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Pertti Saloheimo, Tuuli-Maaria Lapp, Seppo Juvela and Matti Hillbom

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The Impact of Functional Status at Three Months on Long-Term Survival After Spontaneous Intracerebral Hemorrhage

Pertti Saloheimo, MD, PhD; Tuuli-Maaria Lapp, MD; Seppo Juvela, MD, PhD; Matti Hillbom, MD, PhD

Background and Purpose—Few studies have assessed long-term prognosis and risk factors for death after spontaneous intracerebral hemorrhage (ICH). Patients who survive the acute phase may run different prognoses, depending on their disability, treatment, and lifestyle. The present study was performed to find out the predictors for long-term mortality after ICH.

Methods—We assessed 7-year prognosis in a population-based cohort of patients who had survived the first 3 months after ICH (n=140). Controls (n=206) living in the same geographical area were randomly drawn from the population register and followed up for the same time.

Results—Seven-year mortality was significantly higher in ICH patients than in controls (32.9 and 19.4%, respectively; $P=0.0034$). The annual risk for death in ICH patients was 5.6%, and the annual risk for fatal recurrent ICH was 1.3%. The ICH patients with good recovery at 3 months showed similar risk for death as controls. Recurrent ICH and pneumonia were the most common causes of death in ICH patients. Cigarette smoking, age, and diabetes seemed to increase the risk for death in patients and controls.

Conclusions—Survivors of ICH run a higher long-term risk for death than age- and sex-matched controls. However, those who show good recovery at 3 months run a similar outcome as controls. **(*Stroke*. 2006;37:487-491.)**

Key Words: cerebral hemorrhage ■ cigarette smoking ■ diabetes mellitus ■ mortality

Long-term survival after spontaneous intracerebral hemorrhage (ICH) has been reported to be ≈20% to 40% at 2 years after the index stroke.[1–3] The predictors for long-term (>6 months) survival after ICH include the initial level of consciousness, the severity of the handicap caused by the stroke in the early phase, the patient's age, and hematoma volume and location.[4–9]

We followed a cohort of ICH patients for 7 years after the index stroke to assess long-term mortality after ICH and to determine the predictors for death during this extended follow-up. We compared the survival of the patients with the survival of control subjects randomly drawn from the population register of Finland and living in the same geographical area, who were followed up for the same period.

Subjects and Methods

The present study series was drawn from a population-based cohort including all incident cases of spontaneous ICH in the catchment area of Oulu University Hospital between January 1993 and September 1995 (n=208). Oulu University Hospital is the only hospital serving acute stroke patients in Northern Ostrobothnia, Finland (population 356 026). We excluded the patients not living in the catchment area of the hospital and those who had a brain tumor, aneurysm, vascular malformation, hematological malignancy, coagulation disorder, or head trauma. ICH was verified by head computed tomography (CT) scanning or at autopsy in all cases, and secondary structural abnormalities were searched for by repeated brain imaging (CT or MRI) 3 months after the bleed. Angiography was performed if location of ICH suggested occurrence of an aneurysm.

Included were the 140 patients who survived for the first 3 months after ICH. They all were admitted into Oulu University Hospital and followed up for 7 years or until death. Controls were 206 subjects randomly drawn from the population register of the catchment area of Oulu University Hospital who were matched for age (±3 years) and sex for the originally 98 ICH patients admitted into the Department of Neurology. Ten controls refused, and other randomly drawn subjects were interviewed instead. Informed consent was obtained from the patients/proxies and control subjects, and the study protocol was approved by the ethics committee of the hospital.

Ninety of the patients were treated at the Department of Neurology, whereas the others were treated at the Department of Neurosurgery or at the Department of Internal Medicine. Data of the patients' previous diseases, blood pressure histories, medications, and lifestyle factors were gathered by interviewing the patients or their proxies during the inpatient period according to a structured protocol for those who were treated at the Department of Neurology. Data were extracted according to the same protocol from the hospital records of the other patients. Medical complications such as myocardial infarction, heart failure, cardiac arrhythmias, infection, deep vein thrombosis, and pulmonary embolism during hospitalization were recorded, as were neurosurgical interventions (evacuation of the hematoma was performed on 18 patients and ventriculostomy on 3 patients). The time of ICH onset was defined to be the acute onset

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From the Department of Neurology (P.S., T.-M.L., M.H.), Oulu University Hospital, Finland; and Department of Neurosurgery (S.J.), Helsinki University Central Hospital, Finland.

