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Case fatality of hospital-treated intracerebral hemorrhage in Finland – A nationwide population-based registry study

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ABSTRACT

Background: Case-fatality of Intracerebral hemorrhage (ICH) has been reported to have improved in some areas recently. Previous reports have shown that in Finland ICH survival has improved already from the 1980s. We aimed to investigate if this trend has continued and to assess possible predictors for death.
Methods: All patients hospitalized for ICH in Finland in 2004–2018 over 16 years of age were identified from a national registry. Survival was analyzed using the national causes of death registry with median follow-up of 5.1 years (max 15.0 years).
Results: 20,391 persons with ICH (53.5% men) were identified. Patient age increased during the study period with men being younger than women. One-month case-fatality was 28.4% and decreased during the study period. One-month and long-term case-fatality increased with patient age. Five-year survival was over 64% in patients <65 years of age and < 33% in those >75 years of age. In a multivariate analysis patient age, sex, comorbidity burden and diagnoses of atrial fibrillation, hypertension and coagulopathy were all independently associated with both 30-day and long-term survival. Survival was better in men than women at all time points but in the multivariate analysis male sex was associated with a slightly higher risk (hazard ratio 1.10, 95% CI 1.06–1.14) of death in the long-term follow-up. Compared to general population, excess case-fatality was high and highly age-dependent in both sexes.
Conclusions: Case-fatality of hospital-treated ICH has continued to decrease in Finland. Prognosis is strongly associated with patient age and more modestly with patient sex and comorbidities.

1. Introduction

Stroke causes the greatest loss of most age-standardised disability-adjusted life years (DALY) of all neurological disorders [1]. Intracerebral hemorrhage (ICH) is the deadliest form of stroke and its case-fatality remained unchanged for decades [2]. Some recent studies have shown decreasing short- and long-term case-fatality rates, but this trend is not uniform [3–6]. In Finland, short-term case fatality after ICH has consistently declined between 1983 and 2014 while incidence rates remained stable [7,8]. Furthermore, ten-year survival improved between 1999 and 2007, increasing median survival by one year [9]. More recent, long-term data with as complete coverage as possible are needed to verify these trends and to assess possible predictors for death short and long-term. Therefore, we conducted a nationwide registry study spanning 15 years until 2018.

2. Materials and methods

2.1. Data collection

All admissions to neurological, neurosurgical and intensive care wards with ICH (International Classification of Diseases, 10th revision, or ICD-10, codes I61.X) as the primary diagnosis between January 1, 2004-December 31, 2018 were identified from the Care Register for

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Health Care, a mandatory database for all public health care hospital discharges in Finland. All university and central hospitals ($N = 20$) that provide acute stroke care on mainland Finland were included in the search. In Finland, diagnostics of ICH is always verified by neuroimaging and treatment follows international guidelines. Only one admission per patient was included. Patients under 16 years of age, patients with concurrent diagnostic codes of rehabilitation (Z50, $N = 34$), cranial trauma (S06.X, $N = 322$) or previous ICH (I69.1, $N = 97$), and patients with missing survival data ($N = 98$) were excluded. Follow-up was defined as short-term (first 30 days) or long-term; all patients were followed-up until death or the end of the study period (Dec 31, 2018) whichever happened first, with a maximum follow-up being 15 years.

Fatality data were obtained from Statistics Finland, the national census entity. Relevant co-morbidities were identified using ICD-10 coding, and Charlson Comorbidity Index (CCI) score including AIDS/HIV, dementia, diabetes, chronic pulmonary disease, cerebrovascular disease, heart failure, hemi- or paraplegia, liver disease, malignancies, myocardial infarction, peptic ulcer disease, peripheral vascular disease, rheumatic disease, and renal disease was calculated as previously described [10]. Excess case-fatality after ICH was calculated by subtracting the baseline fatality in the corresponding age, sex, and calendar year specific group in the total Finnish population from case-fatality after ICH. This study was approved by the National Institute for Health and Welfare of Finland (THL, permission no: THL/2245/5.05.00/2019) and Statistics Finland (TK-53-484-20). This was a retrospective register study, and thus no ethical board review or informed consent was required, and the participants were not contacted. The legal basis for processing personal data is public interest and scientific research (EU General Data Protection Regulation 2016/679, Article 6(1)(e) and Article 9(2)(j); Data Protection Act, Section 4 and 6).

