Cause-specific mortality of 1-year survivors of subarachnoid hemorrhage

Miikka Korja, MD, PhD
Karri Silventoinen, PhD
Tiina Laatikainen, MD, PhD
Pekka Jousilahti, MD, PhD
Veikko Salomaa, MD, PhD
Jaakko Kaprio, MD, PhD

Correspondence to Dr. Korja: miikka.korja@hus.fi

ABSTRACT

Objective: To assess long-term, cause-specific mortality rates and rate ratios of the patients alive at 1 year after subarachnoid hemorrhage (SAH).

Methods: The population-based, prospective, cohort study with a nested case-control design consisted of 64,349 persons (aged 25–74 years at enrollment) who participated in the National FINRISK Study between 1972 and 2007. Four hundred thirty-seven SAH cases, 233 one-year SAH survivors, and their matched intrinsic controls were identified and followed up until the end of 2009 through the nationwide Finnish Causes of Death Register. All-cause mortality rates and rate ratios of the 1-year SAH survivors and controls were the main outcome measures.

Results: Eighty-eight (37.8%) of 233 one-year SAH survivors died during the total follow-up time of 2,487 person-years (median 8.6 years, range 0.1–35.8 years). The 1-year SAH survivors had a hazard ratio of 1.96 (95% confidence interval 1.57–2.47) for death compared with the matched general population with 10 controls for each SAH survivor. One-year SAH survivors had up to 31 additional deaths per 1,000 person-years compared with controls with minimal cerebrovascular risk factors. The higher long-term risk of death among SAH survivors was attributed solely to cerebrovascular diseases, and most important modifiable risk factors for death were smoking, high systolic blood pressure (≥159 mm Hg), and high cholesterol levels (≥7.07 mmol/L).

Conclusion: One-year SAH survivors have excess mortality, which is attributed to an exceptional risk of deadly cerebrovascular events. Aggressive post-SAH cerebrovascular risk factor intervention strategies are highly warranted. *Neurology*® 2013;80:481–486

GLOSSARY

BP = blood pressure; **CI** = confidence interval; **HR** = hazard ratio; ***ICD*** = *International Classification of Diseases*; **SAH** = subarachnoid hemorrhage; **SMR** = standardized mortality ratio.

Published data on long-term mortality of survivors of subarachnoid hemorrhage (SAH) are scarce and limited. Studies, which have been conducted mainly in the computed tomography angiography era,[1–6] suggest that SAH survivors have increased long-term mortality rates compared with a general population.[1,3,4,6] Not only those with the permanent neurologic sequelae of SAH but also survivors who recover to an independent state from the event seem to have excess long-term mortality.[1,5,6] Given that the etiology of SAH is mainly environmental,[7] it is understandable that long-term mortality of SAH survivors exceeds that of the general population. This holds true especially if post-SAH interventions to minimize exposure to modifiable risk factors are not implemented. However, implementation of secondary prevention measures is impossible if the conditions and diseases causing excess mortality are unknown.

Systemic cardiovascular diseases and cancers are common causes of death not only among SAH survivors[1–6] but also among the general population in high-income countries.[8,9] In this study, we extracted 1-year SAH survivors and controls from the same large and well-characterized population-based cohort.

Patient Page

From the Department of Neurosurgery (M.K.), Helsinki University Central Hospital, Helsinki; Population Research Unit (K.S.), Department of Social Research, University of Helsinki; Departments of Chronic Disease Prevention (T.L., P.J., V.S.) and Mental Health and Substance Abuse Services (J.K.), National Institute for Health and Welfare, Helsinki; The Institute of Public Health and Clinical Nutrition (T.L.), University of Eastern Finland, Kuopio; Hospital District of North Karelia (T.L.), Joensuu; Department of Public Health (J.K.), University of Helsinki; and Institute for Molecular Medicine FIMM (J.K.), Helsinki, Finland.

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Using intrinsic and detailed controls enabled estimations of the effect of risk factors on long-term mortality for the first time. Also for the first time, we analyzed cause-specific, long-term mortality of 1-year SAH survivors.

METHODS **The FINRISK cohort.** The data were drawn from the National FINRISK Study database.[10] The FINRISK surveys were initiated in 1972 in selected regions in Finland, and since then the surveys have been conducted every 5 years. The FINRISK participants filled in a health-related baseline questionnaire and attended a clinical examination, which was conducted by research nurses at enrollment.