Correspondence to Pertti Saloheimo, MD, PhD, Aurorankuja 4 E 20, 02940 Espoo, Finland. E-mail pertti.saloheimo@fimnet.fi

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of headache or neurological deficit. The control subjects were interviewed via telephone during the recruitment period by the same person (P.S.) using the same structured questionnaire. In addition, informed consent was obtained from the controls for reviewing their previous hospital records to check for diseases, medication, and blood pressure histories. Records were available for 166 (81%) of the controls.

Subjects were considered to be hypertensive if their blood pressure readings preceding the index stroke had at least twice exceeded 160/95 mm Hg, or if they were taking antihypertensive medication. The patients were recorded as having diabetes mellitus if they used oral hypoglycemic agents or insulin. Previous hemorrhagic strokes (ICH and subarachnoid hemorrhage) as well as ischemic strokes were recorded. Cardiac disease included myocardial infarction, coronary artery disease, heart failure, and atrial fibrillation. Gastrointestinal bleeding and hematuria in the patients' history were recorded as bleeding disorders. Heavy drinking of alcohol was determined as described previously.[10] However, for the 50 patients treated at other departments of our hospital, the data on drinking habits were gathered from hospital records. The subjects were categorized as current cigarette smokers and nonsmokers. The patients' functional outcome at 3 months was assessed according to the Glasgow Outcome Scale (GOS)[11] on scheduled follow-up visits to the hospital ≈3 months after the ICH. Survival of the patients and controls during the 7-year follow-up was checked from the Causes of Death Register (Statistics Finland). The immediate cause of death (eg, pneumonia, not ICH) was always used in the analyses.

Categorical variables were compared by Fisher exact 2-tailed test and Pearson χ^2 test. Continuous variables were compared between the groups by the Mann–Whitney *U* test, Student *t* test, and ANOVA. For life-table analysis and the Cox proportional hazards regression model, each patient and control subject was followed to death or until 7 years. Cumulative survival rates were estimated by the Kaplan–Meier product-limit method, and the curves of the different groups were compared by the log-rank test. The Cox proportional-hazards model with a forward stepwise-regression procedure served to determine the significance of several variables in predicting relative risks and 95% CIs for death. These variables, known at the beginning of follow-up, were as follows: age; sex; history of hypertension, ischemic or hemorrhagic stroke, cardiac disease, diabetes, and cancer; GOS score at 3 months after ICH; warfarin treatment; regular aspirin use; bleeding disorders; current smoking; and heavy alcohol drinking. The assumption of proportionality was checked. The test for significance was based on changes in the log (partial) likelihood. A 2-tailed *P* value of <0.05 was considered to be statistically significant.

Results

The baseline characteristics and health habits of the cases and controls are shown in Table 1. Hypertension, especially untreated hypertension, was significantly more common in patients than controls.

Cumulative survival of the patients with ICH and controls are shown in Figure 1. The total follow-up period was 820 person years for patients and 1319 for controls. Annual risk for death during follow-up was 5.6% for patients and 3.0% for controls. The 7-year mortality rate was significantly higher among ICH patients than controls (32.9% and 19.4%, respectively; $P=0.0034$). In our original cohort of 208 subjects with ICH, the overall 7-year mortality was 54.8%.

According to GOS, 52 patients (37.1%) showed good recovery, 27 (19.3%) were moderately disabled, and 61 (43.6%) were severely disabled at the beginning of the follow-up. Figure 2 shows the cumulative survival rates of these groups. The mortality of the patients who were severely disabled according to GOS was significantly higher than that of the patients who showed good recovery ($P=0.0056$). Those who showed good recovery at 3 months ran a similar outcome as controls ($P=0.84$).