2.2. Statistical methods

Shapiro-Wilk and Kolmogorov-Smirnov tests were used to assess the distribution of continuous variables. Independent samples *t*-test was used to analyze age between sexes. Patient age trends were analyzed with linear correlation analysis. Survival was analyzed with the Kaplan-Meier method. Predictors of survival were analyzed with Cox regression. Multivariate Cox model included age, sex, CCI, atrial fibrillation, hypertension, coagulopathy (ICD-10 codes D65-D68, D69.1, D69.3-D69.6), and study era which all were deemed clinically relevant for modelling. Follow-up included 71,332 person-years with median duration of 5.1 years in survivors (interquartile range 2.2–9.1, max. 15.0 years). Statistical significance was inferred at P-value <0.05. Analyses were conducted using SPSS Statistics, version 26 and SAS, version 9.4.

3. Results

We identified 20,391 persons hospitalized because of ICH (53.5% men) (Table 1). Men were younger than women and mean patient age increased from 68.9 (standard deviation 13.1) years to 72.3 (standard deviation 13.1) years during the study period ($r = 0.080$, $p < 0.001$). Altogether 12,190 patients (79.3%) died during the follow-up. Case-fatality was 28.4% during the first 30 days but survival improved during the study period (Table 2). Half of these patients died during the first three days with no difference between sexes (Table 2). After the first month, survival decreased more slowly but steadily and was consistently poorer in women compared to men (Table 2). Both 30-day and long-term case fatality were higher the older the patient was (Table 2; Fig. 1). A multivariate Cox model showed that patient age, sex, CCI and diagnoses of atrial fibrillation, hypertension and coagulopathy were all independently associated with both 30-day and long-term survival (Table 2). Compared to general population, excess case-fatality incurred by ICH was high and increased with age in both sexes (Table 3).

Table 1
Baseline characteristics of the study cohort.

Variable	Total	Men	Women	*P*-value
	$N = 20{,}391$	$N = 10{,}891$	$N = 9500$	
Age, years (SD)	70.5 (13.1)	67.8 (12.8)	73.5 (12.8)	<0.0001
16–54	2390 (11.7%)	1551 (14.2%)	839 (8.8%)	
55–64	3550 (17.4%)	2385 (21.9%)	1165 (12.3%)	
65–75	5562 (27.3%)	3359 (30.8%)	2203 (23.2%)	
75–84	6341 (31.1%)	2819 (25.9%)	3522 (37.1%)	
≥ 85	2548 (12.5%)	777 (7.1%)	1771 (18.6%)	
CCI				<0.0001
0	8228 (40.4%)	4358 (40.0%)	3870 (40.7%)	
1	5418 (26.6%)	2740 (25.2%)	2678 (28.2%)	
2	3324 (16.3%)	1769 (16.2%)	1555 (16.4%)	
3	1681 (8.2%)	973 (8.9%)	708 (7.5%)	
≥ 4	1740 (8.5%)	1051 (9.7%)	689 (7.3%)	
Hypertension	9563 (46.9%)	4990 (45.8%)	4573 (48.1%)	0.001
Atrial fibrillation	4077 (20.0%)	2178 (20.0%)	1899 (20.0%)	0.988
Coagulopathy	185 (0.9%)	105 (1.0%)	80 (0.8%)	0.359
Study era				0.261
2004–2008	6603 (32.4%)	3581 (32.9%)	3022 (31.8%)	
2009–2013	6714 (32.9%)	3565 (32.7%)	3149 (33.2%)	
2014–2018	7074 (34.7%)	3745 (34.4%)	3329 (35.0%)	

CCI = Charlson comorbidity index score.

4. Discussion

This nationwide study showed that case fatality after hospital-treated intracerebral hemorrhage has continued to decline in Finland. The prognosis depended primarily on the patients' age but was also affected by sex and comorbidity.

In our study, less than 29% of the ICH patients died within the first 30 days, while three decades ago, half of ICH patients in Central Finland died within the first four weeks [11]. Of note, the study in Central Finland also included patients who died before reaching the hospital but since they only consisted 7.3% of their cohort, the relative decrease in short-term case-fatality is still over 30% between the current study and the old Central Finland cohort. Other previous reports have shown that the trend of declining ICH case-fatality has continued for over three decades in Finland [7,8]. Moreover, long-term survival after ICH increased between 1999 and 2007 [5] and our data showed that this trend has also continued.