Using the eighth, ninth, and tenth revisions of the *International Classification of Diseases* (*ICD*), incident cases of SAH were identified from the National Hospital Discharge Register and from the Causes of Death Register. The *ICD* revision used was changed in Finland from the eighth (*ICD-8*) to the ninth (*ICD-9*) in the beginning of 1987, and from the *ICD-9* to the tenth (*ICD-10*) in the beginning of 1996. Data were retrieved on all persons listed with a diagnosis of subarachnoid hemorrhage (*ICD-8* and *ICD-9* code 430) or nontraumatic subarachnoid hemorrhage (*ICD-10* code I60), and identified cases were linked to the baseline data using unique personal identification numbers assigned to all Finnish residents. The National Institute for Health and Welfare administers the Hospital Discharge Register, and all inpatient stays are recorded from all hospitals in Finland. The Causes of Death Register is administered by the Statistics Finland, where a specialist physician (forensic medicine) and a nosologist check the consistency of the underlying cause of death and correct the diagnosis if necessary. According to a Finnish law, a forensic autopsy has to be done for all people with sudden and unexpected death to confirm diagnosis. The cause of death of 1-year SAH survivors and all controls (see below) was divided into 7 categories: 1) cardiovascular, 2) cerebrovascular, 3) cancer, 4) trauma, 5) psychiatric, 6) infection, and 7) other. The validity of the register-based diagnosis of SAH that was used has been verified previously, and the agreement rate and sensitivity for the recorded SAH diagnoses are 89% to 92%.[11,12] The agreement rate of SAH in the Finnish Causes of Death Register is 95%.[12,13]

The day of diagnosis was defined as the day of hospitalization for SAH. Participants were followed from the onset of SAH (defined as first hospitalization for SAH), whereas censoring occurred at the time of death or emigration (data from the Finnish Population Register), or at the end of the follow-up period in December 2009. Follow-up for all controls started at the same day as the initiation of follow-up of the matched cases. None of the controls had a history of SAH. Completeness of follow-up is 100% for deaths and hospitalizations in Finland. Only 0.4% of the FINRISK study subjects were lost to follow-up because of emigration.[14]

The FINRISK cohort consisted of 64,349 Finnish residents, of which 33,235 (51.7%) were women. Mean age at enrollment was 45.1 years (±12 years, range 25–74 years) with no difference by sex or future case status. Of the 437 identified SAH cases in the FINRISK cohort, 79 (18.1%) died outside hospitals or at emergency rooms. Of the remaining 358 hospitalized patients, 95 (26.5%) died during the first 30 days and an additional 20 (5.6%) during the first year after hospitalization.

Standard protocol approvals, registrations, and patient consents. The approval for the FINRISK surveys has been applied each time from relevant ethics committees. Informed consent (verbal from 1977 to 1992 and written since 1997) was received from all participants.

One-year SAH survivors and controls extracted from the FINRISK cohort. A nested case-control approach was used to assess differences in the rate and cause of long-term mortality among study groups. An intrinsic general population group for 1-year SAH survivors was constructed by selecting 10 controls for each SAH case, and these controls and cases were matched for enrollment year. Each control had to be alive and without a prior SAH at the time of SAH of the case. One-year SAH survivors and the enrollment year–matched general population group did not differ by sex, age, or region of residence.

Of the 437 SAH cases, there were 243 (55.6%) one-year SAH survivors. For the 243 one-year SAH survivors, control selection using individual matching was contingent on each case characteristic. Ten 1-year SAH survivors were selected as controls (random selection from the pool of controls based on eligibility criteria and matching criteria) because they were healthy at the time of selection (when a matched case presented) but later had an SAH. Thus, these 10 participants (cannot be both a case and a control) were excluded from the final analyses, which therefore included 233 one-year SAH survivors (mean age 44.2 years at enrollment). Of these 233 one-year SAH survivors, 131 (56.2%) were women.

The general population control group included 2,330 participants (mean age 43.6 years at enrollment), of which 1,256 (53.9%) were women. The general population group was further divided into 3 subgroups on the basis of our previous study[15]: 1) multiple risk factor subgroup, which included only participants who were current smokers with systolic blood pressure (BP) ≥159 mm Hg (highest fifth when using the cutoff points of quintiles) and had cholesterol levels ≥5.59 mmol/L (3rd to 5th fifths when using the cutoff points of quintiles) at enrollment; 2) minimal risk factor subgroup, including only participants who were never smokers, had systolic BP <135 mm Hg (1st to 2nd fifths when using the cutoff points of quintiles), and had cholesterol levels <5.59 mmol/L at enrollment; and 3) Gaussian subgroup "without extremes" (people with multiple and minimal risk factors excluded), representing people who were not included in the multiple and minimal risk factor subgroups. The same grouping criteria were also used to divide the 1-year SAH survivors into the 3 different risk factor subgroups.