TABLE 1. Baseline Characteristics of 140 Patients With ICH and 206 Controls

Characteristics	ICH	Control
Men, n (%)	74 (52.9)	121 (58.7)
Mean age, y (SD)	65.9 (10.3)	65.8 (10.5)
Mean body mass index, kg/m^2 (SD)	27.5 (5.5)	26.5 (4.0)
Previous diseases, n (%)		
Hypertension	92 (65.7)	103 (50.0)*
Hypertension treated	60 (42.9)	85 (41.3)
Hypertension untreated	32 (22.9)	18 (8.7)†
Cardiac disease	48 (34.3)	70 (34.0)
Ischemic stroke	21 (15.0)	19 (9.2)
Hemorrhagic stroke	14 (10.0)	1 (0.5)
ICH	8 (5.7)	0
Subarachnoid hemorrhage	6 (4.3)	1 (0.5)
Gastrointestinal bleeding	12 (8.6)	24 (11.7)
Hematuria	10 (7.1)	20 (9.7)
Cancer	17 (12.1)	14 (6.8)
Diabetes mellitus	11 (7.9)	17 (8.3)
Lifestyle factors, n (%)		
Current heavy drinking	23/123 (18.7)	47 (22.8)
Current smoking	15 (10.7)	33 (16.0)
Medication (before index stroke)		
Aspirin	25 (17.9)	42 (20.4)
Warfarin	7 (5.0)	5 (2.4)

*$P=0.003$; †$P<0.001$.

The causes of death among patients and controls are shown in Table 2. Significantly more patients (7.9%) than controls (1.0%) died of ICH ($P=0.002$). The annual risk for fatal recurrent ICH was 1.3% in our cohort. Recurrent ICH and pneumonia were the most common causes of death in ICH patients, killing 8% and 10% of the patients, respectively. Mortality attributable to pneumonia was directly associated

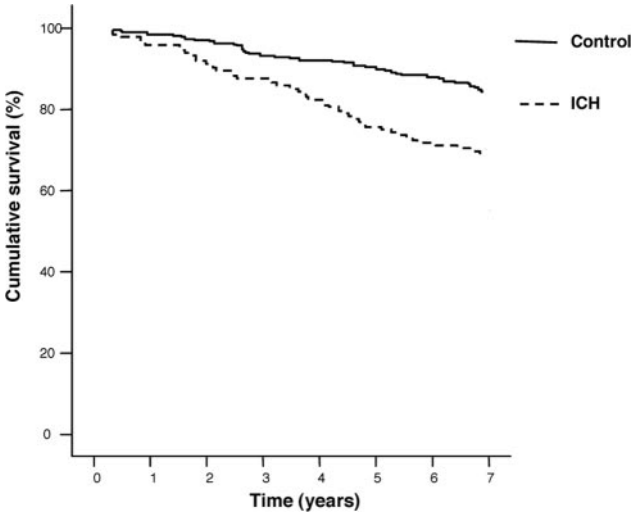

Figure 1. Seven-year survival of patients with ICH and controls.

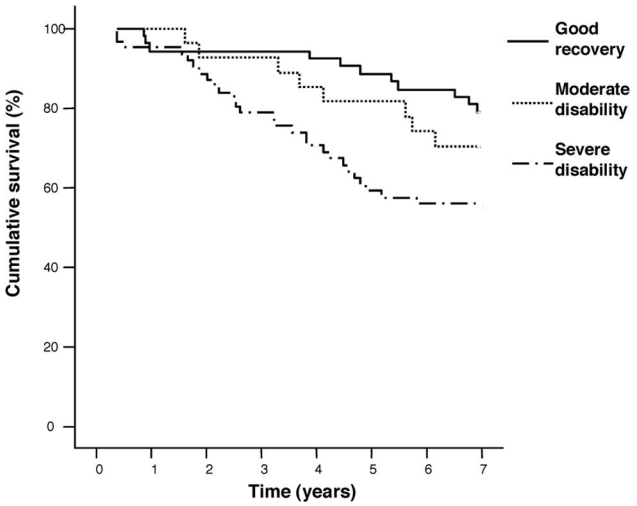

Figure 2. Seven-year survival of patients with ICH according to the GOS score. Forty-one (78.8%), 19 (70.4%), and 43 (55.7%) patients with good recovery, moderate disability, and severe disability at the beginning of follow-up, respectively, survived for 7 years.

with the GOS score at 3 months ($P=0.026$). Eleven (5.3%) controls died of pneumonia, but the difference in mortality from pneumonia between the patients and controls did not reach statistical significance ($P=0.064$). Eight patients (5.7%) with ICH and 11 control subjects (5.8%) died of myocardial infarction or other cardiac causes.