Decreasing ICH case-fatality in Finland has been attributed to improvements in systems of stroke care [9]. Indeed, Finland has attained a high level of acute stroke care capability [12]. Previous data have shown that preceding functional disability predicts severe disability or death after ICH [13]. The improved physical and cognitive performance levels of the Finnish elderly and the generally improved life expectance therefore also contribute [14–16]. Considering that the number and population proportion of elderly people have increased in Finland but ICH admission rates have remained stable [8], it also seems that the Finnish elderly have become less prone to ICH in general. However, since these trends are surely not exclusively Finnish, it is unclear why short-term case-fatality has not decreased more uniformly internationally [2,3]. Regional factors concerning population characteristics, public health and care delivery systems may be implicated. Indeed, there was no apparent change over time in the 12-month case-fatality proportions in the four studies from the United Kingdom included in the recent meta-analysis whereas the three studies included from Italy suggested a slight decreasing trend [3]. Recent studies from the Netherlands and Dijon, France reported declining case fatality while data from Tromsø, Norway show no change [4–6]. Longitudinal data from different countries and in-depth analyses are apparently needed.

Our findings concerning predictors of death after ICH provided few surprises. Association between age and case-fatality is intuitive. In crude rates, women had worse survival. However, they were also older and in the multivariate analysis there was no difference between sexes in short-term case fatality and men were in a slightly higher risk of death in the

Table 2
Predictors of 30-day and long-term case-fatality.

Variable	30-day case-fatality			Long-term case-fatality[a]		
	Case-fatality	Univariate	Multivariate	Case-fatality	Univariate	Multivariate
		HR (95%CI)	HR (95%CI)		HR (95%CI)	HR (95%CI)
Sex						
Female	29.5%	Ref.	Ref.	81.0%	Ref.	Ref.
Male	27.5%	0.92 (0.87–0.97)	1.05 (0.99–1.11)	77.9%	0.90 (0.87–0.93)	1.10 (1.06–1.14)
Age, years						
16–54	16.4%	Ref.	Ref.	42.5%	Ref.	Ref.
55–64	20.2%	1.26 (1.11–1.43)	1.24 (1.10–1.41)	58.5%	1.44 (1.32–1.58)	1.41 (1.30–1.54)
65–75	24.8%	1.59 (1.42–1.77)	1.52 (1.36–1.70)	83.3%	2.33 (2.15–2.52)	2.21 (2.04–2.39)
75–84	33.8%	2.26 (2.03–2.52)	2.09 (1.88–2.34)	97.0%	3.90 (3.61–4.21)	3.59 (3.31–3.88)
≥ 85	42.5%	3.23 (2.88–3.62)	2.98 (2.64–3.36)	100%	6.02 (5.53–6.55)	5.50 (5.04–6.00)
CCI						
0	22.9%	Ref.	Ref.	67.1%	Ref.	Ref.
1	28.7%	1.29 (1.21–1.38)	1.22 (1.14–1.31)	76.6%	1.36 (1.30–1.42)	1.26 (1.20–1.32)
2	31.2%	1.42 (1.32–1.53)	1.31 (1.21–1.42)	85.3%	1.77 (1.68–1.86)	1.53 (1.45–1.62)
3	35.6%	1.68 (1.53–1.84)	1.50 (1.37–1.65)	91.1%	2.10 (1.97–2.24)	1.73 (1.62–1.85)
≥ 4	40.9%	1.98 (1.82–2.16)	1.84 (1.68–2.02)	97.3%	2.79 (2.62–2.97)	2.34 (2.19–2.50)
Hypertension						
No	30.0%	Ref.	Ref.	79.2%	Ref.	Ref.
Yes	26.6%	0.86 (0.82–0.91)	0.75 (0.71–0.79)	79.7%	0.95 (0.92–0.97)	0.77 (0.74–0.79)
Atrial fibrillation						
No	26.0%	Ref.	Ref.	76.8%	Ref.	Ref.
Yes	37.9%	1.57 (1.48–1.66)	1.26 (1.19–1.34)	90.9%	1.76 (1.68–1.83)	1.21 (1.15–1.26)
Coagulopathyy						
No	28.3%	Ref.	Ref.	74.2%	Ref.	Ref.
Yes	43.4%	1.73 (1.38–2.15)	1.74 (1.40–2.17)	76.3%	1.56 (1.30–1.87)	1.54 (1.29–1.85)
Study Era						
2004–2008	30.0%	Ref.	Ref.			
2009–2013	28.3%	0.97 (0.91–1.03)	0.90 (0.85–0.96)			
2014–2018	27.9%	0.95 (0.89–1.01)	0.82 (0.77–0.88)			

CCI = Charlson co-morbidity index score.
[a] Maximum follow-up 15.0 years (except 14.1 years for CCI and 12.3 years for coagulopathy).

