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Mortality among patients treated for aneurysmal subarachnoid hemorrhage in Eastern Denmark 2017–2019

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Abstract

Objective The aim of the study was to investigate (1) the 30-day, 3-month, and 12-month cumulative mortalities for patients who underwent aneurysm occlusion, and (2) the causes of death, and (3) the potential risk factors for death.

Methods All patients who underwent surgical clipping or endovascular treatment of a ruptured aneurysm at Copenhagen University Hospital, during the period of January 1, 2017–December 31, 2019, were included and followed up for 12 months. Data regarding vital status, causes of death, comorbidities, treatment, and clinical presentations on admission was collected. The absolute mortality risk was estimated as a function of time with a 95% confidence interval. The associations between potential risk factors and death were estimated as odds ratios with 95% confidence intervals using logistic regression models.

Results A total of 317 patients were included. The overall cumulative mortalities after 30 days, 3 months, and 12 months were 10.7%, 12.9%, and 16.1%, respectively. The most common cause of death was severe primary hemorrhage (52.9%), followed by infections (15.7%) and rebleeding (11.8%). WFNS score > 3 and Fisher score > 3 on admission, preprocedural hydrocephalus, and preprocedural rebleeding were found significantly associated with higher risk of death.

Conclusions Considerable mortality was seen. Possible preventable causes accounted for approximately 22% of the deaths. The occurrence of both pre- and postprocedural rebleeding's indicates an opportunity of further improvement of the mortality by (1) further reduction of time from aSAH to aneurysm occlusion and (2) continuous efforts in improving methods of aneurysm occlusion.

Keywords aSAH · Mortality · WNFS score · Endovascular treatment · Surgical clipping

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Introduction

The incidence of aneurysmal subarachnoid hemorrhage (aSAH) is 6.3 (95% CI 4.9–8.1) per 100.000 person-years in Europe [13] and previous studies report in-hospital mortalities of 11–26.3% and 30-day mortality risks of 22–34% [1, 10, 16, 19, 24]. Generally, studies regarding mortality and causes of death after aSAH are few, and do not investigate long term follow-up derived from settings with incomplete registration and often of older date. The International Subarachnoid Aneurysm Trial (ISAT), a randomized controlled trial published in 2005, is one of the few well-documented studies with long-term follow-up. The study found 12-month mortalities of 9.9% after surgical clipping and 8.0% after endovascular treatment [23].

The mortality risk seems to have decreased over the past years due to rapid diagnosis and transfer to multidisciplinary subspecialized centers, improved endovascular techniques,

and improved intensive care measures [25, 33]. Parallel to this development, eligibility criteria for treatment became wider during the past decades; consequently, nearly all admitted patients are offered aneurysm occlusion today, regardless of older age or high Fisher scale score and high WFNS (World Federation of Neurological surgeons) score on admission [6, 34]. We believe these developments apply to most neurosurgical centers around the world and they warrant updated studies on mortality rates and risk factors in patients who are admitted after aSAH. Thus, availability of endovascular therapy has changed professional consensus of whom to offer treatment and how to judge treatment alternatives, while comprehensive observational population-based data to evaluate risks and benefits of the new paradigm are lacking.

According to previous studies, suggested risk factors for mortality include timing of surgery, hypertension, smoking, older age, admission to low specialized hospital, intraventricular hemorrhage, global cerebral ischemia, aneurysm size, high Fisher scale score, and high WFNS score, but the study designs and inclusion criteria are highly variable [1, 11, 19, 26, 27, 32, 34]. Today, the different methods of occlusion—surgical clipping and endovascular treatment—are viewed as complementary as they have different strengths and weaknesses, and large-scale observational studies and the randomized ISAT trial illustrate that the two methods need to be carefully balanced [4, 7, 10, 15, 23, 30].

Using the extensive information from the digital medical records covering all hospital admissions in the region, we constructed a population based cohort of patients treated for aSAH in Eastern Denmark (46% of the Danish population), Greenland, and the Faroe Islands during the period 2017–2019 with the specific aims of investigating (1) the 30-day, 3-month, and 12-month cumulative mortality risks, (2) to explore the causes of death, and (3) to identify risk factors for death. Moreover, we compared outcomes in the eastern danish population to Faroe Islands and Greenland to evaluate impact of a long distance to the tertiary center.

Methods

Study design and population

This study was a single-center, population-based cohort study.

Data sources

The digital medical records of all patients who underwent surgical clipping or endovascular treatment for aSAH were accessed through the digital surgical work board, which was used to identify all eligible patients during the study period.

The medical records contain detailed clinical information on all hospital admissions in the entire region of Eastern Denmark, including diagnoses, notes from physicians and other health care personnel, surgical and endovascular treatments, medication, and imaging studies. The digital medical records are continuously updated on vital status by automatic linkage with the Danish Civil Registration System [22]. The causes of death were retrieved from the medical records but were only recorded if the patient had a hospital contact in timely relation to the occurrence of death.

Study population

The study was carried out at Department of Neurosurgery, Copenhagen University Hospital, with a catchment area covering the Eastern part of Denmark (46% of the Danish population), Greenland, and the Faroe Islands. According to local treatment guidelines, all patients who did not have fixed and dilated pupils on admission, who did not have radiological signs of global cerebral ischemia or had limited life expectancy due to severe comorbidities were offered treatment, regardless of age.

