Received: 31 May 2021 | Accepted: 14 June 2021

DOI: 10.1111/ene.14988

european journal of neurology
the official journal of the european academy of neurology

ORIGINAL ARTICLE

Long-term survival after primary intracerebral hemorrhage: A population-based case–control study spanning a quarter of a century

Anna-Maija Lahti[1,2] | Mirva Nätynki[1,2] | Juha Huhtakangas[1,2] | Michaela Bode[3] | Seppo Juvela[4] | Pasi Ohtonen[2,5,6] | Sami Tetri[1,2]

[1]Research Unit of Clinical Neuroscience, University of Oulu, Oulu, Finland

[2]Medical Research Center Oulu Brain Health, Oulu University Hospital, Oulu, Finland

[3]Department of Radiology, Medical Imaging, Physics and Technology Research Unit, Oulu University Hospital, University of Oulu, Oulu, Finland

[4]Department of Clinical Neurosciences, University of Helsinki, Helsinki, Finland

[5]Division of Operative Care, Oulu University Hospital, Oulu, Finland

[6]Surgery, Anaesthesia and Intensive Care Research Unit, University of Oulu, Oulu, Finland

Correspondence
Mirva Nätynki, Research Unit of Clinical Neuroscience, University of Oulu, Oulu University Hospital, Kajaanintie 50, 90029 Oulu, Finland.
Email: mirva.natynki@fimnet.fi

Funding information
Suomen Kulttuurirahasto; Orionin Tutkimussäätiö; Epilepsiatutkimussäätiö

Abstract

Background and purpose: The aim of this study was to determine the differences in life expectancy and causes of death after primary intracerebral hemorrhage (ICH) relative to general population controls.

Methods: In a population-based setting, 963 patients from Northern Ostrobothnia who had their first-ever ICH between 1993 and 2008 were compared with a cohort of 2884 sex- and age-matched controls in terms of dates and causes of death as extracted from the Causes of Death Register kept by Statistics Finland and valid up to the end of 2017.

Results: Of our 963 patients, 781 died during the follow-up time (mortality 81.1%). Cerebrovascular disease was the most common cause of death for these patients, 37.3% compared with 8.2% amongst the controls. The most common reasons for cerebrovascular mortality in the ICH patients were late sequelae of ICH in 12.8% (controls 0%) and new bleeding in 10.6% (controls 1.0%). The long-term survivors had a smaller ICH volume (median 12 ml) than those patients who died within 3 months (median 39 ml). The mortality rate of ICH patients during a follow-up between 12 and 24 years was still higher than that of their controls (hazard ratio 2.08, 95% confidence interval 1.58–2.74, $p < 0.001$).

Conclusions: Very long-term ICH survivors have a constant excess mortality relative to controls even 10 years after the index event. A significantly larger proportion of patients died of cerebrovascular causes and fewer because of cancer relative to the controls.

KEYWORDS
adult, case–control study, cerebrovascular diseases, epidemiology, intracerebral hemorrhage, long-term survival, rehabilitation

INTRODUCTION

One in every six people experience a stroke during their lifetime, and many stroke survivors suffer from major disability afterwards [1]. Intracerebral hemorrhage (ICH) is the most severe form of stroke and accounts for 10%–20% of all cases [2]. Only half of the patients survive the acute phase, and overall mortality from ICH is high. A meta-analysis performed in 2014 estimated 1-year survival at 46%

Anna-Maija Lahti and Mirva Nätynki with equal contribution to the study.

and 5-year survival at only 29% [1]. Well-known risk factors for mortality within 6 months of an ICH are hematoma volume, older age, smoking, low modified Rankin Scale score, pre-stroke cognitive impairment, a previous ischaemic event, prior anticoagulation and the presence of an intraventricular hematoma [3].

Long-term survival is poor, as only 24.1% survive for 10 years [4]. Adoukonou et al. showed, however, that younger patients had better outcomes, as the 10-year mortality rate amongst patients aged 16–49 was only 11%, although male sex and diabetes were independent factors associated with poorer outcomes in young patients [5]. In one 13-year follow-up study, patients who initially survived the acute phase of ICH died later chiefly from cerebrovascular disease (36%) or ischaemic heart disease (19%), with hypertension and poor neurological status at the onset of ICH contributing to this risk [6].

