long-term mortality and functional outcome in patients with young-onset ICH who survived the acute phase, as well as to discover any baseline factors predicting poor long-term outcomes. A better understanding on these issues is vital, since long-term functional outcome data have so far been provided only by one study, involving only 91 patients, and no baseline factors have been analyzed predicting long-term outcome [13].

Methods

Our study, a follow-up study of a cohort of patients, is based on the Helsinki ICH in the Young Study, approved by institutional authorities as a registry [2]. Informed consent for participation in the long-term outcome study came from the surviving patients. Our study was approved by the Ethics Committee of Helsinki University Central Hospital (HUCH).

Patient selection

Patients included had their non-traumatic first-ever ICH between the ages of 16 and 49 treated in HUCH between 1 January 2000 and 31 March 2010 [2]. After an initial determination of mortality from our national cause-of-death registry, surviving patients received an invitation to participate in the follow-up study, with those providing their written informed consent being included (Fig. 1).

Baseline data retrieval

Data on hospital admission, including age at onset, National Institutes of Health Stroke Scale (NIHSS) score on arrival, risk factors, hematoma volume, hematoma location, presence of intraventricular hemorrhage (IVH), hydrocephalus, herniation, multiple hemorrhages, and structural etiology of ICH, as well as whether surgical evacuation of hematoma was performed were recorded in detail in the Helsinki ICH in the Young Study Registry [2,14]. The etiology of ICH was considered non-structural in all but those with arteriovenous malformation or cavernous hemangioma.

Outcomes

The initial all-cause mortality data came from Statistics Finland as of 25 June 2013. The second data collection occurred on 16 June 2014, providing updated long-term mortality data. Surviving patients living within a 50-km radius of HUCH received an invitation to a clinical follow-up and underwent detailed neurological examination by a single investigator (R-JK). Those living more distant than 50 km were interviewed with a structured questionnaire. Employment status, Barthel Index (BI) score, residual symptoms, presence of post-ICH epilepsy, and recurrent strokes reported by the patients were verified by medical records. mRS was judged as well by a single investigator (R-JK) [15]. The definition of unfavorable functional outcome was mRS 2–5 at that follow-up.

Statistical analyses

Normality of continuous variables was tested, and categorical variables were compared with the chi-squared test. The Mann–Whitney U test served to compare continuous variables with a skewed distribution between two groups and the Kruskal–Wallis test between more than two groups. Life table function served to calculate cumulative survival rates, cumulative ICH recurrence rates and cumulative rates for late seizures after ICH. Univariate Cox regression analysis was used to create hazard ratios and their 95% confidence intervals (CIs). All known factors associated with mortality in the studies of ICH were included in the univariate analysis, including surgical treatment [9,16–23]. In addition to age and sex, factors tending to associate with mortality (P < 0.1) were entered in a multivariable Cox regression model to identify independent factors associated with mortality. For analysis of unfavorable outcome (mRS 2–5) at follow-up, the same baseline factors as in the survival analysis were first tested in a univariate analysis. Subsequently, a binary multivariate logistic regression model was constructed with a backward likelihood-ratio method to identify factors independently associated with unfavorable outcome. That analysis included age, gender and parameters tending to associate with unfavorable outcome (P < 0.1). A two-sided P value of <0.05 was considered significant. All analyses used SPSS 22 for Windows (IBM Inc., Armonk, NY, USA).

Results

Of the 336 patients initially included in the Helsinki ICH in the Young Study Registry, 55 (16.4%) had died in the first 30 days after ICH; 13 (3.9%) lived abroad and were lost to follow-up; 101 (30.1%) declined to participate and four (1.2%) withdrew their consent. The mortality analysis included all but those dying in the first 30 days or lost to follow-up, numbering 268
Analysis of long-term functional outcome included ICH recurrence, post-ICH epilepsy, return to work and residual symptoms of those 131 (39.0%) alive and willing to participate (Fig. 1). To define patients’ residual symptoms and current mRS, 77 (22.9%) patients underwent clinical examination and interview, whereas 54 (16.1%) were interviewed only by telephone and structured questionnaire. The median period of follow-up was 9.7 [interquartile range (IQR) 7.0–12.0] years after ICH. Those included, compared to those excluded, more often showed structural etiology, had larger hematoma volumes and had higher NIHSS scores on arrival (Table S1).