The multiple risk factor subgroup, minimal risk factor subgroup, and Gaussian population subgroup, which were extracted from the general population controls, included 77, 198, and 2,055 participants, respectively. Because all controls were selected on the basis of eligibility criteria and matching criteria at the time of diagnosis (i.e., when a matched SAH case was diagnosed), a number of matched controls withdrew (follow-up data <1 year) before the actual follow-up started for 1-year SAH survivors. Therefore, for all subsequent analyses, the multiple risk factor subgroup, minimal risk factor subgroup, and Gaussian population subgroup included 68, 184, and 1,897 participants, respectively.

Mortality estimates and statistical analyses. The estimation of hazard ratios (HRs) with 95% confidence intervals (CIs) for death was calculated using the Cox proportional hazards regression model with a generalization of the Breslow estimator. A mortality rate ratio was calculated as a follow-up, time-dependent (person-years) comparison of the number of the observed deaths among 1-year SAH survivors with the number of observed deaths among the matched and adjusted controls. Mortality rates per 1,000 person-years were calculated for the study controls. The number of excess deaths per 1,000 person-years was calculated for the 1-year SAH survivors. Cumulative survival of the controls was depicted using Kaplan-Meier curves, and differences between the curves were tested for significance by the log-rank test. Statistical significance was defined as $p < 0.05$. All adjustments and statistical analyses were performed using the survival analysis procedures in the Stata statistical software (version 11.2; Stata Corp, College Station, TX).

RESULTS **Recorded deaths and follow-up times.** Among the 233 1-year SAH survivors, 88 (37.8%) deaths were recorded during the follow-up time (time at risk of death) (table). Of the general population controls of 2,330 participants, there were 506 (21.7%) deaths (table). The multiple risk factor subgroup, minimal risk factor subgroup, and Gaussian population subgroup had 36 (52.9%), 9 (4.9%), and 461 (24.3%) deaths during the follow-up times, respectively (table).

HRs for death. In comparison with the matched general population control group, 1-year SAH survivors had an HR of 1.96 (95% CI, 1.57–2.47) for death. Comparing with the Gaussian population subgroup, the multiple risk factor subgroup, minimal risk factor subgroup, and 1-year SAH survivors had HRs of 2.30 (95% CI, 1.64–3.23), 0.25 (95% CI, 0.13–0.47), and 1.94 (95% CI, 1.54–2.43) for death (table).

After adding age (continuous), sex (dichotomous), smoking (divided into never smokers, quit >6 months ago, quit <6 months ago, occasional smokers, and current smokers), systolic BP values (divided into fifths), hypertension diagnosis (dichotomous), and total cholesterol levels (divided into fifths) as covariates for death into Cox proportional hazards regression analyses, 1-year SAH survivors had an HR of 1.76 (95% CI, 1.38–2.23) for death in comparison with the matched general population group. Age (HR 1.09 [95% CI, 1.38–2.23]), the highest fifth (≥159 mm Hg) of systolic BP (HR 1.48 [95% CI, 1.04–2.11]), current smoking (HR 1.88 [95% CI, 1.50–2.34]), and the highest fifth (≥7.07 mmol/L) of cholesterol levels (HR 1.57 [95% CI, 1.06–2.34]) were significant risk factors for death among the whole study population in this multivariate analysis. Male gender seems to confer a decreased risk for death 1 year after SAH (HR of 0.64 [95% CI, 0.52–0.79]).

Mortality rates and rate ratios. Mortality rates for the multiple risk factor subgroup, minimal risk factor subgroup, Gaussian population subgroup, and 1-year SAH survivors are depicted in the table. For 1-year SAH survivors, the mortality rate ratios were 7.75 (95% CI, 3.90–17.51), 0.82 (95% CI, 0.55–1.24), and 1.84 (95% CI, 1.45–2.32) in comparison with the minimal risk factor, multiple risk factor, and Gaussian population subgroup, respectively. Survival rates of 1-year SAH survivors and control subgroups are depicted in a Kaplan-Meier survival curve (figure 1A).