Inclusion criteria

All patients 18 years of age or older, who underwent surgical clipping or endovascular procedures of any type due to a ruptured intracranial aneurysm in the period of January 1, 2017–December 31, 2019. Endovascular treatment included detachable coils, WEBs, and stents, alone or combined. Start of follow-up was the time of first surgical clipping or endovascular treatment procedure, regardless of closure was obtained. All patients were followed up for 12 months from the date of treatment.

Exclusion criteria

Patients who did not receive surgical or endovascular treatment of the aneurysm, patients with previous aSAH, and patients who underwent treatment of the aneurysm at another hospital. Surgical clipping and endovascular treatment were considered a potential risk factor, why patients who underwent both modalities as primary treatment was excluded. As we only included patients with fully accessible digital medical records throughout follow-up, patients who were not Danish citizens or patients admitted under discretion were excluded.

Treatment selection

After diagnosis of SAH, patients are given tranexamic acid and transferred to the tertiary center as soon as possible. Treatment allocation is decided in consensus between a

vascular microsurgeon and an endovascular surgeon. In general, admitted patients were omitted from treatment of the aneurysm only if death was considered immanent from hemorrhage or a comorbidity. Decisions on treatment strategy depended on site and configuration of the aneurysm, the presence of an intracerebral hematoma, patient age, comorbidities, and the neurological condition of the patient.

Data collection

The following variables were collected: sex, age at the time for surgical clipping or endovascular treatment of the aneurysm, hypertension, body mass index (*BMI*), smoking status (previous or current smoker), heart disease, lung disease, psychiatric disease, neurological disease, ongoing cancer, nephrological disease, alcohol consumption, and drug abuse.

The following variables concerning treatment were collected as follows: location of treated intracranial aneurysm, number of intracranial aneurysms, time from admission until surgical clipping, or endovascular treatment of the aneurysm, as well as Fisher scale score and WNFS score upon admission. If the patient was intubated before admission, the latest reported WNFS score before intubation was used.

Neurological complications before surgical clipping or endovascular securing of the aneurysm were recorded and included as follows: rebleeding, hydrocephalus, and vasospasm. Rebleeding was defined as present if verified by computed tomography scan of the brain (brain CT), or in case of strong clinical suspicion by a doctor as documented in the medical record. Hydrocephalus was defined as present, if verified by brain CT. Vasospasm was defined as arterial narrowing on computed tomographic angiography (CTA) obtained as work-up for neurological deterioration or decrease in level of consciousness. Vital status after the date of treatment of the aneurysm was recorded, as well as the cause of death.

Statistical analyses

Absolute mortality risks were estimated as a function of time for the entire study population with a 95% pointwise confidence interval. The association between potential risk factors and death was estimated as odds ratios with 95% confidence intervals using logistic regression models. The estimates were adjusted for age, sex, and method of aneurysm occlusion. A p-value < 0.05 was considered significant. When assessing risk factors for death, Bonferroni correction for multiple testing was applied within the unadjusted (16 tests, a p-value < 0.003 was considered significant) and adjusted tests (13 tests, a p-value < 0.004 was considered significant) separately. These analyses were performed in R version 4.0.3 [35]. Missing information on smoking and *BMI* was handled by (Substantive Model Compatible Fully

Conditional Specification) Multiple Imputation (using 200 imputations) with the R package SMCFCS [5].

Ethics

The study was approved by the Data Protection Board of Copenhagen University Hospital and exemption from individual patient consent was waived. The pseudo-anonymized data were stored in accordance with the Danish Data Protection Agency and the General Data Protection Regulations.

Results

Study population

During the study period, a total of 345 patients were admitted to Department of Neurosurgery, Copenhagen University Hospital with aSAH. A total of 17 patients were not eligible for further treatment of their aneurysm due to either fixed and dilated pupils or severe comorbidity rendering limited life expectancy. Four patients were excluded, because they were not Danish citizens and were transferred to their respective home countries after surgery. Six patients admitted under discretion were excluded, as their medical records were inaccessible under the overall ethical permissions. Finally, one patient who underwent both surgical and endovascular treatment was excluded; the patient was still alive 12 months after treatment, resulting in a total of 317 included patients.

Baseline characteristics

The baseline characteristics of the study population are shown in Table 1. The mean age was 58.5 years, and 211 patients (66.6%) were female. Twenty-three patients (7.3%) were transferred from Greenland or the Faroe Islands, which implied a markedly longer transfer time, up to several days. The distribution of comorbidities can be found in Table 1.