Survival
Amongst the 30-day survivors, 1-year survival was 98.1% (95% CI 96.2%–100%), 5-year survival 93.2%
(95% CI 89.3%–97.1%) and 10-year survival 88.8% (95% CI 84.9%–92.7%). Higher risk of death was independently associated with male sex and diabetes. Those with IVH tended to die slightly earlier than those with no IVH (Tables 1 and 2). Mortality amongst diabetic males with IVH was higher than for females without diabetes and IVH (50.0% vs. 11.4%, \( P = 0.018 \)).

### Functional outcome

As Fig. 2 shows, in the mRS distribution of the 131 patients, 67 (51.1%) achieved favorable functional outcome (mRS 0 or 1), whereas unfavorable functional outcome (mRS 3–5) occurred in 33 patients (25.2%). Median BI score was 100 (IQR 100–100, range 15–100) with an association with age group \((P = 0.004)\) but no association with gender \((P = 0.470)\) or with hematoma evacuation \((P = 0.751)\).

### Baseline factors associated with poor functional outcome

In the univariate analysis, increasing age, hypertension, intraventricular extension of hemorrhage, brain herniation, stroke severity measured by NIHSS score at hospital arrival, and non-structural underlying etiology of ICH were associated with unfavorable outcome (Table 3). In the multivariate logistic regression analysis including these same covariates and other parameters with a univariate trend, independent factors associated with poor outcome at follow-up were higher age, higher initial NIHSS score and intraventricular extension of hematoma (Table 4).

### Intracerebral hemorrhage recurrence

Recurrent ICH occurred 12 times in 10 patients (7.6%), at a median of 3.9 (2.6–4.8) years after the index ICH. Etiology of initial and recurrent ICH was hypertension in two, cavernoma in two, arteriovenous malformation in two, moyamoya disease in one, vasculitis in one and unknown in two patients. Ischaemic stroke struck four patients (3.1%) at a median of 2.7 (1.4–4.1) years after the index ICH. The cumulative rate of ICH recurrence was 1.9% (95% CI 0%–3.8%) during the first year and 11.2% (95% CI 7.3%–15.1%) at 10 years.

### Return to work

Of 131 patients, 119 (90.8%) were employed before the ICH and 63 (48.1%) were employed at follow-up. The rate of current employment was higher amongst younger patients: of 28 patients aged 16–29 years at ICH onset, 21 (75.0%); of 26 aged 30–39, 16 (61.5%);

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**Table 1** Univariable analysis of long-term mortality in young adults with intracerebral hemorrhage

<table>
<thead>
<tr>
<th>Factor</th>
<th>Cumulative mortality (%)</th>
<th>Hazard ratio (95% confidence interval)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>Present 23.1 Absent 8.8</td>
<td>3.9 (1.49–10.08)</td>
<td>0.005</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16–29 years</td>
<td>Present 6.0 Absent N.A.</td>
<td>1</td>
<td>N.A.</td>
</tr>
<tr>
<td>30–39 years</td>
<td>Present 14.5 Absent N.A.</td>
<td>1.81 (0.47–7.01)</td>
<td>0.390</td>
</tr>
<tr>
<td>40–49 years</td>
<td>Present 23.6 Absent N.A.</td>
<td>2.38 (0.71–7.95)</td>
<td>0.160</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>Present 20.9 Absent 16.0</td>
<td>1.27 (0.60–2.68)</td>
<td>0.532</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Present 44.7 Absent 14.8</td>
<td>3.33 (1.37–8.11)</td>
<td>0.008</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>Present 16.7 Absent 17.3</td>
<td>1.42 (0.19–10.42)</td>
<td>0.729</td>
</tr>
<tr>
<td>NIHSS score on arrival</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–6</td>
<td>Present 14.2 Absent N.A.</td>
<td>1</td>
<td>N.A.</td>
</tr>
<tr>
<td>7–14</td>
<td>Present 16.5 Absent N.A.</td>
<td>1.88 (0.78–4.54)</td>
<td>0.163</td>
</tr>
<tr>
<td>&gt;14</td>
<td>Present 23.4 Absent N.A.</td>
<td>1.99 (0.89–4.43)</td>
<td>0.094</td>
</tr>
<tr>
<td>Hematoma volume (ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–30</td>
<td>Present 16.4 Absent N.A.</td>
<td>1</td>
<td>N.A.</td>
</tr>
<tr>
<td>30–60</td>
<td>Present 21.0 Absent N.A.</td>
<td>1.55 (0.63–3.85)</td>
<td>0.343</td>
</tr>
<tr>
<td>&gt;60</td>
<td>Present 17.6 Absent N.A.</td>
<td>1.43 (0.54–3.80)</td>
<td>0.472</td>
</tr>
<tr>
<td>Intratentorial location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infratentor extension</td>
<td>Present 10.5 Absent 18.8</td>
<td>0.86 (0.30–2.46)</td>
<td>0.776</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>Present 20.3 Absent 16.1</td>
<td>2.11 (1.04–4.28)</td>
<td>0.039</td>
</tr>
<tr>
<td>Multiple</td>
<td>Present 14.7 Absent 17.8</td>
<td>1.33 (0.57–3.08)</td>
<td>0.510</td>
</tr>
<tr>
<td>Herniation</td>
<td>Present 20.9 Absent 17.1</td>
<td>1.40 (0.33–5.89)</td>
<td>0.643</td>
</tr>
<tr>
<td>Hematoma evacuation</td>
<td>Present 8.0 Absent 18.3</td>
<td>0.66 (0.16–2.78)</td>
<td>0.575</td>
</tr>
<tr>
<td>Non-structural etiology</td>
<td>Present 19.8 Absent 16.2</td>
<td>1.32 (0.66–2.66)</td>
<td>0.438</td>
</tr>
</tbody>
</table>