The very long-term survival of ICH patients (up to 20 years) nevertheless remains unclear, as does the outcome relative to the general population. A long-term population-based follow-up of the outcome after primary ICH was performed covering more than 20 years. The outcomes and the cause of death (COD) were compared with data for sex- and age-matched controls living in the same area. The aim was to clarify the differences in life expectancy and in the actual CODs between those suffering from this devastating form of stroke and controls.

METHODS

Patient selection and clinical data

Included in our cohort were all the patients who had been admitted to Oulu University Hospital for primary ICH between January 1993 and January 2008 and who were living at the time in its catchment area (Northern Ostrobothnia, population 356,026–389,671 inhabitants during that period). There are no other hospitals treating acute stroke patients in the area. Up to September 1995 the patients were enrolled prospectively [7]. Patients with a secondary cause for the bleeding, for example brain tumor, head trauma, vascular malformation or a bleeding disorder, were not included. This resulted in an eventual population of 963 patients with a first-ever ICH.

Data on the patients' previous diseases, blood pressure values and current medication at the onset of ICH were extracted from the hospital records regarding comorbid diseases, hypertension, diabetes and other cardiovascular diseases as conditions of particular interest. Patients with blood pressure levels exceeding 160/90 mmHg at least twice prior to the ICH were recorded as having untreated hypertension according to the World Health Organization/International Society of Hypertension (WHO/ISH) definition [8]. In addition, all patients receiving antihypertensive medication at the onset of ICH were considered to have hypertension. Diabetes was defined as the use of insulin and/or oral antihyperglycemic medication. Our definition of cardiac disease included previous myocardial infarction, coronary artery disease, heart failure and/or atrial fibrillation.

Neuroradiological methods

All the patients underwent a computed tomography scan of the brain on admission. These images were used to verify the diagnosis and to determine the site and volume of the bleeding. Due to the retrospective nature and long duration of the study, two different methods were used to estimate the ICH volume: an accurate planimetric method and the ABC/2 method, as reported earlier [9]. The location of the hemorrhage was categorized as reported previously [10]. The hematomas were categorized according to the presumed origin point of the hemorrhage. Follow-up imaging was performed with either computed tomography or magnetic resonance imaging 2–3 months after the index ICH for all surgically treated patients and the majority of patients who did not undergo operative treatment. If an aneurysmal origin was suspected, the patient underwent angiography immediately after admission. The majority of those patients who survived the acute phase underwent follow-up imaging.

Outcome

All the patients who did not show good recovery during their initial hospitalization period were summoned for a follow-up visit to the outpatient clinic of either neurology or neurosurgery. In the case of patients admitted to the rehabilitation ward within 3 months of the index event the follow-up evaluation was performed in that ward.

Causes of death

Dates and CODs were extracted from the Causes of Death Register kept by Statistics Finland for all patients who had died by 31 December 2017. An underlying COD must be indicated on the death certificate of every deceased individual in Finland, in addition to which immediate, intermediate and contributing COD categories may be used [11]. The CODs were categorized here based on the International Classification of Diseases 10 (ICD-10) and corresponding ICD-9 codes.

Controls

A control group was acquired for our study through Statistics Finland, taking up to three controls for each patient whenever available. This gave us a total of 2884 controls matched with the patients for age, sex and region. There was no overlapping between the patient group and the control group. There was one

patient for whom it was not possible to find any matching controls based on these criteria.

Statistical methods

All the statistical analyses were performed using R version 3.5.0 and SAS (version 9.4, SAS Institute Inc., Cary, NC, USA) and used the conventional $p < 0.05$ definition to evaluate statistical significance in all the models and tests. The chi-squared test, Fisher's exact test and the Mann–Whitney *U* test were used in the ICH subgroup analyses as appropriate for evaluating differences between groups.

