Long-Term Excess Mortality After Aneurysmal Subarachnoid Hemorrhage
Patients With Multiple Aneurysms at Risk

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Background and Purpose—There is high case-fatality rate and loss of productive life-years related to aneurysmal subarachnoid hemorrhage (aSAH) but data on long-term survival of patients with aSAH are scarce. We aim to evaluate long-term excess mortality and related risk factors after an aSAH event.

Methods—Survivors (n=3078) of aSAH who had survived for ≥1 year were reviewed for this retrospective follow-up study, which was conducted in the Department of Neurosurgery in Helsinki between 1980 and 2007. Follow-up started 1 year after the aSAH and continued until death or the end of 2012 (48,918 patient-years). Mortality and relative survival ratios were derived using a matched general population.

Results—Survivors of aSAH after 20 years showed 17% excess mortality compared with the general population. Even young patients and patients with good recovery showed excess mortality. The highest excess mortality was among patients with multiple aneurysms, old age, poor preoperative clinical condition, conservative aneurysm treatment, and unfavorable clinical outcome at 1 year.

Conclusions—Even after initially favorable recovery from an aSAH, survivors experience excess mortality in the long run in comparison to a matched general population. Cardiovascular disease at younger age and cerebrovascular events were overrepresented as causes of death, which indicates the importance of treatment of vascular risk factors. Young patients and patients with multiple aneurysms who are recovering from an aSAH should be followed-up and treated most actively. (Stroke. 2015;46:1813-1818. DOI: 10.1161/STROKEAHA.115.009288.)

Key Words: cerebrovascular disorders • intracranial aneurysm • mortality • subarachnoid hemorrhage

Aneurysmal subarachnoid hemorrhage (aSAH), caused by a ruptured cerebral aneurysm, is a serious disease with a high mortality.1-7 Despite the known early, high case fatality rate of aSAH (27%-44%), there are only scarce data on what happens to patients with aSAH later on.7-11 Is their life expectancy similar to that of someone who has never had aSAH or are they more prone to develop other medical conditions leading to a higher morbidity and mortality?

There are only a few publications on the long-term survival of patients with aSAH. Most studies have shown at least some excess mortality among patients with aSAH when compared with a matched general population.7-12-17 Knowledge on prospects of long-term survival and recovery after aSAH is important not only for the patients and their families but also to those deciding on the use of health economy resources. More information is needed about the long-term mortality of patients with aSAH and the risk factors related to unsatisfactory survival. Some of the risk factors may be treatable and the prognosis may be improved. Previous studies have suggested that conservative treatment, older age, male sex, aneurysm location, severe hydrocephalus on admission, impaired clinical outcome at early stage, smoking, and hypertension are factors that may be related to the long-term outcome of patients with aSAH.12-14,16

The aim of this study was to examine long-term survival and mortality among patients with aSAH compared with matched general population. We attempted to identify possible risk factors for impaired survival and to evaluate the possibility of their preventive treatment in this study.

Patients and Methods

Patients
This was a single-center, retrospective follow-up study that was carried out in the Department of Neurosurgery at Helsinki University Central Hospital, Finland. This facility is the sole provider of neurosurgical services for the catchment population of 1.8 million people who live in Southern Finland. The Finnish healthcare system is...
Clinical Data and Follow-Up

The follow-up started 1 year after the initial aSAH event and continued until death or until the end of the year 2012. There was a theoretical minimum follow-up of at least 5 years for each patient. The diagnosis of SAH was based on computed tomography or lumbar puncture. A ruptured aneurysm was identified by using digital subtraction angiography, computed tomographic angiography or magnetic resonance angiography. The time of death or vital status at the end of the year 2012 was obtained from the Population Register Center, which contains the information on all residents in Finland. Death certificates of the deceased patients were collected from Statistics Finland.