Independent significant predictors for death during the follow-up in patients and controls are shown in Table 3. Smoking was a significant predictor for mortality in both groups, whereas diabetes reached significance only in patients. Age was significantly associated with mortality in controls but not in patients.

Discussion

The mortality of the patients who had survived for 3 months after ICH was significantly higher than that of controls during a follow-up of 7 years. The increased mortality of ICH patients compared with controls was attributable to rebleedings and pneumonia. However, the mortality rates differed significantly according to the GOS score at 3 months after ICH. Mortality was highest among the severely disabled ICH patients, pneumonia being their most common cause of death. On the other hand, the patients with good recovery at 3 months after ICH survived equally to controls. Smoking was a significant preventable risk factor for death in ICH patients and controls.

To our knowledge, the long-term survival of patients with ICH has not before been compared with the survival of a prospectively followed cohort of control subjects from the same population. We found that patients with ICH show excess mortality after the first 3 months up to 7 years. There is only 1 previous study suggesting a similar finding in ICH patients.[2] The Oxfordshire Community Stroke Project compared the risk of death for stroke patients with that for people of similar age and sex from the general population. A higher than expected mortality rate among those who survived beyond the first month was observed in ICH patients, the average annual risk of death being 8% during a follow-up of 5 years. The annual risk for death was slightly lower (5.6%) in our study. A previous Finnish study also compared the survival of ICH patients to the probability of survival in a general population of similar age and sex.[1] In that study, the long-term prognosis up to 5 years of the ICH patients who survived for the first month did not differ from that of the average Finnish population. In other studies, the patient series have consisted of hospitalized patients, controls have been lacking, or the observation periods have been shorter than 2 years.

We observed a lower long-term mortality after ICH than reported previously.[1–3] Fogelholm et al reported a 65% mortality rate during a median follow-up of 2.7 years in central Finland in the 1980s.[1] However, recently, a decline in mortality from ICH in Finland has been observed.[12–14] Improved acute care of stroke patients, which allows more patients with moderate-to-severe disability to survive beyond the first critical days, may explain somewhat lower mortality in our study compared with some previous ones.[1,12]

TABLE 2. Causes of Death of Patients With Spontaneous ICH Who Survived the First 3 Months and Controls During 7-Year Follow-up

Variable	ICH				Control
GOS at the Beginning of Follow-up	Good Recovery	Moderate Disability	Severe Disability	Total	
Died during follow-up (%)	11/52 (21.2)	8/27 (29.6)	27/61 (44.3)	46/140 (32.9)	40/206 (19.4)
Cause of death					
ICH	4	1	6	11	2
Ischemic stroke	0	2	1	3	1
Pneumonia	2	2	10	14	11
Cardiac disease	2	1	5	8	12
Trauma	0	0	2	2	1
Cancer	1	0	0	1	4
Pulmonary embolism	0	0	0	0	1
Miscellaneous	2	2	3	7	8

TABLE 3. Multivariate Relative Risks of Death During 7-Year Follow-up in Patients With ICH and Controls

	ICH			Controls		
Variable	Relative Risk*	95% CI	*P*	Relative Risk*	95% CI	*P*
Age	1.04	0.99–1.09	0.084	1.16	1.10–1.21	<0.001
Diabetes	3.62	1.27–10.29	0.016	2.41	0.91–6.39	0.077
Smoking	3.09	1.30–7.36	0.011	2.73	1.03–7.19	0.043

*Relative risks have been adjusted for sex and the variables listed in the table and, in patients, also for GOS score at the beginning of follow-up (3 months after the onset of the index stroke).

