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Increased mortality after post-stroke epilepsy following primary intracerebral hemorrhage

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ABSTRACT

Objectives: This study aimed to determine whether post-stroke epilepsy (PSE) predicts mortality, and to describe the most prominent causes of death (COD) in a long-term follow-up after primary intracerebral hemorrhage (ICH).

Methods: We followed 3-month survivors of a population-based cohort of primary ICH patients in Northern Ostrobothnia, Finland, for a median of 8.8 years. Mortality and CODs were compared between those who developed PSE and those who did not. PSE was defined according to the ILAE guidelines. CODs were extracted from death certificates (Statistics Finland).

Results: Of 961 patients, 611 survived for 3 months. 409 (66.9%) had died by the end of the follow-up. Pneumonia was the only COD that was significantly more common among the patients with PSE (56% vs. 37% of deaths). In the multivariable models, PSE (hazard ratio [HR] 1.41, 95% confidence interval [CI] 1.06–1.87), age (HR 1.07, 95% CI 1.06–1.08), male sex (HR 1.35, 95% CI 1.09–1.67), dependency at 3 months (HR 1.52, 95% CI 1.24–1.88), non-subcortical ICH location (subcortical location HR 0.78, 95% CI 0.61−0.99), diabetes (HR 1.43, 95% CI 1.07–1.90) and cancer (HR 1.45, 95% CI 1.06–1.98) predicted death in the long-term follow-up.

Conclusion: PSE independently predicted higher late morality of ICH in our cohort. Pneumonia-related deaths were more common among the patients with PSE.

1. Introduction

The incidence of post-stroke epilepsy (PSE) is notable after stroke (2.6–6.4%) and even higher (4.3–13.5%) among patients with intracerebral hemorrhage (ICH) (Chen et al., 2012; Rossi et al., 2013; Biffi et al., 2016; Lahti et al., 2017). We already know that epilepsy in general is attributable to excess mortality, e.g. through the immediate effects of epileptic seizures (e.g. traumatic events, status epilepticus), but little is known of its effect on overall survival in this group of patients (Thurman et al., 2017). While PSE is known to be associated with an increased risk of death among younger patients, our overall current knowledge of this topic is inconclusive (Arntz et al., 2015; Zelano et al., 2016; Keezer et al., 2016; Hansen et al., 2017).

It has previously been observed that, in patients with PSE after any type of stroke, the most common underlying CODs are diseases of the circulatory system, and mortality from these causes is higher than in the general population (Hansen et al., 2017). However, since ICH is attributed to more severe disability among its survivals, this group of patients needs to be studied separately to properly establish the role of cardiovascular mortality after ICH and PSE.

Our main hypothesis for this study was that PSE increases the risk of mortality in long-term follow-up. We also aimed to determine the most common and relevant CODs in this population after a long-term follow-up focusing on cardiovascular disease, traumatic events and other likely CODs among the elderly.

Abbreviations: ICH, intracerebral hemorrhage; PSE, post-stroke epilepsy; COD, cause of death; AED, antiepileptic drug; GOS, Glasgow outcome scale.

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2. Methods

2.1. Study population

Our population-based base cohort consisted of all patients who presented with primary ICH in Northern Ostrobothnia, Finland, and were admitted to Oulu University Hospital (a catchment area population of 356,026–389,671 persons in 1993–2008) for treatment between January 1993 and January 2008. Patients who were admitted before October 1995 were collected prospectively, the rest were identified retrospectively from the hospital database by ICD codes (Saloheimo et al., 2006a,b). The hospital was and is the only hospital treating patients with suspected acute stroke in the area. Patients who died before reaching the hospital were identified from the Causes of Death Register kept by Statistics Finland. We only included patients with their first-ever primary ICH and who were residents in the area. Patients with brain tumors, aneurysms, vascular malformations, head trauma, hematological malignancies and/or hemophilia were excluded. To focus on long-term mortality, we excluded all patients who died within 3 months of the index ICH. We also excluded patients with prior diagnosis of epilepsy and patients with missing hospital records, resulting in a final sample of 611 patients, 119 of which were recruited prospectively (Fig. 1).