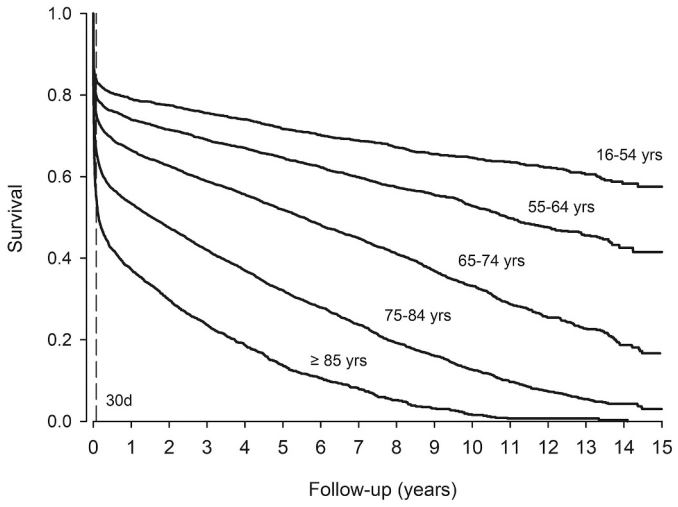

Fig. 1. Survival by age. Numbers of patients at risk are presented in Supplement Table.

Table 3
Fatality rates by age and sex in the general population (baseline) and the ICH patients.

	Patients	Baseline-fatality (%)		ICH case-fatality (%)		Excess fatality (%)	
Men	N	1-year	30-day	1-year	30-day	1-year	30-day
16–54	1551	0.38	0.03	20.86	16.12	20.48	16.09
55–64	2385	1.08	0.09	26.87	20.77	25.79	20.68
65–74	3359	2.27	0.19	35.30	25.70	33.03	25.51
75–84	2819	5.85	0.48	48.41	35.64	42.56	35.16
85-	777	14.51	1.19	65.97	48.42	51.46	47.23
Overall	10,891	1.98	0.16	36.95	27.45	34.97	27.29
	Patients	Baseline-fatality (%)		ICH case-fatality (%)		Excess fatality (%)	
Women	N	1-year	30-day	1-year	30-day	1-year	30-day
16–54	839	0.17	0.01	21.08	16.81	20.91	16.80
55–64	1165	0.48	0.04	24.35	19.16	23.87	19.12
65–74	2203	1.14	0.09	30.83	23.48	29.69	23.39
75–84	3522	3.73	0.31	45.06	32.38	41.33	32.07
85-	1771	11.18	0.92	61.34	43.85	50.16	42.93
Overall	9500	2.45	0.20	40.10	29.45	37.65	29.25

ICH, intracranial hemorrhage.

long term like they are in the general population [16]. Compared to general population, excess case-fatality rates of ICH patients were also slightly higher in men compared to women, but the relative difference was very small. Earlier studies have provided conflicting results on sex differences in case fatality after ICH [2,17,18]. These discrepancies may result from differences in ethnic backgrounds and baseline characteristics of the investigated populations, study inclusion criteria and sample sizes.

Our data showed that comorbidities were associated with a higher risk of death and a higher number of comorbidities was associated with a higher risk of death. Increasing CCI score has also previously been reported to be a predictor of severe disability or death within 3 months [13]. The only exception in our data was hypertension, a recorded diagnosis of which was associated with a smaller risk of death. This could be a chance finding, but patients without a hypertension diagnosis might also have more often had causes such as amyloid angiopathy or anticoagulation behind their ICH. Both of these become more common with increasing age so the increase in mean patient age we observed suggests that a shift in the case mix is possible towards more of these conditions as underlying causes of ICH. Moreover, decreases in blood pressure levels and in the proportion of smokers over recent decades in Finland have probably decreased the prevalence of hypertensive

vasculopathy [19].

Main strength of the study is the use of mandatory data with complete coverage in a nationwide setup as only public hospitals treat acute stroke in Finland. However, retrospective studies and administrative data have their inherent problems. Thus, we have no patient-level data on neuroimaging, medications, or functional outcome after ICH. Main discharge diagnosis codes in the Care Register for Health Care have been proven valid, but coding of co-diagnoses is not as complete [20].

In conclusion, short-term ICH case-fatality has continued to decline in Finland. Survival was strongly associated with patient age, and more modestly with sex and comorbidities.

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Disclosures

Jussi Sipilä has received honoraria (Merck, Pfizer, Sanofi), consultancy fees (Medaffcon), travel grants and congress sponsorship (Abbvie, Orion Pharma, Merck Serono, Novartis) and holds shares (Orion Corporation).

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Päivi Rautava has nothing to declare.

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Data availability

We are not permitted to disclose data to third parties. Requests to access the data set may be sent to Findata.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2021.117446.

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