Our study indicates that mortality during long-term follow-up is significantly higher in patients who are severely disabled according to GOS at 3 months after the index stroke compared with those who show good recovery. Pneumonia as a cause of death was most common in the severely disabled patients, probably being a complication of immobility. The moderately disabled also showed somewhat higher mortality than those with good recovery. In previous studies, the severity of stroke assessed by the initial level of consciousness according to the Glasgow Coma Scale score[15] on admission and the handicap caused by the stroke according to the modified Rankin scale[16] in the early phase were shown to predict long-term mortality after ICH.[5–9] Stroke severity predicts functional outcome and residual disability similarly in ischemic and hemorrhagic strokes.[17] Our findings suggest that the functional status reached after rehabilitation may be a major factor determining future survival.

Diabetes and current smoking predicted long-term mortality of ICH patients in our study. These are novel findings. In 2 previous studies, diabetes was shown to be an independent risk factor for in-hospital mortality from ICH.[18,19] Lifestyle factors have been analyzed in very few studies of survival after ICH. Alcohol consumption within a week before ICH has been shown to predict poor functional outcome, but it did not significantly associate with 1-year mortality.[6] Nor did heavy drinking of alcohol associate with mortality in our study. Smoking also predicted death in the group of healthy controls.

Patient age tended to predict mortality in our cohort of ICH patients who survived the first 3 months after the stroke, but the association was not significant. In a number of previous studies, patient age has been found to significantly predict long-term survival after ICH.[1,5,7–9,20] However, Juvela did not find patient age to predict mortality within 1 year after ICH.[6] Hematoma volume[8] and location[4,6] have also been associated with long-term survival after ICH.

Recurrent ICH accounted for 24% of deaths among patients. An annual recurrence rate of 2.4% for ICH has been reported,[21] but because of our study design, we were only able to detect fatal rebleedings. The prognosis after recurrent ICH has been shown to be worse than that after the first ICH, and in-hospital mortality from 32% to 56% after the second ICH has been reported.[22,23] Rebleedings have been observed to associate with poor control of hypertension.[22,23] Therefore, adequate control of hypertension is probably the most important primary and also secondary prophylaxis of ICH. However, some patients may have other, undetected risk factors that are difficult to target. The $\epsilon 2$ or $\epsilon 4$ alleles of the apolipoprotein E gene have been shown to increase the risk for recurrent lobar ICH attributable to cerebral amyloid angiopathy.[24]

The strengths of the study include the population-based design and the complete follow-up of patients and controls. The causes of death were extracted from the Causes of Death Register of Finland, which is considered a reliable source of data.[25] However, the findings about predictors for long-term survival must be interpreted with caution because the patient data (eg, lifestyle data) were collected during the period of hospitalization attributable to the index stroke and are thus indicative of the patients' preictal health habits. Some of the smokers probably gave up smoking after the index stroke. In consequence, not all of the patients classified as smokers continued smoking during the follow-up years. However, if these previous smokers had been classified as nonsmokers, the association between smoking and excess mortality might have been even stronger. In addition, case findings may have been incomplete for 3 reasons. First, some elderly subjects dying outside our hospital may have died of ICH without verification by head CT or autopsy. Second, those subjects who may have had an ICH when on holiday were not included previously. However, if such a patient was transferred to our hospital during the acute phase, he/she was included. Third, we may have missed subjects with mild strokes who were not admitted or who were admitted so late that ICH was no longer detectable by CT. However, the proportion of possible missing cases is likely low and does not affect the reliability of our study. The different methods used for obtaining data of cases and controls and of cases admitted to different departments of our hospital are another limitation. However, we believe that current diseases, such as hypertension and diabetes, as well as smoking status were accurately recorded in patient charts. In addition, telephone interview has been found to be a method comparable to personal interview for assessing smoking status.[26]

In conclusion, we found increased long-term mortality in patients with ICH who had survived the first 3 months after the stroke compared with controls. Excess mortality was especially marked among the ICH patients who were severely disabled at 3 months after ICH, and it was mainly because of pneumonia, which is a complication of immobility. Rebleedings were also quite common but unrelated to the grade of disability. Our observations suggest that more attention should be paid to the prevention of infections and the treatment of cardiovascular risk factors such as hypertension,

diabetes, and smoking in patients surviving their first ICH. Active treatment in the acute phase and rehabilitation may improve not only the short-term outcome but also long-term survival.

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