The risk of death was modeled using the Kaplan–Meier survival curve method and the Cox regression model with shared frailty. The frailty model was chosen because the controls were matched by age, sex and region, and so it could not be assumed that the patients and controls were independent cases. In a frailty model all observations that are dependent are clustered based on their dependence, and in this case the patients were clustered with their matched controls. Since there was no access to the previous history of the controls, no other factors were taken into account in the model.

Ethical approval

The protocol was approved by the ethics committee of the Northern Ostrobothnia Hospital District. Due to the nature of the research, no patient consent was required.

RESULTS

The mean follow-up time for all the ICH patients was 6.1 years, median 4.1 years, range 0–24.9 years. The median follow-up was 9.6 years (interquartile range 5.3–13.3 years) when only those who survived the first year were included. The cumulative short-term mortality rates were 41.7% in the first 3 months and 47.9% during the first year. The cumulative survival rate at 1 year was 0.61. Out of the total of 963 patients, 781 died within the study period, that is, the overall mortality was 81.1%.

The underlying CODs for both the patients who survived for at least 1 year and their controls are presented in Table 1. One patient who died of late sequelae of ICH was excluded because it was not possible to find any matching controls. Cerebrovascular disease was the most significant cause of mortality amongst the ICH patients accounting for 37.2% of deaths as opposed to only 8.2% amongst the controls (*p*-value <0.05). This appeared to be entirely attributed to deaths resulting from the late effects of ICH and cases of recurrent ICH. "Late sequelae of ICH" is used as the underlying COD for those patients for whom the impairment due to the previous hemorrhage is seen as the primary underlying cause for the chain of events leading to their death. Pneumonia was the immediate COD for 71% of patients whose underlying COD was late sequelae of ICH.

TABLE 1 Underlying causes of death in patients with primary intracerebral hemorrhage who survived for at least 1 year after the event and their controls

	Patients	Proportion of deceased patients (%)	Controls	Proportion of deceased controls (%)	Disease codes
Cerebrovascular disease[a]	151	37.2	71	8.2	I60–I69, 430–438
Late effects of ICH[a]	52	12.8	0	0.0	I69.1
ICH (new-onset)	43	10.6	9	1.0	I61, 431
Ischaemic stroke	46	11.3	59	6.9	I63, I69.3, 4330A, 4331A, 4339A, 4340A, 4341A, 4349A
Other cerebrovascular disease	10	2.5	3	0.3	I60, I62, I64, I67–I68, 430, 432, 4360A, 437
Ischaemic heart disease	82	20.2	284	33.0	I20–I25, 410–414
Diabetes	7	1.7	9	1.0	E10–E14, 250
Pulmonary disease	19	4.7	38	4.4	J00–J99, 460–519
Dementia	51	12.6	113	13.1	F00–F01, F03, G30, 2900A, 2941A, 3310A, 4378A
Cancer	40	9.8	166	19.3	C00–C97, 140–208, 2386, 2733
Others	56	13.8	180	21.0	All remaining codes

Note: Disease codes are presented according to the ICD-10 and ICD-9 systems. $p < 0.0001$ for the difference between patients and controls.

Abbreviations: ICD, International Classification of Diseases; ICH, intracerebral hemorrhage.

[a]One patient was excluded due to the absence of controls.

TABLE 2 Baseline characteristics for long-term survivors 10 and 20 years after the event compared with patients who died during the first 3 months

	Dead at 3 months	Alive at 10 years	Alive at 20 years
Age at ICH onset (median, years)[a]	75.9	61.4	59.1
ICH volume (median, ml)[a]	39	10	12
On-admission GCS (median)[a]	7	15	15
Cardiac disease[a,b]	186 (57.4%)	52 (19.3%)	8 (20.0%)
Diabetes[a,b]	77 (23.8%)	22 (8.1%)	0 (0.0%)
Cancer[b]	29 (9.0%)	15 (5.5%)	2 (4.9%)
ICH location	–	–	–
Subcortical	60 (18.4%)	66 (24.3%)	13 (31.7%)
Deep[a]	53 (16.3%)	96 (35.3%)	15 (36.6%)
Pontine	17 (5.2%)	11 (4.0%)	1 (2.4%)
Cerebellar	29 (8.9%)	20 (7.4%)	5 (12.2%)
Multiple/several regions[a]	119 (36.5%)	46 (16.9%)	7 (17.1%)

Abbreviations: GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage.