2.2. Definition of epilepsy

In accordance with the diagnostic guidelines of the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE) that were available at the time of data collection, PSE was defined as single or multiple clinical seizures occurring later than two weeks after admission (Fisher et al., 2005). The time frame for acute seizures vs. late-onset seizures after acute stroke was not addressed in this version of the guidelines, and we chose to use a cut-off point of two-weeks. The decision was based on the approach used in several other studies as well as our personal views (Cervoni et al., 1994; Bladin et al., 2000; Yang et al., 2009; Gilad et al., 2011).

All patients with PSE were prescribed continuous daily medication with antiepileptic drugs (AEDs). The incidence of seizures and the use of AEDs were double-checked from hospital records and the national register of prescribed medicines maintained by the Social Insurance Institution of Finland. This was to verify that no PSE diagnoses had been missed and to confirm that all patients with PSE had commenced their prescribed medication. The data on PSE cases up to December 31 st 2012 had been obtained for our previous study (Lahti et al., 2017). As we had observed that the occurrence of PSE remained at 0–1 new cases per year, we chose not to update our data since any error in our results would presumably have been minimal. The effect of different AEDs on mortality was not addressed because of insufficient sample size.

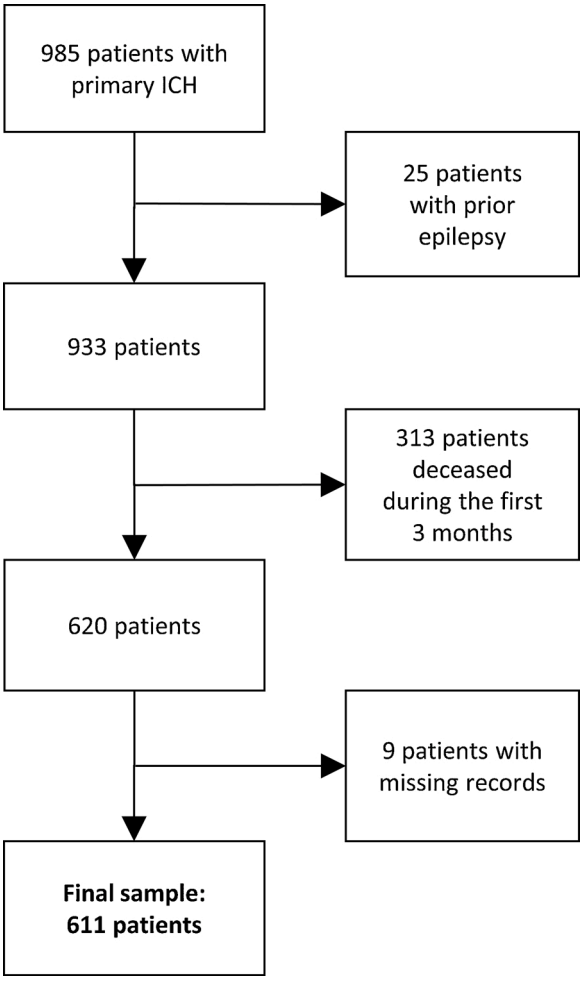

Fig. 1. Patient selection for the final sample.

2.3. Clinical data

Data on comorbidities, blood pressure and medication at the onset of ICH were obtained for every patient from our hospital records. Hypertension, diabetes and cardiac disease were conditions of interest. Hypertension was defined according to the World Health Organization/International Society of Hypertension (WHO/ISH) description (Whitworth and Chalmers, 2004). We also considered patients to have hypertension if they were receiving antihypertensive medication. Those who were taking oral antihyperglycemic medication and/or insulin were considered to have diabetes. Cardiac disease included myocardial infarction, coronary artery disease, heart failure and/or atrial fibrillation diagnosed prior to the index ICH.