N.A., not applicable; NIHSS, National Institutes of Health Stroke Scale.

*Any one amongst coronary artery disease, atrial fibrillation or heart failure.

\( P < 0.05 \) in bold.

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**Table 2** Cox regression analysis of factors associated with increased long-term mortality in young adults with intracerebral hemorrhage

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds ratio (95% confidence interval)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>3.36 (1.28–8.80)</td>
<td>0.014</td>
</tr>
<tr>
<td>Age in years</td>
<td>1.04 (0.99–1.09)</td>
<td>0.147</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.64 (1.01–6.89)</td>
<td>0.047</td>
</tr>
<tr>
<td>NIHSS score on points</td>
<td>1.02 (0.99–1.06)</td>
<td>0.218</td>
</tr>
<tr>
<td>Intraventricular extension</td>
<td>1.89 (0.93–3.84)</td>
<td>0.081</td>
</tr>
<tr>
<td>Non-structural etiology</td>
<td>1.11 (0.37–3.27)</td>
<td>0.858</td>
</tr>
</tbody>
</table>

NIHSS, National Institutes of Health Stroke Scale.

\( P < 0.05 \) in bold.
of 77 patients aged 40–49, 25 (32.5%) \( (P < 0.001) \). No association emerged, however, between current employment and gender \( (P = 0.324) \) or hematoma evacuation \( (P = 0.879) \).
following ICH, and 13.7% (95% CI 7.8%–19.6%) during the following 10 years. Post-ICH epilepsy developed amongst 13 (36.1%) patients with lobar hematoma, six (11.8%) with deep hemispheric location, one (5.3%) with infratentorial and nine (45%) with mixed location ($P = 0.001$).

**Residual neurological symptoms at follow-up**

Some level of one-sided motor dysfunction symptoms was reported by 55 (42.0%) patients, and some kind of one-sided sensory dysfunction by 52 (39.7%). Difficulties in producing or understanding speech were reported by 27 (20.6%), spasticity by 36 (27.5%), visual field impairment by 21 (16.0%) and diplopia by 14 (10.7%).

**Discussion**

In this analysis of long-term prognosis of ICH in young adults, cumulative mortality 10 years after ICH onset was about 11%, and diabetes and male sex were independently associated with shorter survival. Half the survivors achieved a favorable outcome, but less than half were by then employed. Higher age, higher NIHSS score on arrival, and intraventricular extension of hemorrhage were prognostic factors for poor functional outcome. In contrast to expectations, hematoma volume and surgical evacuation of the hematoma were not independently associated with outcome.

Long-term survival of young ICH patients has been reported only once. The Dutch investigators reported a cumulative 5-year mortality of 6.1%, 10-year mortality of 10.3% and 20-year mortality of 13.7% amongst 91 patients surviving 1 month, findings in accordance with ours [12]. In comparison to young adults with ischaemic stroke, their reported 7.9% mortality at 5 years looks comparable to that of young ICH patients [24]. Young ICH patients have far lower early mortality rates than do elderly ones [2]. Furthermore, long-term survival also appears to be markedly better amongst young adults, since a recent meta-analysis reported, amongst unselected ICH patients, fewer than one-third surviving for the first 5 years [7]. One reason for this may be that the young have fewer risk factors and comorbidities affecting survival [2]. Younger patients more frequently have structural causes for their ICH and also more often undergo surgical hematoma evacuation, factors probably associated with higher odds in favor of early-onset survival [25]. Male gender and diabetes were identified as independent factors predicting survival. Both factors have also been identified as prognostic for poor outcome in ischaemic stroke [26,27], with diabetes specifically associated with increased mortality amongst ICH patients [28,29]. The cause may be that diabetes results in deleterious effects on the microvasculature, this resulting in hematoma expansion and impaired neuroregeneration [30].