[a]The differences between those who had died before 3 months and the long-term survivors (at least 10 years) were statistically significant (chi-squared/Fisher's exact test $p < 0.05$).

[b]Information on cardiac disease was missing for two patients, on diabetes for three patients and on cancer for four patients who were excluded.

No significant differences were observed between the patients and controls regarding ischaemic stroke mortality, even though primary ICH and ischaemic stroke share many common risk factors. The ICH survivors were also less likely to die from ischaemic heart disease (20.2% vs. 33.0%) or cancer (9.8% vs. 19.3%) than their controls.

Differences in hematoma locations and volumes and in age were assessed as well as some other baseline characteristics at ICH onset between those who died during the first 3 months after the index event, those who survived for 10 years or more after the hemorrhage and those who survived for 20 years or more (Table 2). These cut-off points for the table were chosen based on our data. It was observed that the patients in both long-term survivor groups were younger, had smaller hemorrhages and had less bleeding that affected multiple regions of the brain than did those who died during the first 3 months. Both groups of long-term survivors also had more hemorrhages located in a single deep region (the putamen, capnocaudal area or thalamus) than those who died earlier.

Upon fitting a Kaplan–Meier survival curve (Figure 1) to the complete follow-up data for 24.9 years it was observed that mortality was greatest during the first 3 months after the ICH and remained higher during the period from 3 months to 1 year than afterwards. A slight decrease in the slope at 12 years relative to the controls was also observed. Therefore Cox regression was performed separately for these four different intervals to meet the proportional hazards assumption. As seen in the Kaplan–Meier curve, the excess mortality in the patients was highest at the beginning and remained elevated after the first year until the end of our follow-up (Figure 1, Table 3).

DISCUSSION

Our findings demonstrate increased mortality from primary ICH even after a very long follow-up of over 20 years, and also a higher proportion of cerebrovascular mortality in 1-year survivors than in the controls. Comparison of the late survivors with those who died during the first 3 months after ICH shows low ICH volume and younger age at ICH onset to be predictive of survival even after 20 years.

The mortality rates over 10–13 years in previous studies have ranged from 76% to 82% [4, 6, 12–14], and Hansen et al. have shown that the mortality rate of ICH patients after 13 years of follow-up (77%) is distinctly higher than that of a control population (32%) [6], that is, the ICH survivors had substantial and persistent excess mortality. Fogelholm et al. reported an increased mortality rate only during the first 6 years after onset [15], a difference that could be due to the small number of late survivors or to how the late survivors were defined. Saloheimo et al. believed that long-term survival relative to the general population was affected by the functional status of the survivors at 3 months, their age and smoking status and the presence or absence of diabetes [7].

Our model is not very accurate in predicting increased mortality at the acute phase compared with controls (as only three controls died during this time), nor was this the purpose of the model. Instead, our goal was to provide an insight into the late mortality risk between the groups. To our knowledge, this is the first time a Kaplan–Meier survival curve and a regression model have been presented for the period from ICH onset to the end of a very long-term follow-up and compared with data for controls without ICH.

Cerebrovascular diseases were a leading COD in our data, with notable excess mortality due to recurrent ICH, which suggests that there is a serious weakness in the cerebrovascular system of ICH patients. This is unsurprising since most cases of ICH are attributable to cerebral amyloid angiopathy and hypertensive cerebral small vessel disease [16]. A recent study by Pasi et al. showed that signs of cerebral atrophy in magnetic resonance imaging were associated with higher long-term mortality [17]. This supports the idea of underlying cerebral pathology, which might also explain our finding of excess mortality after ICH persisting for decades after the index event.