2.4. Neuroradiological methods

Every patient had undergone a CT scan on admission to verify the diagnosis of ICH, and to assess the location and volume of the hemorrhage. The images were assessed by experienced neuroradiologists. A planimetric method and the ABC/2 method were used for measuring the volume of bleeding during the long course of the study (Huhtakangas et al., 2011). All hemorrhages that seemed to originate from the subcortical arteries but did not extend to the basal ganglia and only occurred at a single site simultaneously were categorized as subcortical. All subcortical hemorrhages were in contact with cortical regions. In the rare cases that a hemorrhage seemed to be restricted to the cortex only, it was categorized as subcortical. If a structural abnormality was deemed possible, but not seen in the first CT scan, follow-up scan by CT or MRI was performed 2–3 months after the first CT. Over 75% of the patients underwent follow-up imaging, which was performed at the discretion of the treating physician.

2.5. Mortality and outcome

Dates and causes of death were obtained up to December 31 st 2016 from the Causes of Death Register kept by Statistics Finland, in which the causes are registered as underlying, intermediate, immediate and contributing CODs according to the WHO guidelines. We used underlying CODs for our analyses whenever possible, since they are verified by Statistics Finland and corrected according to the WHO guidelines if necessary - e.g. if an inappropriate ICD-10 code is used. In Finland, pneumonia is never registered as an underlying COD according to WHO guidelines, and was therefore assessed from other COD types. The role of dementia in the COD event chain is often very challenging to assess, and to minimize error we included all COD types to evaluate how many

deaths were on some level attributable to this group of disease.

Those who showed good recovery (normal or minimal deficit) at discharge were assumed to have maintained their good condition for three months unless they had been re-admitted to hospital; our hospital is the only hospital treating stroke and PSE patients in its catchment area. The other survivors were examined at the outpatient clinic three months after the index ICH and their functional outcome was assessed with the Glasgow Outcome Scale (GOS) (Teasdale and Jennett, 1974).

2.6. Statistical methods

All statistical analyses of the data were performed using R version 3.4.3 and IBM (Armonk, NY) SPSS Statistics version 24.0 for Windows. We used the conventional $P < 0.05$ definition for statistical significance in all the models and tests. The Chi-squared test for categorical variables, Student's *t*-test for independent samples and the Mann-Whitney *U* test were used to assess possible correlations between baseline characteristics and death. Where applicable, we assessed the normality of a distribution by comparing the mean and median of the variable, and by a Q-Q plot. The COD correlations were assessed using the Chi-squared test and year-by-year mortality by life-table analysis and Kaplan-Meier survival curves.

We chose the Cox proportional hazards regression model for evaluating the risk factors for mortality. We assessed the proportional hazards assumption with Kaplan-Meier survival curves. First, we fitted univariable Cox models with death as the dependent variable for all the independent variables of interest. PSE occurrence was the primary variable of interest in this study. In addition, sex, age at ICH onset, subcortical ICH location, ICH volume, prior diabetes, cardiac disease, hypertension, extracranial cancer, and the GOS score at 3 months after the ICH were tested.

With five exceptions, all variables that showed a statistically significant correlation with mortality in the univariable models were fitted into multivariable models. PSE was not a risk factor for death at the chosen significance level in the univariate model ($P = 0.067$), but was included since it was the primary variable of interest. We also adjusted the model for sex, subcortical ICH location and ICH volume, since these have been attributed to increased risk of PSE (Haapaniemi et al., 2014; Neshige et al., 2015; Lahti et al., 2017). We chose to omit hypertension from the model to avoid collinearity with cardiac disease as a proxy for cardiovascular disease. Moreover, we only had data from before the onset of ICH, and the hypertension status (treated, untreated or no hypertension) might have had changed for many patients during the long follow-up. Hypertension was not a risk factor (HR 1.07–1.1, $P > 0.3$) in any of the fitted multivariable models when included. Even when addressed as a dichotomous variable (treated and untreated hypertension vs. no hypertension), hypertension did not have a statistically significant effect on mortality in univariable or multivariable models. All multivariable models were adjusted for sex and age. Four patients had missing data for one or more of the model variables and were excluded from the analysis. We chose the final model on the grounds of the inclusion of relevant variables and the goodness of fit as measured with the -2Log-likelihood statistic. A two-tailed *P*-value of 0.05 was considered significant in all analyses.