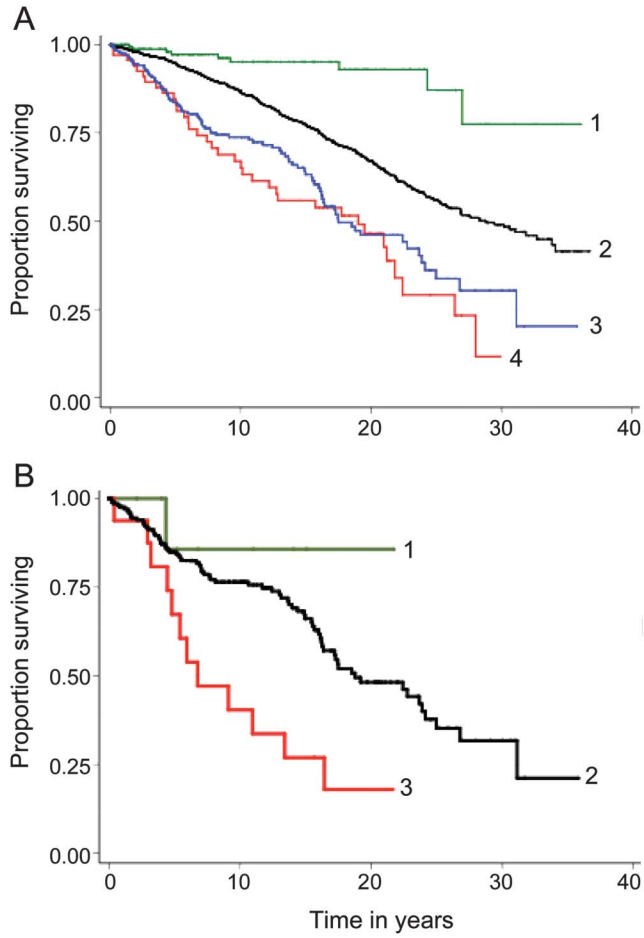
The effects of risk factors on long-term survival of 1-year SAH survivors were estimated using a Kaplan-Meier survival analysis in which 1-year SAH survivors were divided into 3 subgroups: the multiple risk factor SAH subgroup, minimal risk factor SAH subgroup, and Gaussian population SAH subgroup. Results suggested that 1-year SAH survivors who were current smokers, had a high systolic BP (≥159 mm Hg), and total serum

Table Characteristics of 1-year survivors of SAH and adjusted subgroups

	1-year SAH survivors	Gaussian population subgroup[a]	Minimal RF subgroup	Multiple RF subgroup
No. of persons	233	1,897	184	68
Females, n (%)	131 (56.2)	1,013 (50.1)	147 (79.9)	11 (16.2)
Deaths, n (%)	88 (36.2)	461 (24.3)	9 (4.9)	36 (52.9)
Age,[b] y				
Mean	57.5	57.7	51.6	58.1
Median	58.4	59.0	51.9	57.4
Follow-up time, y				
Total	2,487	24,031	1,972	830
Median (range)	8.6 (0.1–35.8)	11.4 (0–38.8)	8.4 (0–36.1)	10.5 (0.2–29.9)
Current smokers, n (%)	98 (42.0)	502 (26.4)	0 (0.0)	68 (100.0)
Systolic BP ≥159 mm Hg, n (%)	55 (23.6)	352 (18.6)	0 (0.0)	68 (100.0)
Cholesterol ≥5.59 mmol/L, n (%)	171 (73.4)	1,449 (76.4)	0 (0.0)	68 (100.0)
HR for death (95% CI)	1.94 (1.54–2.43)	1	0.25 (0.13–0.47)	2.30 (1.64–3.23)
Mortality rate per 1,000 person-years (95% CI)	35.4 (28.7–43.6)	19.2 (17.5–21.0)	4.6 (2.4–8.8)	43.4 (31.3–60.2)
Excess deaths per 1,000 person-years[c]	16	0	NA	24

Abbreviations: BP = blood pressure; CI = confidence interval; HR = hazard ratio; NA = not applicable; RF = risk factors; SAH = subarachnoid hemorrhage.
[a] Gaussian population subgroup represents the matched general population (see the Methods section).
[b] Mean and median age for each group was calculated using the age of the patient at diagnosis.
[c] The difference between observed deaths in the adjusted subgroups compared with the Gaussian population subgroup.