The initial clinical condition of patients on admission was evaluated using Hunt and Hess (HH) grading scale. Patients were grouped into active or conservative treatment groups for data analyses. Treatment was considered conservative when the patient did not receive any kind of neurosurgical or endovascular intervention aimed at the occlusion of the ruptured aneurysm at any point during the whole follow-up period. The postoperative radiological results were checked routinely by digital subtraction angiography or computed tomographic angiography. Clinical condition at 3 and 12 months after the aSAH event was evaluated using the Glasgow outcome score (GOS). After favorable initial outcome at 3 months, another evaluation at 12 months was not routinely organized. The information on clinical condition was carried forward from the clinical control closest to the 1-year mark for those patients for whom the 1-year clinical follow-up data were missing. The total follow-up time was 48,918 patient-years with a median follow-up of 15 years per patient (range, 1–33 years).

Statistical Methods

Excess mortality describes the excess hazard of death that a patient has compared with the hazard of death of people with similar demographic characteristics in the same population. To measure excess mortality in this study, a relative survival ratio (RSR) was calculated by dividing the observed survival of treated patients with aSAH by the expected survival. The expected survival was derived by using the Ederer II method for the mortality rates of the Finnish population. The RSRs were calculated using Greenwood’s method for the mortality rates of the Finnish population. The RSRs were constructed on the log cumulative hazard scale, and the variance of the observed survival proportion was estimated using Greenwood’s method. Statistical analyses were carried out using the R environment for statistical computing and graphics.

Results

Causes of Death and Recurrent SAH

A total of 971 patients (32%) of the 3078 patients died during follow-up. Table 2 shows the causes of death in relation to follow-up periods. There were a total of 162 deaths caused by aSAH during the whole time period. The majority of those (n=113, 70%) were related to the initial aSAH. Rebleeding was the cause of death in 24 patients (2%), and 25 patients (3%) died because of rupture of another aneurysm. The incidence of lethal recurrent aSAH was 100/100,000 person-years. This is 3× the incidence of aSAH in general Finnish adult population (29/100,000).

Among the study group, the mean age at the time of death was 67 years (median, 68 years; range, 23–90 years). The most common causes of death were cardiovascular disease for 249 (26%) and cancer for 215 patients (22%). Patients <65 years also had cardiovascular disease as the leading cause of death in 142 (29%) patients. Aneurysmal subarachnoid hemorrhage was the cause of death for 51 patients (10%). Table 1 shows the characteristics of the 3078 aSAH follow-up patients. The mean age at the onset of aSAH was 49 years (range, 1–88 years).

Table 1. Characteristics of 3078 aSAH Follow-Up Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>1700 (55%)</td>
</tr>
<tr>
<td>Men</td>
<td>1378 (45%)</td>
</tr>
<tr>
<td>No. of aneurysms</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2176 (71%)</td>
</tr>
<tr>
<td>2</td>
<td>589 (19%)</td>
</tr>
<tr>
<td>3</td>
<td>211 (7%)</td>
</tr>
<tr>
<td>4</td>
<td>68 (2%)</td>
</tr>
<tr>
<td>&gt;4</td>
<td>34 (1%)</td>
</tr>
<tr>
<td>Location of ruptured aneurysm</td>
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</tr>
<tr>
<td>ICA</td>
<td>593 (19%)</td>
</tr>
<tr>
<td>MCA</td>
<td>1047 (34%)</td>
</tr>
<tr>
<td>AcomA and A1</td>
<td>1092 (36%)</td>
</tr>
<tr>
<td>DACA</td>
<td>138 (5%)</td>
</tr>
<tr>
<td>Posterior circulation</td>
<td>206 (7%)</td>
</tr>
<tr>
<td>Active treatment</td>
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<tr>
<td>Yes</td>
<td>3033 (99%)</td>
</tr>
<tr>
<td>No</td>
<td>45 (1%)</td>
</tr>
<tr>
<td>Preoperative HH</td>
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</tr>
<tr>
<td>1</td>
<td>736 (24%)</td>
</tr>
<tr>
<td>2</td>
<td>1069 (35%)</td>
</tr>
<tr>
<td>3</td>
<td>691 (22%)</td>
</tr>
<tr>
<td>4</td>
<td>483 (16%)</td>
</tr>
<tr>
<td>5</td>
<td>98 (3%)</td>
</tr>
<tr>
<td>GOS at 1 yr</td>
<td></td>
</tr>
<tr>
<td>5 Good recovery</td>
<td>1449 (37%)</td>
</tr>
<tr>
<td>4 Moderate disability</td>
<td>863 (22%)</td>
</tr>
<tr>
<td>3 Severe disability</td>
<td>479 (12%)</td>
</tr>
<tr>
<td>2 Persistent vegetative state</td>
<td>22 (1%)</td>
</tr>
<tr>
<td>1 Death*</td>
<td>871 (22%)</td>
</tr>
<tr>
<td>Vital status at the end of follow-up</td>
<td></td>
</tr>
<tr>
<td>Alive</td>
<td>2107 (68%)</td>
</tr>
<tr>
<td>Dead</td>
<td>971 (32%)</td>
</tr>
</tbody>
</table>