All Cox univariable and multivariable models were first fitted using the complete follow-up time. Based on the curve presented in Fig. 2, we estimated that the few patients with the longest follow-up time might have a disproportionate influence as outliers and cause error in the models. Therefore, we also fitted all models to a follow-up restricted to a maximum of 16 years (5844 days) as sensitivity analysis. There were no significant differences in hazard ratios, confidence intervals or *P*-values between models using the complete follow-up time and the time-restricted models. Only the models with the complete follow-up time are presented in this paper.

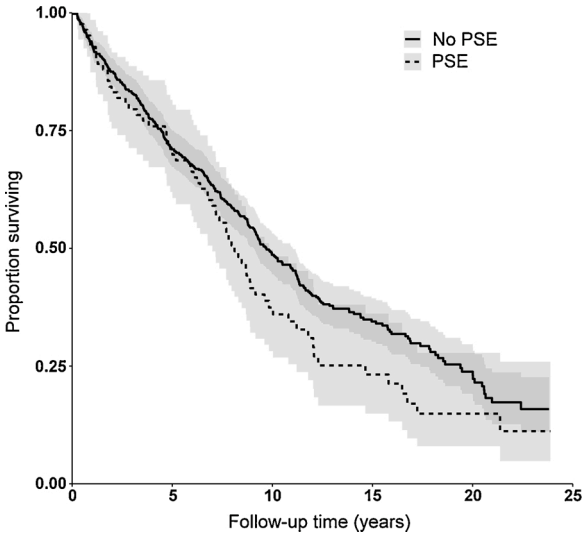

Fig. 2. Kaplan-Meier survival curves for patients with and without post-stroke epilepsy (PSE). The highlighted area represents the 95% confidence interval. Difference between the groups: $P = 0.066$.

2.7. Protocol approval

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

2.8. Data availability statement

The data is available on request due to privacy/ethical restrictions.

3. Results

In total, 409 of the 611 3-month survivors had died by the end of 2016 (66.9%); 42 (7%) had died after 1 year of follow-up, 177 (29%) after 5 years and 318 (52%) after 10 years. 64 of 83 patients with PSE died altogether. The median duration from PSE diagnosis to death was 5.0 years; the lower quartile was at 1.5 years and the upper quartile at 8.8 years. Follow-up times of individual patients ranged from 3 months to 23.9 years, with a median of 8.8 years. The person-time was 5520 person-years for the complete follow-up. The mean mortality rate was 7.4 per 100 persons per year, which remained relatively stable throughout the whole follow-up period.

Baseline characteristics for all the patients are shown in Table 1. The ICH was larger and more often subcortical in patients with PSE, and they suffered from hypertension less frequently. Those who died during the follow-up were more likely to have PSE ($P = 0.034$), to be dependent of a caretaker (severe or worse disability on the GOS at 3 months; $P = 0.001$), to have been older at the onset of ICH (mean age 70.6 years vs. 58.6 years; $P < 0.001$), to have a cardiovascular disease ($P < 0.001$) or diabetes ($P = 0.037$), and to have been diagnosed with extracranial cancer of any type prior to the index ICH ($P = 0.001$). Patients with PSE died slightly younger than those without PSE (mean age 75.1 years vs. 77.8 years respectively, $P = 0.03$).

A summary of the relevant CODs is presented in Table 2. The risk of death due to pneumonia was higher among patients with PSE than in those without ($P = 0.004$), but we did not detect any statistically significant correlation between a worse functional outcome (requiring daily assistance) at 3 months and a pneumonia-related death ($P = 0.140$) or PSE ($P = 0.71$). Dementia was the underlying COD for 44 patients (11% of all deaths), and a myocardial or cerebral ischemic event for 110 patients (27%), but there was no significant difference in mortality due to these causes between the patients with and without PSE. Falling was

Table 1
Baseline characteristics. ICH = intracerebral hemorrhage; PSE = post-stroke epilepsy.