Treatment and preprocedural complications

In total, 180 patients (56.8%) underwent endovascular procedures, and 137 patients (43.2%) underwent surgical clipping of the aneurysm. The most common aneurysm location was the anterior circulation (265 patients). Four patients were treated for more than one aneurysm in the same procedure, as it was impossible to detect which aneurysm caused the SAH. The proportion of patients with a single aneurysm was 72.0%. Before surgical or endovascular procedures, 32 (10.1%) had rebled, 132 patients (41.6%) had developed hydrocephalus or needed ventricular drainage due to elevated ICP, and 15 (4.7%) were diagnosed with symptomatic

Table 1 Baseline characteristic and comorbidities present at the time of treatment for the study population of 317 patients with aneurysmal subarachnoid hemorrhage (aSAH) in Eastern Denmark 2017–2019

	Total $N = 317$ (%)
Mean age in years (range)	58.4 (23.6–86.6)
Sex	
Female	211/317 (66.6)
Male	106/317 (33.4)
Transferred from Greenland or The Faroe Island	23/317 (7.3)
Comorbidities	
Hypertension	99/317 (31.2)
Heart disease	21/317 (6.6)
Lung disease	29/317 (9.1)
Psychiatric disease	31/317 (9.8)
Nephrological disease	8/317 (2.5)
Ongoing cancer	9/317 (2.8)
Neurological disease	46/317 (14.5)
BMI > 30*	47/306 (15.3)
Smoking**	198/292 (67.8)
Alcohol consumption > 7/14 units per week#	37 /307 (12.1)
Drug abuse	6/317 (1.9)
Clinical characteristics on admission	
Fisher score	
1	16/317 (5.0)
2	67/317 (21.1)
3	78/317 (24.6)
4	156/317 (49.2)
WFNS score	
1	98/317 (30.9)
2	91/317 (28.7)
3	5/317 (1.6)
4	50/317 (15.8)
5	73/317 (23.0)
Location of aneurysm	
Anterior circulation	265/317 (83.6)
Posterior circulation	48/317 (15.1)
More than one location	4/317 (1.3)
Number of aneurysms	
1	228/317 (72.0)
>1	89/317 (28.0)
Time until surgical or interventional securing	
<24 h	282/317 (89.0)
>24 h	35/317 (11.0)
Treatment method	
Endovascular treatment	180/317 (56.8)
Surgical ligature or clipping	137/317 (43.2)
Complications before surgical or interventional securing	
Rebleeding	32/317 (10.1)
Hydrocephalus	133/317 (42.0)
Vasospasm	15/317 (4.7)

*Percentage of the observed. Missing data for 11 patients (3.5%)

**Percentage of the observed. Missing data for 25 patients (8.0%)

#Alcohol consumption above the limits set by the Danish Health Authorities of 7/14 units per week for women/men. Data were missing for 10 patients (3.2%)

vasospasm. Of the 32 patients with preprocedural rebleeding, 20 patients had preprocedural hydrocephalus, and two patients also had preprocedural vasospasm.

Mortality

The overall cumulative mortalities are presented in Fig. 1. Out of the 317 included patients, 51 (16.1%) patients died within 12 months after the date of first treatment procedure. The overall cumulative mortalities at the time points 30 days, 3 months, and 12 months were as follows: 10.7% (95% CI 7.3–14.1%), 12.9% (95% CI 9.2–16.6%), and 16.1% (95% CI 12.0–20.1%), respectively.

The mortalities of each of the studied years 2017–2019 were investigated separately to explore differences due to external factors, such as the COVID-19 pandemic. The pandemic could potentially affect patients admitted from late March throughout 2019 due to interlacement between their 12-month follow-up and the lockdown periods, the first being March 11, 2020. We observed a 12-month cumulative mortality for patients treated in 2019 of only 12.5% (95% CI 6.4–18.6), whereas the corresponding mortality risk for the years 2017 and 2018 was 17.9% (95% CI 10.6–25.2) and 18.2% (95% CI 10.6–25.8), respectively. The trend towards a lower mortality for patients treated in 2019 was not statistically significant, as presented in the supplementary Table 5.
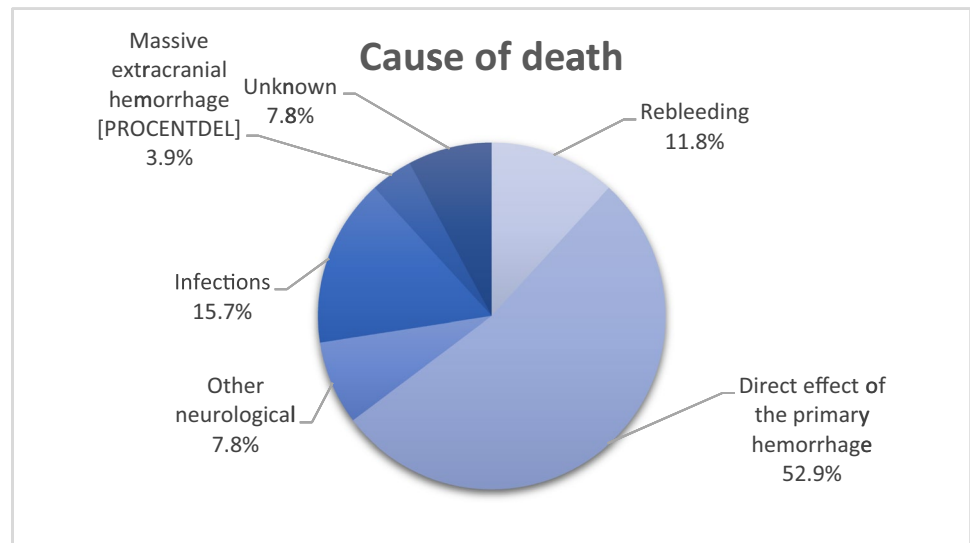
Causes of death

The causes of death are presented in Fig. 2, and the causes of death, according to temporal appearance of death during follow-up, are presented in Table 2. Twenty-seven patients (52.9% of those who died within 12 months) died because of severe primary aSAH, e.g., long-standing increased ICP and global ischemia despite intensive medical care and external ventricular drainage. All these deaths occurred within the first month. Deaths because of infections occurred at least one month after treatment. A total of eight patients died because of an infection; all these patients had bad clinical outcomes after treatment for aSAH with modified Rankin scale scores ≥ 3.