AcomA and A1 indicates anterior communicating artery and A1; aSAH, aneurysmal subarachnoid hemorrhage; DACA, distal anterior cerebral artery; GOS, Glasgow outcome score; HH, Hunt and Hess; ICA, internal carotid artery; and MCA, middle cerebral artery.

*Patients who died during the first year after aSAH.
death in 210 cases (24%). Deaths caused by cerebrovascular disease, other than SAH, were also common in our study group (n=26; 16% for ≥65 years and n=95; 12% <65 years).

Excess in Long-Term Mortality

There was constant excess mortality throughout the whole study period in the study population compared with the matched general population. Cumulative RSR was 0.83 (95% confidence interval [CI], 0.80–0.85) at 20 years and 0.68 (95% CI, 0.63–0.73) at 30 years. This indicates an excess mortality of 17% and 32% at 20 and 30 years, respectively. Graphical representation of the cumulative RSRs for the whole study population is presented in Figure 1.

Risk Factors for Long-Term Excess Mortality

Age

Patients who were >60 years of age (n=583) had markedly higher excess mortality (20-year cumulative RSR, 0.72; 95% CI, 0.61–0.83) than patients aged ≤44 years (n=1207; 20-year cumulative RSR, 0.89; 95% CI, 0.86–0.91) (Figure 2A). However, younger patients (age ≤44 years) also had significant long-term excess mortality compared with their matched counterparts in the general population (30-year cumulative RSR 0.79; 95% CI, 0.74–0.84). The most frequent causes of death in young patients were aSAH (n=46), cardiovascular disease (n=52), cancer (n=47), and other cerebrovascular disease (n=18) accounting for 19%, 22%, 20%, and 8% of all causes of death in this age group, respectively. Proportion of lethal SAH from another aneurysm (n=14; 6% of all causes of death) was greater among young patients than others.

Multiple Aneurysms

Patients with a single aneurysm at the beginning of the follow-up had a better survival (n=2176; 30-year cumulative RSR, 0.74; 95% CI, 0.68–0.79) than patients with multiple aneurysms (n=902; 30-year cumulative RSR, 0.54; 95% CI, 0.44–0.63). New and lethal SAH from another aneurysm were more common among patients who had multiple aneurysms at the start of follow-up, than for single aneurysm patients who subsequently developed de novo aneurysms (n=14; 20% versus n=11; 12% of patients with SAH-related cause of death). Incidences of other vascular causes of death in these 2 groups were practically the same: cardiovascular disease 24% (multiple) versus 26% (single), and other cerebrovascular causes 12% versus 12%. Cumulative RSRs are shown in Figure 2B.

Preoperative Clinical Condition

Those with severe neurological impairments before treatment had significantly higher excess long-term mortality than those with mild symptoms only. Poor grade patients (HH, 4–5) showed excess mortality from the beginning of the follow-up, which continued. Patients with better preoperative condition (HH, 1–3) started to show significant excess mortality later in the follow-up, even those patients with HH grade 1 had a clear excess mortality. The cumulative RSR at 30 years of follow-up for HH 1: 0.80 (95% CI, 0.72–0.87), for HH 2: 0.73 (95% CI, 0.64–0.81), for HH 3: 0.55 (95% CI, 0.44–0.67), and for HH 4: 0.43 (95% CI, 0.25–0.64). Cumulative RSRs for different HH groups are shown in Figure 2C.