Ischaemic heart disease and cancers were much less frequent as underlying CODs in the 1-year ICH survivors than they were in the controls, possibly as a result of the reciprocal high mortality due to the late effects of ICH, recurrent ICH and other cerebrovascular diseases. Hansen et al. have reported that 36% of deaths amongst 1-year ICH survivors are caused by cerebrovascular disease, 19% by ischaemic heart disease and 11% by cancer, and our

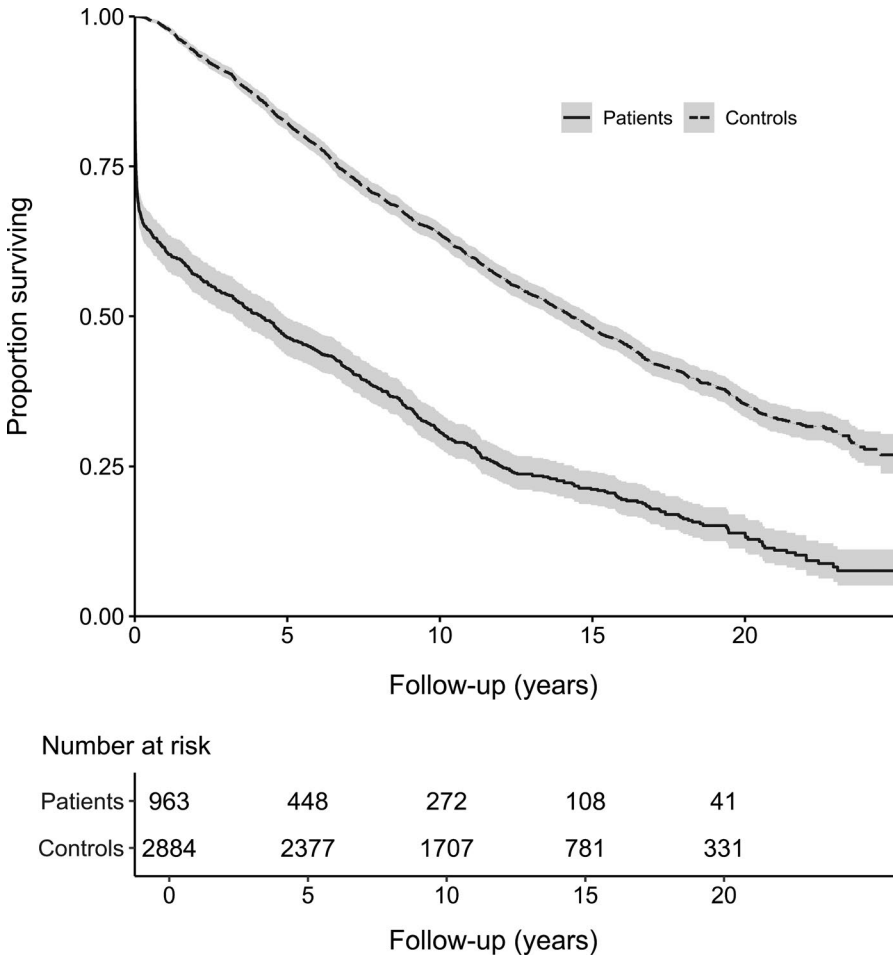

FIGURE 1 Kaplan–Meier survival curve (patients vs. controls). The gray area represents the 95% confidence intervals

TABLE 3 Cox regression model describing hazard ratios for mortality (patients vs. controls) adjusted for age and sex using a frailty model

Time interval	HR	95% CI	*p* value
0–3 months	453.1	145.29–1412.86	<0.001
3 months–1 year	6.0	4.00–8.90	<0.001
1 year–12 years	2.3	2.01–2.60	<0.001
12 years–24 years	2.1	1.58–2.74	<0.001

Note: Hazard ratios (HR) with 95% confidence intervals (95% CI) for mortality (patients vs. controls) according to a Cox regression model with shared frailty.

results are remarkably well in line with their findings [6]. It is therefore unlikely that there is any bias in our results that could have led to our observations. Casolla et al. found in their recent study that patients with ICH had a high risk for future ischaemic events [18]. Possibly for the aforementioned reason, a higher mortality due to ischaemic heart disease was not observed. In addition, Casolla et al. studied the incidence of ischaemic events whilst our study concentrated on CODs and therefore our findings are not directly comparable.