Eight patients (15.7% of those who died within 12 months) died from infections occurring either during the primary hospitalization or several months after discharge. Infections included pneumonia (five patients) and sepsis (three patients). Six patients (11.8% of those who died within 12 months) died from a rebleeding and five of these deaths occurred within the first month. Four of these patients had difficult-to-treat intracranial dissections. Two patients underwent endovascular treatment, one of them post stent-assisted coiling of a V4 dissection being on dual antiplatelet medication (DAP). The second patient with unclear anatomy underwent only partial treatment of a

Fig. 1 The survival probability with 95 % confidential interval for patients treated for aSAH in the period January 1, 2017 – December 31, 2019. Time is days from treatment after aSAH. Subjects count the number of patients alive at a given time
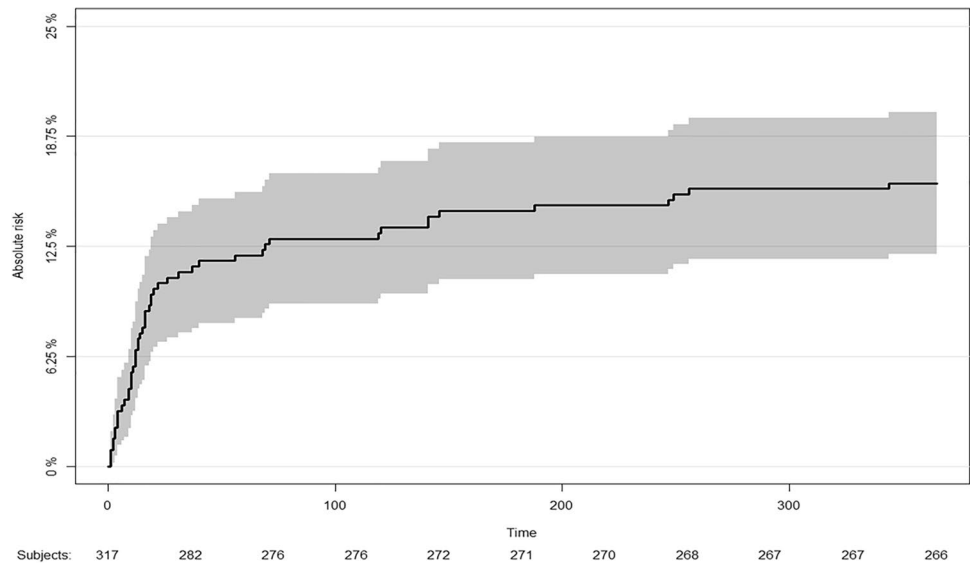
Fig. 2 The causes of death for patients treated for aSAH in the period January 1, 2017 – December 31, 2019. Other neurological disease, included acute subdural hemorrhage, brain death after multiple syncopal episodes and tumor-related hemorrhage. Infections included pneumonia, urinary tract infection and intracranial infection

Table 2 Causes of deaths according to temporal appearance after surgical or endovascular treatment of the aneurysm

	Total $N=51$ (%)	Within 1 month $N=34$ (%)	1–3 months $N=7$ (%)	3–12 months $N=10$ (%)
Severe primary hemorrhage	27 (100)	27 (100)	0 (0)	0 (0)
Aneurysmal rebleeding	6 (100)	5 (83.3)	1 (16.7)	0 (0)
Other neurological complications	4 (100)	1 (25.0)	2 (50.0)	1 (25.0)
Infection	8 (100)	0 (0)	3 (37.5)	5 (62.5)
Massive extracranial hemorrhage	2 (100)	1 (50.0)	1 (50.0)	0 (0)
Unknown	4 (100)	0 (0)	0 (0)	4 (100)

[*]Other neurological disease included acute subdural hemorrhage, sudden cardiac arrest preceded by neurological symptoms, and tumor-related hemorrhage

[**]Infection included pneumonia and sepsis

P1/P2 dissection due to hesitation to use DAP in the acute phase. Two other patients were not treated; one of them because of unfavorable anatomy and a high risk of associated complications, the other had a re-rupture of a severe supraclinoid ICA dissection during diagnostic angiography. A fifth patient with a PcomA aneurysm was treated with coiling and presented with a second bleeding in a different territory. The patient who underwent surgical clipping had a complex AcomA aneurysm with both A2 branches leaving the aneurysm dome. Four patients (7.8% of those who died within 12 months) died from other neurological diseases: One patient died from cardiac arrest preceded by neurological symptoms. It is suspected that the patient may have had an aneurysmal rebleeding or suffered Sudden Unexpected Death in Epilepsy, but this remains unknown. Another two patients died from severe acute traumatic subdural hemorrhage (unrelated to aneurysmal rebleeding), and one patient due to tumor-related hemorrhage. Two patients (3.9% of those who died within 12 months) died from hypovolemic shock, one due to spontaneous hemorrhage from a tracheotomy, and the other due to upper gastrointestinal hemorrhage. Four patients (7.8% of those who died within 12 months) died outside the hospital, and therefore, the causes of death were not registered in the patient records. All these deaths occurred at least 3 months after treatment.