Figure 1 Kaplan-Meier survival analysis



A Kaplan-Meier survival analysis in which the general population controls (A) and 1-year subarachnoid hemorrhage (SAH) survivors (B) are divided into subgroups on the basis of risk factors: minimal risk factor subgroup (A1), Gaussian control population (A2), 1-year SAH survivors (A3), multiple risk factor subgroup (A4), 1-year SAH survivors with minimal risk factors (B1), Gaussian 1-year SAH survivors (B2), 1-year SAH survivors with multiple risk factors (B3). A1 and B1 = never smokers with systolic blood pressure (BP) <135 mm Hg and cholesterol levels <5.59 mmol/L. A4 and B3 = smokers with systolic BP ≥159 mm Hg or cholesterol levels ≥5.59 mmol/L.

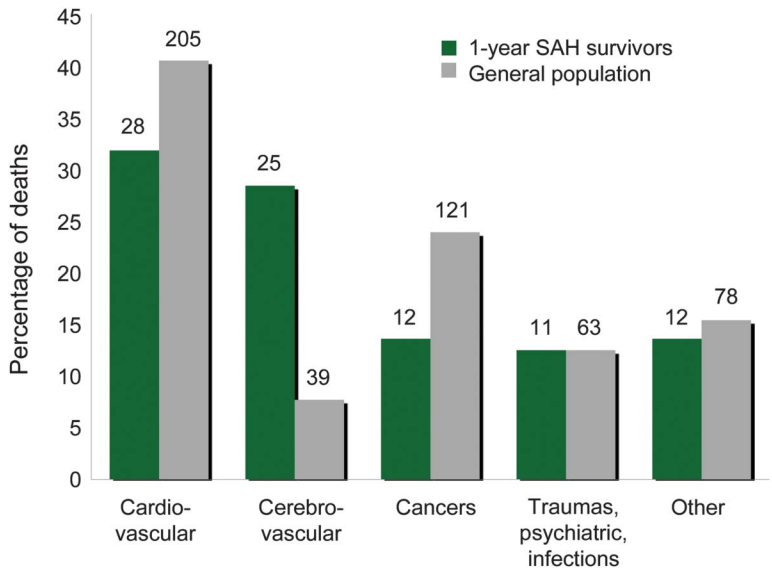
cholesterol levels of ≥5.59 mmol/L at enrollment had a much higher risk of death than 1-year SAH survivors with less risk factors (figure 1B). However, because of a limited number of the 1-year SAH survivors with minimal or multiple risk factors, the data are insufficient to conduct statistically reliable estimates of HRs for death in these SAH subgroups.

Causes of death. Compared with the matched general population group, excess deaths of 1-year SAH survivors were attributed solely to cerebrovascular diseases (figure 2). In the matched general population, cerebrovascular diseases accounted for only 7.7% of all deaths, whereas this number was 28.4% for 1-year SAH survivors (figure 2). Ischemic cerebrovascular diseases or their sequelae accounted for 5.5% and 11.4%, intracerebral hemorrhages accounted for 1.4% and 3.4%, SAHs accounted for 0.2% and 4.5%, and sequelae of SAH accounted for 0% and 6.8% of all deaths in the matched general population and 1-year SAH survivors, respectively.

DISCUSSION The approximately 2 times higher long-term risk of death among 1-year SAH survivors is attributed to cerebrovascular diseases, such as brain infarcts and intracerebral hemorrhages. Changes over time in the risk of death of 1-year SAH survivors are not noticeable, suggesting that the higher risk of death cannot be attributed only to SAH-related health effects in the early years after SAH, even though sequelae of SAH accounted for 6.8% of all deaths among 1-year SAH survivors. After adjustment for multiple cerebrovascular risk factors, the risk of death among 1-year SAH survivors decreases but still exceeds that of the general population. Age, high systolic BP, current smoking, and high cholesterol levels were significant risk factors for death among the whole study population. The cutoff values used for cholesterol levels and high systolic BP were defined on the basis of previous results,[15] and do not follow any clinical practice guidelines. The risk of death did not differ significantly between 1-year SAH survivors and the population with multiple risk factors. This is probably attributable to the fact that 1-year SAH survivors do not all have multiple risk factors, like the multiple risk factor controls. In any case, it seems evident that cerebrovascular risk factor profiles have great impact on long-term life expectancy in SAH survivors and people in general, and that the variation in the risk factor profiles between study groups can explain the vast difference in mortality estimates. Overall, 1-year SAH survivors experienced up to 16 and 31 additional deaths per 1,000 person-years compared with the matched general population and population with minimal cerebrovascular risk factors, respectively. Those 1-year SAH survivors who have high systolic BP and high cholesterol levels, and who are already smokers before an SAH event, are at greatest risk of post-SAH death. Bearing in mind the extreme variation in the risk of death, not only primary but also secondary prevention strategies addressing smoking, hypertension, and high cholesterol are warranted.