Regarding functional outcome amongst the young long-term survivors, our results are in agreement with those of the Dutch study that reported approximately half the survivors achieving an mRS score of 0 or 1 [12]. Poor functional outcome in 57% (mRS 3–5) and an independence rate of 47% amongst the acute phase survivors were the figures for unselected ICH patients, implying that young patients recover better also with regard to functional outcome [22–25,31,32]. Several studies investigate the predictors of functional outcome in the general ICH population, but with no studies concerning this issue particularly for young patients [8,19,21–23,32]. With few differences, they have reported consistent prognostic factors for poor outcome: larger hematoma volume, intraventricular extension, infratentorial hematoma, more severe symptoms on arrival and greater age.

In young patients, the impact of these prognosticators seems not so straightforward. In our analysis, increasing age, initial symptom severity and intraventricular extension were associated with unfavorable outcome at long-term follow-up. Surgical treatment for spontaneous supratentorial hemorrhages has improved functional outcome in patients with subcortical or putaminal hematomas, but failed to improve survival rates [25,33]. Another study found that those surgically treated for cerebellar hemorrhage had less often a favorable outcome [34]. ICH has been reported to cause more severe functional impairment than does ischaemic stroke, but with recovery also being faster than for patients with a similar disability [5,35]. Those with ICH have reportedly recovered up to 10 weeks post-stroke, but those with ischaemic stroke only up to 26 weeks post-stroke [4].

Our results concerning return to work are in line with the only other results from a study investigating this aspect after young-onset ICH. They reported a 2- to 3-fold higher risk for unemployment than in the general population [36]. Only 48.1% of our patients were employed at follow-up, despite the fact that more than half had no or only mild residual symptoms. This indicates that returning to modern-day vocational activity after young-onset ICH is a major challenge, and that need for and room for development in rehabilitation schemes may be unmet.

The rate of recurrent ICH has been under-investigated. Several studies and one meta-analysis reported annual rates ranging from 1.3% to 7.4% [7,25,37–45]. Age
≥65 years, lobar hematoma and previous ischaemic stroke have all been associated with increased risk for recurrence [7,37–40,42,43,45]. These ICHs most probably resulted from hypertension or cerebral amyloid angiopathy. One study found IVH to predict recurrence of ICH [41]. Our results indicate also that the risk for recurrence is lower in a young than in a general ICH population. Reasons for this may include more frequent surgically treatable structural causes underlying young-onset ICH, absence of amyloid angiopathy, and lower frequency of advanced small-vessel pathology.

One study reported the spasticity prevalence in unselected ICH patients 12 months after stroke to be 36%, an only slightly larger proportion than in our patients [46]. Early seizures occurred approximately as often as in an unselected cohort of ICH patients. Late seizures, however, occurred more frequently amongst our young individuals (17%) than amongst unselected ICH patients (9%) [47]. The young more often receive neurosurgical treatment for ICH, which may predispose to epilepsy per se. Our results and others’ findings indicate that post-ICH epilepsy is associated with hematoma location [47].

Our study has limitations and strengths. The main limitation is that almost half the survivors failed to participate in the in-person follow-up, and so our results in such areas as functional outcome should be treated with caution. Furthermore, some of the residual symptoms may have gone unrecorded in patients not examined in person. The patients excluded represented a group with more severe baseline deficits and fewer structural ICH causes. Probably being too disabled was the major reason for declining. This may cause a shift towards those less disabled being included; the true proportion of young ICH patients with favorable outcome was thus probably overestimated. This makes ICH in the young an even more dismal disease than it has been possible to show. The main strength of our study is that, to the best of our knowledge, it is the largest to date to include long-term data on young ICH patients and it provides the longest follow-up time. In fact, the number of patients in our cohort is similar to that in other follow-up studies with general ICH patients [32,44,45]. Moreover, mortality data from Statistics Finland were 100% complete.

In conclusion, most young adults lived for at least 10 years following ICH onset, but only half of these survivors had no or minor residual symptoms; fewer than half were employed at follow-up. Our study identified a few baseline factors that may prove useful in modifying long-term outcomes. Large-scale studies are warranted to confirm these results in this understudied patient population. Failing to do these may produce disastrous consequences such as unnecessary mortality and morbidity.

Acknowledgements

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Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S2. Residence and functional outcome after intracerebral hemorrhage at a young age

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