The causes of death by year are presented in Table 3. The most common cause of death was severe primary hemorrhage in all three time periods. Death from infection was the second most common cause of death for patients included in 2017 and 2018.

Mortality risk factors

The 12-month cumulative mortality risks according to potential risk factors are presented in Table 4.

Unadjusted analysis

We observed significant associations between hypertension ($OR = 2.4$, 95% CI 1.3–4.4, $p = 0.006$), Fisher scale score > 3 ($OR = 4.1$, 95% CI 2.1–8.3, $p < 0.0001$), WFNS score > 3 ($OR = 5.5$, 95% CI 2.8–10.8, $p < 0.0001$), and death, but not between sex and death ($OR = 1.0$, 95% CI 0.5–1.9). Smoking was associated with a lower mortality risk ($OR = 0.4$, 95% CI 0.2–0.7, $p = 0.004$). We observed a trend towards higher mortality in patients with heart or respiratory disease, psychiatric disorders, neurological diseases, or $BMI > 30$, however not reaching statistical significance, possibly due to insufficient numbers of affected cases. The numbers of aSAH patients with nephrological disease, ongoing cancer, and alcohol or drug abuse were not sufficient to perform logistic regression analyses (< 5). Preprocedural rebleeding and hydrocephalus were associated with higher mortality in the unadjusted analyses ($OR = 3.8$, 95% CI 1.7–8.3, $p = 0.001$; $OR = 2.5$, 95% CI 1.3–4.6, $p = 0.004$, respectively), whereas multiple aneurysms, aneurysm location, and method of aneurysm occlusion were not associated with mortality risk. One could speculate if patients presenting with WFNS score > 3 were more prone to selection for endovascular treatment, but this was not the case according to a sub-analysis ($OR = 0.98$, 95% CI:0.8–1.2, $p = 0.91$).

Time from admission to intervention was not significantly associated with higher mortality ($OR = 2.0$ 95% CI 0.9–4.5, $p = 0.14$). The time from admission to intervention did not change during the study period. In 2017, 96/106 (91.5%) patients were treated within 24 h; the numbers from 2018 and 2019 are 83/99 (83.8%) and 103/112(91.9%) receptively.

Adjusted analysis

After adjustment for age, sex, and method of aneurysm occlusion, the following risk factors were significantly associated with a higher risk of death: high Fisher scale score ($OR = 4.7$, 95% CI 2.2–9.8, $p < 0.0001$), WNFS score > 3 ($OR = 6.2$, 95% CI 3.0–12.7, $p < 0.0001$), preprocedural rebleeding ($OR = 3.1$, 95% CI 1.3–7.2, $p = 0.008$), and preprocedural hydrocephalus ($OR = 2.1$, 95% CI 1.1–4.0, $p = 0.030$). After Bonferroni correction for multiple testing, preprocedural hydrocephalus was no longer significantly

Table 3 Causes of death by year of inclusion

	Total $N=51$ (%)	2017 N = 19 (%)	2018 N = 18 (%)	2019 N = 14 (%)
Severe primary hemorrhage	27/51(52.9)	10/19 (52.6)	7/18 (38.9)	10/14 (71.4)
Rebleeding	6/51 (11.8)	2/19 (10.5)	2/18 (11.1)	2/14 (14.3)
Other neurological	4/51 (7.8)	1/19 (5.3)	2/18 (11.1)	1/14 (7.1)
Infection	8/51 (15.7)	3/19 (15.8)	5/18 (27.8)	0/14 (0)
Massive extracranial hemorrhage	2/51 (3.9)	2 /19(10.5)	0/18 (0)	0/14 (0)
Unknown	4/51 (7.8)	1/19 (5.3)	2/18 (11.1)	1/14 (7.1)

*Other neurological disease, included acute subdural hemorrhage, brain death after multiple syncopal episodes and tumor-related hemorrhage

**Infection included pneumonia and sepsis

Table 4 Mortality risk presented as odds ratios (OR), according to potential risk factors. Both unadjusted and adjusted estimated are presented