When the bleeding sites were compared between our long-term survivors and those who had died within 3 months of the index ICH, it was noticed that there was considerably less bleeding located in the deep regions of the brain in the early mortality group. This is likely to be due to the way the hemorrhages were classified: bleedings categorized as "deep" were limited to a single region, whereas all hemorrhages affecting more than one region were placed in the "multiple/several regions" category. Not surprisingly, the deep hemorrhages were smaller than those that were not limited to a single location (median volumes 7 ml and 33 ml respectively), so that the large, and therefore more severe, deep hemorrhages would have found their way into the latter category, which most likely explains our findings.

Our study has the advantage of involving a large population-based cohort of ICH patients. There are no private hospitals treating patients with acute stroke in Finland, and consequently our results are likely to apply well to the general population. In addition, the Causes of Death Register kept by Statistics Finland is a high-quality and reliable statistical source that covers all the relevant data concerning Finnish citizens. The WHO instructions are followed in recording the CODs and all the codes are verified before being entered in the register. The national personal identification numbers then allow reliable long-term follow-up procedures to be undertaken via Statistics Finland. To our knowledge, our follow-up is the longest one to date in an investigation into mortality after primary ICH.

The retrospective design is one limitation of our study. No information was available on comorbid diseases or changes in the patients' functional status after the follow-up visit. In addition, the autopsy rate in Finland was only 20% in 2017, and an autopsy is only performed when it is not obvious that the person has died on account of a known disease or condition. This might affect the accuracy of COD data in some cases [19]. Another limitation of this study concerns the absence of lifestyle risk factors and diseases affecting mortality, which are important in long-term follow-up situations (e.g. blood pressure, smoking and alcohol status, body mass index or diabetes information).

CONCLUSIONS

Very long-term ICH survivors have a constant excess mortality relative to sex- and age-matched controls even 10 years or more after the bleeding. The 3-month and 1-year mortality figures are highest, but mortality remained elevated in our cohort up to the end of the follow-up (24.9 years). Cerebrovascular disease was the most common COD category amongst these patients. Our findings indicate that patients with ICH have underlying cerebrovascular frailty, for example in the form of small vessel disease, but further research is still warranted. The long-term survivors were younger, had smaller hemorrhages and less bleeding that could have affected multiple regions of the brain.

DATA AVAILABILITY STATEMENT

For ethical reasons, the data are available on reasonable request.

CONFLICT OF INTEREST

The authors declare no conflict of interests.

AUTHOR CONTRIBUTIONS

Anna-Maija Lahti: Data curation (supporting); formal analysis (supporting); investigation (equal); project administration (equal); visualization (equal); writing—original draft (equal); writing—review and editing (equal). Mirva Anna Maria Nätynki: Investigation (equal); project administration (supporting); writing—original draft (equal); writing—review and editing (equal). Juha Huhtakangas: Data curation (equal); supervision (equal); validation (equal). Michaela Bode: Conceptualization (equal); formal analysis (supporting); supervision (supporting). Seppo Juvela: Conceptualization (equal); data curation (equal); formal analysis (supporting); methodology (equal); supervision (equal); validation (equal). Pasi Ohtonen: Data curation (equal); formal analysis (equal); software (equal). Sami Tetri: Conceptualization (equal); data curation (equal); project administration (lead); resources (equal); supervision (lead); validation (equal); writing—review and editing (supporting).

DISCLOSURE

This study was approved by the ethical committee of Oulu University Hospital and by Oulu Provincial Administration.