Previous studies have used varying methods and criteria in studying and reporting long-term mortality rates of SAH survivors. The largest study to date recently reported 12% excess mortality of 1-year SAH survivors at 15 years after SAH.[6] Another recent study based on the International Subarachnoid Aneurysm Trial cohort observed that the standardized mortality ratio (SMR) of 1-year SAH survivors was 1.57 times that of the general population.[4] A Dutch study published in 2009 concluded that the SMR of all SAH survivors (discharged alive) was 1.7 times that of the general population.[3] A decade-old Finnish study reported that the SMR of 1-year SAH survivors with good recovery was 2 times that of the general population.[1] Inconsistency in, for

Figure 2 Causes of death in 1-year survivors of subarachnoid hemorrhage (SAH) and matched general population controls



Number of deaths in each category is reported on the top of bars.

example, survival statistics, follow-up times, and patient selection criteria limits conclusive interpretations, but also the previous results give a reasonable impression that SAH survivors, despite the neurologic outcome, have approximately 2 times higher long-term mortality compared with the general population. Causes of reported excess mortality among SAH survivors were unclear until this study. Contrary to the current and previous results, one study suggests that 3 years after SAH, survivors have a survival rate similar to that of the general population.[5] Because SAH is a cerebrovascular disease with modifiable risk factors, the contrary results are confusing. The varying interpretations[5] may be attributable to the statistical methods used and the study population selected. In general, adopting cancer survival statistics (with extrinsic control populations) to cerebrovascular diseases should be implemented cautiously.

Compared with the previous long-term SAH survival studies,[1–6] the current study has some strengths. First, the current study had the possibility of matching and adjusting controls to a variety of covariates assessed before an SAH event. Our results suggest that differences in the prevalence of cerebrovascular risk factors in age- and sex-adjusted study controls can confound mortality estimates. Differences in risk factors of study controls may cause comparisons of mortality rates, for example, between SAH cohorts treated with microsurgery (clipping) or endovascular coiling[4] difficult to interpret correctly if matching or adjusting to covariates cannot be done. Second, the current study was based on a large, prospective, population-based study, the FINRISK, whereas most of the previous cohorts were gathered from 1 or 2 hospitals. The large-scale, population-based recording of deaths in the current study may thus further strengthen the provision of unbiased and reliable risk estimates of late mortality among SAH survivors. Third, instead of using a register-based extrinsic general population as a comparison group, all controls were intrinsic and extracted from the same main cohort, the FINRISK. The main drawback in using an extrinsic general population as a comparison group is that it is usually less exposed to disease risk factors, all of which are not always known. Possible drawbacks of the current study include the fact that register-based data may have inaccuracies. However, mortality studies in general rely on population-based cause-of-death registries. Furthermore, the registries used have been utilized for more than 1,000 scientific publications during the last decades and their validity has been tested in a number of occasions. A further limitation of the study is that all SAH patients, not only surgically or endovascularly treated ones, were included in the study. Thus, the few recurrent SAH events among 1-year SAH survivors could have been caused by aneurysms that were left untreated in the primary occasion. However, these few SAH events occurred years after the primary event and the limited number of them does not skew the results or interpretations.

Not only high-quality primary treatment of SAH but also effective secondary prevention of post-SAH cerebrovascular events would likely prevent a considerable number of early deaths. This is especially true for relatively young SAH survivors. A history of smoking, high systolic BP, and high cholesterol levels dramatically shortens the life expectancy of SAH survivors. Long-term SAH mortality studies seem to give a higher estimation of mortality ratios when SAH survivors are compared with the general population instead of risk factor–adjusted control populations. Finding ways to efficiently reduce potentially preventable early deaths of SAH survivors as well as people with SAH risk factors will be a future challenge.

AUTHOR CONTRIBUTIONS

M.K. had the main responsibility of study design and writing the manuscript. K.S. contributed to acquisition of data, study design, data analysis, and revision of the manuscript. T.L., P.J., and V.S. contributed to acquisition of data and revision of the manuscript. J.K. coordinated the study and contributed to study design, acquisition of data, data analysis, and critical revision of the manuscript.

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DISCLOSURE

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