	Total N = 317 (%)	Survivors N = 266 (%)	Non-survivors N = 51(%)	OR (95%CI)	p-value	Adjusted OR (95% CI)*	Adjusted p-value *
Mean age years (range)	58.4 (23.6–86.6)	56.8 (23.6–86.6)	66.8 (33.8–86.6)	1.1 (1.0–1.1)	< 0.0001	-	-
Sex							
Female	211 (100)	177 (83.9)	34 (16.1)	1.0 (0.5–1.9)	1.0	-	-
Male	106 (100)	89 (84.0)	17 (16.0)	1 (ref.)	-	-	-
Transferred from							
Hospital in Eastern Denmark	294 (100)	248 (84.4)	46 (15.6)	1 (ref.)	-	1 (ref.)	-
Hospital in Greenland or The Faroe Islands	23 (100)	18 (78.3)	5 (21.7)	1.5 (0.5–4.2)	0.4	2.2 (0.7–6.7)	0.17
Comorbidities							
Hypertension							
No	218 (100)	192 (88.1)	26 (11.9)	1 (ref.)	-	1 (ref.)	-
Yes	99 (100)	74 (74.7)	25 (25.3)	2.4 (1.3–4.4)	0.006	1.6 (0.8–3.1)	0.15
Heart and/or respiratory disease							
No	270 (100)	231 (85.6)	39 (14.4)	1 (ref.)	-	1 (ref.)	-
Yes	47 (100)	35 (25.3)	12 (74.5)	2.0 (1.0–4.2)	0.06	1.3 (0.6–2.8)	0.55
Psychiatric and/or neurological disease							
No	246 (100)	207 (84.1)	39 (15.9)	1 (ref.)	-	1 (ref.)	-
Yes	71 (100)	59 (83.1)	12 (16.9)	1.1 (0.5–2.2)	0.8	1.2 (0.6–2.6)	0.60
Nephrological disease							
No	309 (100)	259 (83.8)	50 (16.2)	NA	-	NA	-
Yes	8 (100)	7 (87.5)	1 (12.5)	NA	-	NA	-
Ongoing cancer							
No	308 (100)	261(84.7)	47 (15.3)	NA	-	NA	-
Yes	9 (100)	5 (55.6)	4 (44.4)	NA	-	NA	-
Body mass index							
< 30	259 (100)	219 (84.5)	40 (15.4)	1 (ref.)	-	1 (ref.)	-
> 30	47 (100)	39 (83.0)	8 (17.0)	1.1 (0.5–2.6)	0.8	1.3 (0.6–3.2)	0.51
Unknown	11 (100)	8 (72.7)	3 (27.3)				
Smoking							
No	94 (100)	74 (78.7)	20 (21.3)	1 (ref.)	-	1 (ref.)	-
Yes	198 (100)	180 (90.9)	18 (9.1)	0.4 (0.2–0.7)	0.004	0.5 (0.2–1.0)	0.05
Unknown	25 (100)	12 (48.0)	13 (52.0)				
Alcohol and/or drug abuse							
No	264 (100)	219 (83.0)	45 (17.0)	NA	-	NA	-
Yes	43(100)	39 (90.7)	4 (9.3)	NA	-	NA	-
Unknown	10 (100)	8 (80.0)	2 (20.0)				
Clinical status on admission							
Fisher scale score							
Low: 1–3	161 (100)	149 (92.5)	12 (7.5)	1 (ref.)	-	1 (ref.)	-
High: 4	156 (100)	117 (75.0)	39 (25.0)	4.1 (2.1–8.3)	< 0.0001	4.7 (2.2–9.8)	< 0.0001
WFNS score							
Low: 1–3	194 (100)	180 (92.8)	14 (7.2)	1 (ref.)	-	1 (ref.)	-
High: 4–5	123 (100)	86 (69.9)	37 (30.1)	5.5 (2.8–10.8)	< 0.0001	6.2 (3.0–12.7)	< 0.0001

Table 4 (continued)

	Total $N = 317$ (%)	Survivors $N = 266$ (%)	Non-survivors $N = 51$ (%)	OR (95%CI)	*p*-value	Adjusted OR (95% CI)*	Adjusted *p*-value *
Location of the ruptured aneurysm							
Anterior circulation	265 (100)	225 (84.9)	40 (15.1)	1 (ref.)	-	1 (ref.)	-
Posterior circulation	48 (100)	37 (77.1)	11 (22.9)	1.7 (0.8–3.5)	0.20	1.3 (0.6–3.1)	0.49
More than one location	4 (100)	4 (100)	0 (0)	NA	-	NA	-
Number of aneurysms							
1	228 (100)	194 (85.1)	34 (14.9)	1 (ref.)	-	1 (ref.)	-
>1	89 (100)	72 (80.9)	17 (19.1)	1.3 (0.7–2.6)	0.40	1.5 (0.7–2.9)	0.28
Time until intervention							
<24 h	282 (100)	240 (85.1)	42 (14.9)	1 (ref.)	-	1 (ref.)	-
>24 h	35 (100)	26 (74.3)	9 (25.7)	2.0 (0.9–4.5)	0.14	2.0 (0.8–4.8)	0.14
Treatment method							
Endovascular treatment	180 (100)	146 (81.1)	34 (18.9)	1 (ref.)	-	-	-
Surgical ligature or clipping	137 (100)	120 (87.6)	17 (12.4)	0.6 (0.3–1.1)	0.12	-	-
Complications before treatment							
Rebleeding							
No	285 (100)	246 (86.3)	39 (13.7)	1 (ref.)	-	1 (ref.)	-
Yes	32 (100)	20 (62.5)	12 (37.5)	3.8 (1.7–8.4)	0.001	3.1 (1.3–7.2)	0.008
Hydrocephalus							
No	184 (100)	164 (89.1)	20 (10.9)	1 (ref.)	-	1 (ref.)	-
Yes	133 (100)	102 (76.7)	31 (23.3)	2.5 (1.3–4.6)	0.004	2.1 (1.1–4.0)	0.030
Vasospasms							
No	302 (100)	252 (83.4)	50 (16.6)	NA	-	NA	-
Yes	15 (100)	14 (93.3)	1 (6.7)	NA	-	NA	-

*Adjusted for sex, age, and method of aneurysm occlusion

NA, not applicable due to low number of patients

associated with the risk of death, however this does not rule out an association.