Conservative Treatment

Conservative treatment resulted in poor long-term survival, cumulative RSR at 20 years was 0.39 (95% CI, 0.22–0.58). The 20-year cumulative RSR for actively treated patients was 0.83 (95% CI, 0.81–0.86).

Conservatively treated patients were in worse clinical condition on admission to the hospital (HH 4–5: 44%; HH 3: 31%) than the actively treated patients (HH 4–5: 19%; HH 3: 22%). The proportion of lethal rebleedings was higher in the conservatively treated group than in actively treated group (n=5; 11% of conservatively treated versus n=19; <1% of actively treated patients).

Aneurysm Location and Sex

Aneurysm location did not affect the long-term survival. A greater portion of patients with SAH who had ruptured posterior circulation aneurysm died during the first year after aSAH.
compared with those with ruptured anterior circulation aneurysm (38% versus 26%). However, there were no significant differences between the different aneurysm locations at later time points during the follow-up.

The sex of patients did not affect the long-term excess mortality; at 20 years, the excess mortality was 17% for men and 18% for women, and at 30 years, it was 32% for both.

**Outcome at 1 Year**

As expected, patients who had serious disabilities at 1 year after the aSAH event also had greater long-term excess mortality compared with patients with good recovery (Figure 2D). Interestingly, even patients with good recovery (GOS 5) at 1 year had notable long-term excess mortality compared with their matched counterparts in the general population (30-year cumulative RSR, 0.80; 95% CI, 0.73–0.86). This difference did not start to show until after 8 years of follow-up. The most common causes of death in this group were cardiovascular disease (30%) and cancer (27%). The proportion of SAH-related deaths in this group was the lowest (9% GOS 5 versus 12% GOS 4 and 22% GOS 3).

**Discussion**

**Long-Term Excess Mortality**

Our follow-up study of 3078 patients with aSAH showed there was constant excess mortality throughout the whole study period. The patients with aSAH experienced 17% excess mortality at 20 years and 32% excess mortality at 30 years compared with their matched counterparts. Even young patients and patients with good recovery showed excess mortality in the long run. This is in line with another population-based study of 1746 patients with aSAH based in Eastern Finland, which showed excess mortality of 12% at 15 years (median follow-up, 12 years; cumulative RSR, 0.88; 95% CI, 0.85–0.91).14

The general belief earlier had been that aSAH should have no further effect on survival in patients after successful initial recovery. There are only few studies that address patients’ outcome later than 5 years after the initial aSAH. Most of these long-term follow-up studies showed, that despite surviving the initial aSAH, many of the patients die earlier than their peers. Some of the results partly contradict each other, especially when it comes to survival of young patients and the patients with good initial recovery.7,12–17,25

**Risk Factors for Excess Mortality**

Risk factors for long-term excess mortality turned out to be (1) multiple aneurysms, (2) age (especially >60 years), (3) poor preoperative clinical condition, (4) conservative treatment, and (5) unfavorable clinical outcome at 1 year. Factors (2)–(5) have also been identified in previous studies.15–14,16 A completely new finding in this study was the unfavorable effect of multiple aneurysms. Patients presenting with multiple aneurysms had higher excess mortality. These patients should be followed-up more actively than patients with only a single aneurysm. Whether preventive treatment of all the additional aneurysms would decrease the excess mortality of patients with multiple aneurysms remains to be evaluated in future studies.

One previous study suggested that male sex and aneurysm location at the basilar tip were related to long-term excess mortality of patients with aSAH.14 Our results did not support these findings.

**Causes of Death**

Cardiovascular disease (26%) and cancer (22%) were the most common causes of death during the long-term follow-up of patients with aSAH. Among general Finnish population, the rates are 30% and 23%, respectively.26 Interestingly, even patients <65 years had cardiovascular disease as their leading cause of death (26%). This finding differed from general Finnish population of <65 year olds (cardiovascular disease death, 19%).26 The patients with aSAH may have increased mortality because of cardiovascular disease, especially at younger ages. The recent study on 1765 patients with aSAH made similar conclusions in stating that increased risk of vascular disease and death are pronounced in younger patients.15 A previous Finnish study on 1537 patients with aSAH suggested that aSAH can be a manifestation of general vascular disease.12 This is indeed 1 possible explanation, but the risk of cardiovascular disease may also be because of the impact of SAH on the cardiovascular system or because of shared risk factors, such as elevated blood pressure and smoking. Overall, treatment of cardiovascular risk factors is important and should be emphasized in patients <65 years of age.