	With PSE (% of column)	Without PSE (% of column)	All (% of column)	*P*-value
Sex				
Male	47 (57)	287 (54)	334 (55)	0.789
Female	36 (43)	241 (46)	277 (45)	
Mean age at ICH, years (interquartile range)	65.2 (60.6–72.9)	66.8 (59.0–76.0)	66.6 (59.1–75.2)	0.245
Median ICH volume, ml (interquartile range)	21 (7.0–37.8)	11 (4.0–25.0)	11 (5.0–28.0)	< 0.001
ICH location				
Subcortical	52 (63)	148 (28)	200 (33)	< 0.001
Non-subcortical	31 (37)	380 (72)	411 (67)	
Outcome at 3 months*				
Independent in daily life	53 (64)	346 (66)	399 (66)	0.810
Requires daily assistance	30 (36)	179 (34)	209 (34)	
Hypertension				
No hypertension	42 (51)	177 (33)	219 (36)	0.010
Treated hypertension	31 (37)	253 (48)	284 (46)	
Untreated hypertension	10 (12)	98 (19)	108 (18)	
Cardiovascular disease†				
Yes	32 (39)	149 (28)	181 (30)	0.076
No	51 (61)	378 (72)	429 (70)	
Diabetes				
Yes	13 (16)	73 (14)	86 (14)	0.781
No	70 (84)	455 (86)	525 (86)	
Cancer diagnosed prior to ICH				
Yes	8 (10)	49 (9)	57 (9)	1.000
No	75 (90)	479 (91)	554 (91)	

* Data were missing for three patients, who were excluded from the analyses requiring this information.
† Data missing for one patient, who was excluded from the analyses requiring this information.

Table 2
Most prominent causes of death separately for patients with and without post-stroke epilepsy (PSE). The categories include only underlying CODs, unless otherwise specified. Corresponding ICD-9 codes according to the National Institute of Health documentation were used for patients whose death occurred during the ICD-9 era. ICH = intracerebral hemorrhage.

	n with PSE (% of deaths with PSE)	n without PSE (% of deaths without PSE)	Total (% of all deaths)	ICD 10 -coding
Cerebrovascular disease	27 (42)	135 (39)	162 (40)	G45-G46, I60-I69
Late effects of ICH*	9 (14)	42 (12)	51 (12)	I69.1
Recurrent ICH	9 (14)	48 (14)	57 (14)	I61
Ischemic stroke	4 (6)	22 (6)	26 (6)	I63
Other	5 (8)	23 (7)	29 (7)	G45-G46, I60, I62, I64-I68
Ischemic heart disease	16 (25)	68 (20)	84 (21)	I20-I25
Falling	0 (0)	7 (2)	7 (2)	W00-W19
Cancer	6 (9)	31 (9)	37 (9)	C00-C97
Dementia (any COD)	8 (13)	69 (20)	77 (19)	F00-F03, G30
Pneumonia (any COD)†	36 (56)	127 (37)	163 (40)	J11.0, J12-J18, J69

* One patient died due to late effects of a stroke during the ICD-9 period, and since we could not determine the type of the underlying stroke, the patient was excluded from this part of the analysis.
† *P*-value < 0.05.

the underlying COD for 7 patients, none of whom had PSE. No patient with PSE died of traumatic causes, accidents or likely self-harm in our cohort. Epilepsy itself was the immediate or intermediate COD for 5 patients, and a contributing COD for an additional 13 patients.

Of all the variables tested, age, requiring daily assistance, non-subcortical hemorrhage, untreated hypertension and a diagnosis of diabetes, cardiac disease or cancer prior to the ICH predicted higher mortality in the univariable models. In the final multivariable model, greater age at ICH onset, male sex, PSE, the need for daily assistance at 3 months after ICH, diabetes and a prior cancer diagnosis all independently predicted higher mortality whereas cardiac disease or greater ICH volume did not (Table 3).