ORCID

Anna-Maija Lahti https://orcid.org/0000-0002-7688-8267
Mirva Nätynki https://orcid.org/0000-0002-6146-4648
Seppo Juvela https://orcid.org/0000-0003-4944-4983
Sami Tetri https://orcid.org/0000-0002-1387-9136

REFERENCES

1. Feigin VL, Forouzanfar MH, Krishnamurthi R, et al. Global and regional burden of stroke during 1990–2010: findings from the Global Burden of Disease Study 2010. *Lancet*. 2014;383:245-254.
2. Koivunen RJ, Tatlisumak T, Satopää J, Niemelä M, Putaala J. Intracerebral hemorrhage at young age: long-term prognosis. *Eur J Neurol*. 2015;22:1029-1037.
3. Banerjee G, Ambler G, Wilson D, et al. Baseline factors associated with early and late death in intracerebral haemorrhage survivors. *Eur J Neurol*. 2020;27:1257-1263.
4. Sacco S, Marini C, Toni D, Olivieri L, Carolei A. Incidence and 10-year survival of intracerebral hemorrhage in a population-based registry. *Stroke*. 2009;40:394-399.
5. Adoukonou T, Agbétou M, Bangbotché R, et al. Long-term mortality of stroke survivors in Parakou: 5-year follow-up. *J Stroke Cerebrovasc Dis*. 2020;29:104785.
6. Hansen BM, Nilsson OG, Anderson H, Norrving B, Säveland H, Lindgren A. Long term (13 years) prognosis after primary intracerebral haemorrhage: a prospective population based study of long term mortality, prognostic factors and causes of death. *J Neurol Neurosurg Psychiatry*. 2013;84:1150-1155.
7. Saloheimo P, Lapp T-M, Juvela S, Hillbom M. The impact of functional status at three months on longterm survival after spontaneous intracerebral hemorrhage. *Stroke*. 2006;37:487-491.
8. Whitworth JA, Chalmers J. World Health Organisation–International Society of Hypertension (WHO/ISH) hypertension guidelines. *Clin Exp Hypertens*. 2004;26:747-752.
9. Huhtakangas J, Tetri S, Juvela S, Saloheimo P, Bode MK, Hillbom M. Effect of increased warfarin use on warfarin-related cerebral hemorrhage: a longitudinal population-based study. *Stroke*. 2011;42:2431-2435.
10. Lahti AM, Huhtakangas J, Juvela S, Bode MK, Tetri S. Increased mortality after post-stroke epilepsy following primary intracerebral hemorrhage. *Epilepsy Res*. 2021;172:106586.
11. Vala U. Näin kirjoitan hyvän kuolintodistuksen (How to write a good death certificate)
. *Duodecim*. 2020;136:922-926.
12. Brønnum-Hansen H, Davidsen M, Thorvaldsen P. Long-term survival and causes of death after stroke. *Stroke*. 2001;32:2131-2136.
13. Flaherty ML, Haverbusch M, Sekar P, et al. Long-term mortality after intracerebral hemorrhage. *Neurology*. 2006;66:1182-1186.
14. McGuire AJ, Raikou M, Whittle I, et al. Long-term mortality, morbidity and hospital care following intracerebral hemorrhage: an 11-year cohort study. *Cerebrovasc Dis*. 2007;23:221-228.
15. Fogelholm R, Murros K, Rissanen A, et al. Long term survival after primary intracerebral haemorrhage: a retrospective population based study. *J Neurol Neurosurg Psychiatry*. 2005;76:1534-1538.
16. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. *Lancet Neurol*. 2010;9:689-701.
17. Pasi M, Casolla B, Kyheng M, et al. Long-term mortality in survivors of spontaneous intracerebral hemorrhage. *Int J Stroke*. 2020;16(4):448-455. https://doi.org/10.1177/1747493020954946

18. Casolla B, Moulin S, Kyheng M, et al. Five-year risk of major ischemic and hemorrhagic events after intracerebral hemorrhage. *Stroke*. 2019;50(5):1100-1107.
19. Official Statistics of Finland (OSF): Causes of death [e-publication]. ISSN=1799-5078. 2017, Quality Description: Causes of death 2017. Helsinki: Statistics Finland [accessed: May 21st 2021]. Access method: http://www.stat.fi/til/ksyyt/2017/ksyyt_2017_2018-12-17_laa_001_en.htm

How to cite this article: Lahti A-M, Nätynki M, Huhtakangas J, et al. Long-term survival after primary intracerebral hemorrhage: A population-based case–control study spanning a quarter of a century. *Eur J Neurol*. 2021;28:3663–3669. https://doi.org/10.1111/ene.14988