Mortality among patients from Greenland and the Faroe Islands

Out of the 317 included patients, 23 patients were transferred from a local hospital in Greenland or The Faroe Islands. Depending on weather conditions, the transfer time from these distant locations may be up to several days, whereas the transfer time in Eastern Denmark is only a few hours. In both the unadjusted and the adjusted analysis, we observed a higher risk of death among patients from Greenland or The Faroe Islands compared to patients from Denmark, however

not significant: OR adjusted for sex, age, and method of aneurysm treatment was 2.2 (95% CI 0.7–6.7, *p* = 0.17).

Another issue is the longer transfer times may imply that patients from Greenland and The Faroe Islands are more prone to clinical deterioration before aneurysm treatment. Therefore, a sub-analysis was conducted with further adjustment for Fisher scale and WFNS scores. As presented in Table 6 in the supplementary, this risk of death remained high compared to patients from Eastern Denmark (*OR* = 2.07, 95% CI 0.6–7.7), even though it did not reach level of significance.

The WFNS score at admission did not differ between patients from Greenland or the Faroe Islands and patients from Eastern Denmark (*OR* = 0.67, 95% CI 0.3–1.7, *p* = 0.51).

Discussion

In this cohort study encompassing unselected patients who underwent surgical treatment or endovascular procedures due to a ruptured intracranial aneurysm in Eastern Denmark, Greenland, and the Faroe Islands during the period 2017–2019 and with complete 12-month follow-up, we found postprocedural cumulative mortalities of 10.7% within 30 days, 12.9% within 3 months, and 16.1% within 12 months. From a broad range of potential risk factors among baseline characteristics, comorbidities, and preprocedural complications, the following risk factors were found to be significantly associated with increased risk of death in the adjusted analyses: WFNS score > 3, Fisher scale score > 3, preprocedural rebleeding, and preprocedural hydrocephalus.

Mortality risk

Mortalities reported by other observational studies are comparable to our finding of a cumulative mortality of 10.7% within 30 days after aneurysm occlusion, despite our wide treatment criteria including high Fisher and WFNS scores, which are prognostically unfavorable. Deutsch et al. (2018) reported in-hospital mortalities of 11.4% after surgical clipping, and 12.2% after endovascular treatment, but longitudinal results were not reported[3]. Ikawa et al. (2020) likewise reported in-hospital mortalities of 7.1% and 12.2% after surgical clipping and endovascular treatment of the aneurysm, respectively [15]. A multicenter study from the UK and Ireland published in 2009, which included 2,198 patients treated for a ruptured intracranial aneurysm, reported an in-hospital mortality of 7.0% and a 30-day mortality of 8.1% but did not report long-term mortalities [18].

As opposed to most previous studies, we were able to report complete 12-month follow-up on all patients and observed 12-month postprocedural cumulative mortalities of 12.4% among patients who underwent surgical clipping and 18.9% among patients who underwent endovascular procedures ($p = 0.12$). A 12-month follow-up was important, since ten of the 51 case fatalities (20%) in our study occurred 3–12 months after aneurysm occlusion. Notably, the International Subarachnoid Aneurysm Trial (ISAT), a randomized controlled trial published in 2005, found lower 12-month mortalities than ours: 9.9%, 95% CI 8.2–11.9 after surgical clipping and 8.0%, 95% CI 6.4–9 after endovascular treatment [23]. These lower mortality rates reflect the selective inclusion criteria in the ISAT trial as only patients eligible for both surgical clipping and endovascular treatment were included. Furthermore, the patients in

the ISAT trial were in better clinical condition at inclusion (88% were WFNS 1–2 versus 60% in our study). According to our results and previous findings, WFNS score > 3 is strongly associated with a higher mortality risk.

A total of 88.9% of the patients in our study underwent surgical treatment or endovascular procedures within 24 h after admission; time from admission to treatment did not change during follow-up in this study. Unfortunately, we did not have sufficient information of the time spans from aSAH to admission. The short distance across Denmark allows admission at the neurointensive care unit at Copenhagen University Hospital within a few hours after diagnosis of the aSAH at the local hospitals, whereas the transfer time for patients from Greenland and the Faroe Islands may be up to several days in case of bad weather conditions. This obviously enhances the risk of preprocedural deterioration due to rebleeding, hydrocephalus, brain edema, and ischemia. Patients from Greenland or the Faroe Islands have a trend towards lower WFNS score at admission compared to patients from Eastern Denmark ($OR = 0.67$, 95% CI 0.3–1.7), even though it is not statical significant. This could potentially indicate a selection of which patients were found to be able to survive the long transfer time before final treatment. The mortality risk for this subgroup of 23 patients ($OR = 2.07$, 95% CI 0.6–7.7) points towards an association between a long transfer time and increased mortality. Rapid transfer to a tertiary center and early occlusion of the aneurysm was repeatedly shown to improve survival so long transfer times remain a preventable source of deterioration [8, 17, 18, 29, 32]. The transfer from Greenland and The Faroe Island represents a geological obstacle which may be optimized if urgent transport is prioritized.

Causes of death

Our finding of severe primary aSAH as the leading cause of death is in line with the literature [1, 16, 19]. The 12-month follow-up revealed that the second leading cause of death was infection, which occurred after discharge from the neurosurgical setting and throughout follow-up, e.g., information from all local hospitals in Eastern Denmark is available in the digital medical records. Of the eight patients who died from infection, five infections were hospital acquired and included aspirations pneumonia, other pneumonia, and urosepsis. Abulhasan et al. found that 15.8% of all patients treated for aSAH developed a health care associated infection (HAI) [2].