4. Discussion

We found that PSE was an independent predictor of mortality among 3-month survivors of primary ICH in our cohort. The effect was independent from ICH location and volume. Other risk factors for death were higher age, male sex, a poorer functional outcome at 3 months, non-subcortical (deep or multiple regions) ICH, diabetes and cancer prior to the index ICH. Patients with PSE were more likely to die of a pneumonia-related cause than those without PSE. Mortality due to cardiovascular events (excluding ICH sequelae) was not higher in patients with PSE.

There is little previous evidence available on the effect of PSE on mortality after ICH after several years of follow-up. In fact, a fairly recent study reported no significant differences in cumulative survival between patients with no seizures, early seizures and late seizures after ICH (Claessens et al., 2017). Interestingly, the authors of a nationwide Swedish stroke register study observed PSE to associate with higher mortality after ischemic stroke, although no statistical significance was observed in other stroke subtypes (Zelano et al., 2016). One prospective study described PSE as a risk factor for functional decline and incident dementia after ICH, but not for mortality (Biffi et al., 2016). It should be noted that the median of the follow-up ranged from 3.9 to 4.8 years in the aforementioned studies, whereas ours was notably longer: 8.8 years. Our results suggest that PSE might be a predictor for mortality, but the effect might become visible only after a longer course of time.

Only 19 patients (23%) with PSE were still alive at the end of our follow-up. 56 (67%) of patients with PSE were alive 2 years and 44 (53%) at 5 years after PSE diagnosis. The register study by Zelano et al. reported that after the first post-stroke seizure diagnosis, 66% and 45% of patients were alive at 2 and 5 years respectively (Zelano et al., 2016). The population was limited to 2-month stroke survivors, but incorporated bot ICH and ischemic stroke patients. Thus, our results are not directly comparable, but seem to be in line with these findings.

A poorer functional outcome at 3 months was an independent predictor of mortality in our sample. Unfortunately, we did not have any data on the further development of the patients' functional status.

Table 3
Univariable and multivariable Cox proportional hazards models. ICH = intracerebral hemorrhage.

		Univariable			Multivariable		
Variable	Unit/value	HR	95 % CI	*P*-value	HR	95 % CI	*P*-value
Age at ICH onset	Per 1 year	1.07	1.06 - 1.08	< 0.001	1.07	1.06 - 1.08	< 0.001
Sex	Male	1.06	0.87 - 1.28	0.588	1.41	1.15 - 1.73	0.001
ICH volume	Per 10 mL	1.028	0.98 - 1.08	0.231	1.03	0.98 - 1.09	0.270
Subcortical ICH location	Yes	1.07	0.87 - 1.31	0.515	0.78	0.61 - 0.99	0.049
Post-stroke epilepsy	Yes	1.28	0.98 - 1.68	0.067	1.46	1.10 - 1.93	0.009
Functional status at 3 months	Requires daily assistance	1.78	1.45 - 2.17	< 0.001	1.40	1.12 - 1.77	0.004
Cardiac disease	Yes	1.91	1.56 - 2.34	< 0.001	1.17	0.93 - 1.46	0.175
Diabetes	Yes	1.69	1.30 - 2.21	< 0.001	1.45	1.09 - 1.92	0.011
Cancer	Yes	1.87	1.39 - 2.53	< 0.001	1.38	1.01 - 1.87	0.042

However, a study by Claessens et al. reported that patients with late seizures are more likely to experience functional decline as well, so it is plausible that the effect of PSE on mortality will only become evident after a longer follow-up (Claessens et al., 2017). The clearer separation of the survival curves from the 6th year of follow-up onwards observable in Fig. 2 supports this possibility. The study in question also had a markedly stricter limit for early mortality: only patients who died during the first 7 days of the hemorrhage were excluded, as opposed to our limit of 3 months (Claessens et al., 2017). Thus our patient population focuses more on the long-term effects, with early mortality having a minimal confounding effect. Furthermore, patients with PSE were younger at baseline, but even so did not show a better outcome.