Cerebrovascular deaths other than aSAH were also over-represented among our study patients (16% for ≥65 years; 12% for <65 years) when compared with the general Finnish population (10% for ≥65 years; 4% <65 years).26 Sequelae of the initial aSAH accounted for about one fifth of all deaths in the first 10-year period but were less prominent later on. A similar finding was reported by a previous study on 233 1-year aSAH survivors.16 It showed excess mortality among patients with aSAH caused by deadly cerebrovascular events (SAH and others) in comparison to the general population (28% versus 8% of all deaths). A Dutch study has also shown
an elevated incidence of cerebrovascular and cardiovascular events in patients with aSAH and suggested treatment of vascular risk factors.\textsuperscript{13}

Recurrent SAH

Long-term risk of lethal rebleeding from a previously treated aneurysm was greatest during the first 5-year period of follow-up and decreased thereafter. However, the risk of a new lethal SAH from another aneurysm did not follow the same trend. It remained elevated, higher among patients with multiple aneurysms, as well as among young patients. We recommend an active approach in implementing preventive treatment of additional unruptured aneurysms, especially among the younger patients with aSAH.

The total incidence of a lethal, recurrent aSAH was $\approx 3\times$ that of the incidence of aSAH in the general population (100/100000 person-years versus 29/100000).\textsuperscript{24} The similar trend of increased incidence of recurrent aSAH was shown earlier in the International Subarachnoid Aneurysm Trial (ISAT) study (144/100000 person-years).\textsuperscript{17} The majority of our patients were treated by microsurgical clipping and only lethal recurrent cases were included in this study, which could be the reasons for lower rate of SAH recurrences than in the ISAT study.

Figure 2. Cumulative relative survival ratios (RSRs) as a function of follow-up time for (A) 3 age groups: $\leq 44$ years (blue), 45 to 59 years (green), and $\geq 60$ years (purple), (B) patients with multiple (green) and single (blue) aneurysm, (C) preoperative clinical condition of patients (Hunt and Hess [HH] grade), and (D) clinical outcome of patients at one year after subarachnoid hemorrhage (SAH): Glasgow outcome score (GOS): GOS 5 Good Recovery (yellow), GOS 4 moderate disability (purple), GOS 3 severe disability (green), and GOS 2 persistent vegetative state (blue).

GOS1 (n=871) died during the first year
Statistical Methods
Long-term excess mortality after aSAH has been detected in most of the latest studies, even though the respective statistical methods used were different.8,12-17 In our study, we used the RSR, that summarizes the excess hazard of death that an aSAH survivor experiences within a given follow-up period when compared with the hazard of death of a matched person in the general population. This method should fade the special features of the population it’s based on and describe only the effect of the aSAH. The RSR does not make assumptions about causes of death and can be used in evaluating excess mortality for different illnesses, irrespective of whether the excess mortality is directly or indirectly attributable to the illness. RSR should not be confused with standardized mortality ratio, which is the ratio of observed and expected deaths. The standardized mortality ratio has often been used in the earlier studies.7,12,13,17

The standardized mortality ratio is a measure of relative mortality, whereas the cumulative RSR summarizes the excess mortality within a given time period, which makes cumulative RSR a measure of relative mortality instead of the aSAH in this case, would thereafter have the same excess hazard as the patients remaining alive for a longer follow-up time. We made calculations with both the above-mentioned methods and they resulted in virtually the same results, that is, the 20-year estimates differed by only 1%.

Conclusions
Despite initial good recovery, patients with aSAH are burdened by excess mortality during long-term follow-up when compared with a matched general population. Cardiovascular disease at a younger age and cerebrovascular events are overrepresented as causes of death, which indicate the importance of treatment of cardiovascular and cerebrovascular risk factors in these patients. Young patients and patients with multiple aneurysms who are recovering from aSAH should be followed-up and treated most actively.

Disclosures
None.

References
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