The third leading cause was postprocedural rebleeding, which occurred in six patients (11.8% of the deaths). A Cochrane Review from 2018 encompassing 2,458 patients reports that the risk of postprocedural rebleeding was higher after endovascular treatment compared to surgical clipping [21] and the ISAT trial reported 2 rebleeds in 1,063 patients

allocated to endovascular treatment [23]. We were unable to perform comparative analyses between treatment modalities due to the low number of patients with a second rebleeding during the procedure or postprocedural rebleeding, and, as mentioned above, endovascular treatment was not found to be a risk factor for death. Furthermore, granular analyses of these patients revealed that none of these cases was regular saccular aneurysms. Four occurred in dissecting aneurysms which treatment can be problematic as it may involve DAP, one patient rebled at another site than the treated aneurysm, and another aneurysm incorporated the entire ACOM complex making surgical clipping technically challenging. Thus, our findings suggest that the risk of rebleeding may be slightly higher in a "real-world" context an unselected study population.

Notably, none of the deaths was attributable to vasospasm alone but vasospasms may have been a contributing factor, particularly among patients with high Fisher scale and WFNS scores. This finding agrees with generally decreased mortality from symptomatic vasospasm, probably due to attentive intensive care and early endovascular treatment [3, 12].

Deaths from infections or rebleeding could be considered preventable. However, infections may also be a terminal event for patients with a bad clinical outcome. Most rebleeding were caused by complex intercranial dissections and therefore difficult to prevent.

Risk factors

A poor clinical condition and severe aSAH on admission, measured as WFNS score > 3 and Fisher scale score > 3, were corroborated as risk factors for death in agreement with other studies [1, 23]. We also found preprocedural rebleeding was a risk factor for mortality, which is in line with findings in other studies [1, 23, 31], in one of which Stienen et al. reported that rebleeding (not specified if pre- or postprocedural) was a strong independent predictor of in-hospital mortality with a case fatality rate of 62% [31]. Preprocedural hydrocephalus is often a consequence of intraventricular hemorrhage in aSAH patients and may lead to rapid deterioration due to elevated ICP and global brain ischemia, a risk factor reported by other studies as well [6, 16, 27].

Surprisingly, we found that smoking was associated with lower mortality risk, nevertheless Slettebø et al. and Hammer et al. reported similar findings [14, 28]. They both found that the 30-day mortality among aSAH patients admitted to a hospital was lower for smokers than non-smokers, but smokers were younger, in poorer clinical condition, had more comorbidities, and were more likely to have multiple aneurysms [14, 28]. The fact that these two studies, and our study, only included patients who were admitted to

the hospital with aSAH, and not patients who died prior to admittance and treatment, may reflect patient selection in terms of smoking status. This notion was investigated by Lindbohm et al., who also found smoking (and hypertension) to be protective factors for death among admitted patients with aSAH [20]. But if sudden-death aSAH patients were included in the analyses as well, the authors found patients with hypertension and active smoking status had a higher mortality risk [20]. A nationwide American cohort study from 2018 included 5,784 patients who underwent surgical or endovascular treatment for aSAH and no significant differences in mortality risk among smokers and non-smokers was reported [9].

Limitations and strengths

The limitations of this study include the single-center retrospective design. However, our center covers 46% of the Danish population, a region represented with both urban and rural areas. The retrospective design resulted in partly missing information on smoking status, alcohol consumption, and *BMI*.

Four patients who underwent treatment were excluded for further analysis because they were not Danish citizens and therefore did not meet the inclusion criteria. A total of six patients were admitted under discretion. Due to the ethical approval of this study, it was not possible to access their medical clinical flies, why they were excluded and are missing in the study population. Finally, four patients died outside the hospital and the causes of deaths was therefore missing in the medical records.

In this population, clipping and colling were selected to obtain best clinical outcome for the patient. Thus, patients who underwent clipping or colling represent different subpopulations and do not allow comparison of treatment modalities or technical outcomes.

The strength of this study was that comprehensive, accurate clinical information on all patients was retrievable from the digital medical records for an entire region covering nearly half of the Danish population and no patients were lost to follow-up. Treatment of ruptured aneurysms is centralized with a high degree of interlacement in treatment along international standards. Thus, our findings are population-based and generalizable.

Conclusions

We observed a considerable mortality risk throughout the follow-up time of 12 months, however comparable to other observational studies despite our wide patient eligibility criteria for aneurysm treatment. The main cause of death was severe primary hemorrhage, but possible preventable causes

such as infections and postprocedural rebleeding's accounted for approximately 22% of the deaths. The occurrence of both pre- and postprocedural rebleeding's indicates an opportunity of further improvement of the mortality by (1) further reduction of time from aSAH to aneurysm occlusion and (2) continuous efforts in improving methods of aneurysm occlusion.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00701-022-05303-w.

Declarations

Ethics approval and consent to participate This article does not contain any studies with human participants performed by any of the authors. The study was approved by the Data Protection Board of Copenhagen University Hospital and exemption from individual patient consent was waived.

Competing interests The authors declare no competing interests.

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