We found pneumonia to be a significant contributing factor in 40% of all the deaths. Pneumonia was a more common COD among the patients with PSE compared to those without. As noted above, we did not have any data on possible functional decline in our patients after the 3-month follow-up visit, but it would be a sensible explanation for our finding. Recent evidence suggests functional decline might occur later on (Biffi et al., 2016). Pneumonia-associated deaths are also known to be a common feature of epilepsy (Neligan and Shorvon, 2011; Keezer et al., 2016). Pneumonia was also an important risk factor for mortality in the earlier prospective phase of our work (Saloheimo et al., 2006b).

We observed only a few cases where PSE was documented as having contributed to the patient's death. However, our numbers are likely to be an underestimation, since epilepsy is not usually listed as an immediate or intermediate COD unless a witnessed seizure has occurred, a seizure is strongly suspected or the patient has no other comorbid disease likely to have started the chain of events leading to the individual's death. Since most death certificates are written without an autopsy (national autopsy rate 20% in 2017), there are uncertainties also regarding other disease groups (Official Statistics of Finland (OSF), 2017). E.g. mortality due to cardiovascular causes might be overestimated, since these are often chosen as the underlying COD by default if the person had a known cardiovascular condition and no evidence of an alternative cause was present. We also did not find a single death from external causes in the patients with PSE, although our small sample size might also affect this. Taking into account this possible bias, our overall cohort turned out to be too small to draw definite conclusions on the matter.

Our study has several strengths. First, our hospital is the only one treating acute stroke patients in its catchment area. Therefore, it is unlikely that we missed any cases of symptomatic ICH for which the patient sought treatment. Therefore, our sample represents well the 3-month survivor subset of a population-based cohort of primary ICH patients in Northern Ostrobothnia. Similarly, patients presenting with seizure-like symptoms in the area are either directly assessed and treated in, or referred to, this same hospital. Thus, we were equally unlikely to miss cases of PSE. Second, our median follow-up duration of 8.8 years is by far the longest one reported with this particular setting. Third, the data recorded in Finland's death register are highly consistent and reliable, since all death certificates are checked for errors and possible deviation from the WHO guidelines and revised if necessary.

There are also some evident limitations to our study. EEG was not routinely used in PSE diagnostics, and the diagnosis was made based on clinical observations of seizures in most cases. However, since all ICH patients have a structural lesion, EEG does not provide similar complementary benefit in PSE diagnosis as it does in other types of epilepsy - e.g. providing the basis for diagnosis in some patients with one seizure episode, no structural lesion and irritative EEG recording (Fisher et al., 2014). As mentioned earlier, we did not update the information on possible new cases of PSE after our previous study for the last years of this study, and thus might have missed some PSE cases with very long latency. However, based on our knowledge of PSE incidence in our sample, the effect is minimal (Lahti et al., 2017).

Regrettably, we did not have data on lifestyle factors — e.g. smoking — after ICH. We were also unable to record comorbidity and the development of functional status over time. We did have data on cardiac disease and diabetes before the occurrence of ICH, however, which could be extracted from the hospital records. Due to the chronic nature of these diseases, this gave us a solid proxy for the risk of future cerebrovascular and cardiovascular morbidity. We did not observe notable cardiovascular or traumatic mortality after PSE, possibly due to insufficient sample size to detect subtler differences.

5. Conclusions

PSE increased mortality in our cohort. In addition, higher age at ICH onset, male sex, poor functional status at 3 months, non-subcortical ICH location, diabetes and cancer predicted higher mortality during a long-term follow-up after primary ICH. Pneumonia was the only significantly more common COD among patients with PSE. We did not observe excess cardiovascular or traumatic mortality after PSE. Our follow-up was to our knowledge the longest one to date in this particular setting, allowing us to properly study the long-term effects. However, further research is needed to evaluate our findings.

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Declaration of Competing Interest

The authors declare that there is no conflict of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the

online version, at doi:https://doi.org/10.1016/j.eplepsyres.2021.106586.

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