Outcome of aneurysmal subarachnoid hemorrhage in a population-based cohort: Retrospective registry study.

Mathilde V. Iversen, MS,[1] Tor Ingebrigtsen, MD, PhD,[1,2] Jon A. Totland, MD,[2] Roar Kloster, MD,[1,2] Jørgen Isaksen, MD, PhD[1,2]

[1]Department of Clinical Medicine, UiT Arctic University of Norway; [2]Department of Neurosurgery, University Hospital of North Norway

Corresponding Author's name and current institution:

Prof. Tor Ingebrigtsen,

UiT the Arctic University of Norway

University Hospital of North Norway

Corresponding Author's Email address: tor.ingebrigtsen@unn.no

Corresponding Author's address: Department of Neurosurgery, ophthalmology and otorhinolaryngology

University Hospital of North Norway

Mail box 100

9038 Tromsø, Norway

Cover title:	Outcome of subarachnoid hemorrhage: Registry study
Number of tables:	3
Number of figures:	2
Word count:	5887

Structured abstract

Background: Studies of aneurysmal subarachnoid hemorrhage (aSAH) report an association between higher patient volumes and better outcomes. In regions with dispersed settlement, this must be balanced against the advantages with shorter pre-hospital transport times and timely access. The aim of this study is to report outcome for unselected aSAH-cases from a well-defined rural population treated in a low-volume neurosurgical center.

Methods: This is a retrospective population-based observational cohort study from northern Norway (population 486,450). The University Hospital of North Norway (UNN) provides the only neurosurgical service. We retrieved data for all aSAH cases (n = 332) admitted during 2007 through 2019 from an institution specific register. The outcome measures were mortality rates and functional status assessed with the modified Rankin Scale (mRS).

Results: The mean annual number of cases was 26 (range 16-38) and the mean crude incidence rate 5.4 per 100,000 person-years. 279/332 (84 %) cases underwent aneurysm repair, 158 (47.5 %) with endovascular techniques and 121 (36.4 %) with microsurgical clipping, while 53 (15.9 %) did not. The overall mortality rate was 16.0 % at discharge and 23.8 % at 12 months. The proportion with a favorable outcome (mRS scores 0-2) was 36.1 % at discharge and 51.5 % at 12 months. In subgroup analysis of cases who underwent aneurysm repair, the mortality rate was of 4.7 % at discharge and 11.8 % at 12 months, and the proportion with a favorable outcome 42.3 % at discharge and 59.9 % at 12 months.

Conclusions: We report satisfactory outcomes after treatment of aSAH in a low-volume neurosurgical department serving a rural population. This indicates a reasonable balance between timely access to treatment and hospital case volume.

Non-standard Abbreviations and Acronyms

- aSAH: aneurysmal subarachnoid hemorrhage
- UNN: The University Hospital of North Norway
- mRS: modified Rankin Scale
- EHR: electronic health record

Clinical Perspective

What is new?

- We studied outcomes after treatment of unselected aneurysmal subarachnoid hemorrhage-cases from a well-defined rural population treated in a low-volume (mean annual number of cases n = 26) neurosurgical center in northern Norway, and found that 51.5 % of all patients and 59.9 % of those who underwent treatment with aneurysm repair achieved a favorable outcome (modified Rankin Scale scores 0-2) after 12 months.

What are the clinical implications?

- In regions with dispersed settlement, health systems must balance the quality gain of high patient volumes against the disadvantages with longer pre-hospital transport times caused by centralization. The advantages of shorter pre-hospital transport times and timely access could favor decentralization to lower volume units.
- Our findings indicate that satisfactory outcomes can be achieved in lower-volume decentralized institutions with ample resource availability, but such neurosurgical centers cannot be expected to be as cost-efficient as larger volume ones.

Cerebrovascular disease is the fourth most prevalent cause of lost life years in the Norwegian population [1], and aneurysmal subarachnoid hemorrhage (aSAH) contributes disproportionally because it strikes relatively young patients and has a high case fatality rate. The incidence is estimated to 9 per 100,000 person-years [2].

Nieuwkamp and co-workers reviewed and performed meta-analysis of outcomes in population-based prospective cohorts published between 1973 and 2002 [3]. Few subsequent studies have reported long-term outcomes in such unselected cohorts [4-6]. The nationwide Swiss Study on Subarachnoid Hemorrhage (Swiss SOS) and the Danish Stroke registry have registered aSAH cases prospectively since 2009 and 2017, respectively [5, 7].

An association between high patient volumes and better outcomes has been established for the management of aSAH [8, 9]. In regions with dispersed rural populations, this must be balanced against the advantages with shorter pre-hospital transport times and timely access. This consideration entails a decentralized hospital structure with small neurosurgical departments in countries with dispersed settlements, such as Norway.

The decentralized structure is, however, increasingly challenged by the sub-specialization caused by introduction of new endovascular techniques. A recent study of temporal trends in the management of aSAH in the USA from 2003 to 2017 found that mortality rates increased in rural hospitals and decreased in urban hospitals [9].

The University Hospital of North Norway (UNN) provides the only neurosurgical service for a well-defined rural population in northern Norway. Since the quality of care in low-volume institutions is difficult to assess continuously because of the risk for random variation in outcomes, we register all patients admitted with aSAH in an institution specific clinical quality register. The aim of this study is to report overall outcome after treatment of unselected aSAH-cases in this well-defined population.

Methods

<u>Study design</u>

This is a retrospective population-based observational cohort study. The study was approved by the institutional data protection officer (file nr. 02546). The Strengthening of the Reporting of Observational Studies in Epidemiology (STROBE) statement guided the conduct and reporting. The data that support the findings of this study are available from the corresponding author upon reasonable request.

<u>Setting</u>

Study region and hospital system

The study region is northern Norway, which is populated by 486,450 (2019) inhabitants[10]. The Northern Norway Regional Health Authority operates all the 11 hospitals in the region. The UNN is the regional referral center, a teaching hospital affiliated with UiT the Arctic University of Norway, and a local hospital for 132,595 inhabitants in Troms county. All hospitals have immediate 24/7 access to computed tomography (CT) and CT angiography (CTA).

The hospitals are linked through a joint electronic health record (EHR) and picture archiving and communication system (PACS). This ensures real-time access to all clinical and imaging data. Neurosurgeons and radiologists at the UNN also have immediate access to the EHR and the PACS at home. This supports joint decision making between physicians on call at local hospitals and neurosurgeons on call at the UNN. All cases with aSAH are routinely transferred. An advanced air ambulance service continuously operates six rotor wing and six fixed wing air ambulances. This enables rapid transfer despite long geographical distances (air-line 942 km from the south of Nordland to the Russian border in the east of

Finnmark county, and a total area of 112 985 km^2, corresponding to the land area of Pennsylvania [10]). In exceptional situations, weather conditions, logistic or capacity problems can obstruct transfer.

Institutional treatment principles

The UNN has continuous access to diagnostic imaging with CT, magnetic resonance (MR) imaging, and digital subtraction angiography (DSA). Neurosurgeons managing most techniques except bypass surgery, and neurovascular interventionists are continuously on call. Two general neurosurgeons and two interventionists do the treatment decisions and aneurysm repairs. There is no formal sub-specialization (fellowship) in vascular neurosurgery or interventional neuroradiology in Norway. Residents in training in neurosurgery and radiology participated in the procedures. To compensate for low case-numbers, the surgeons usually operate together with a four-hand microsurgical technique. Endovascular treatment options in the study period included regular and balloon supported coiling and flow-diverting stents.

The intensive care unit (ICU) is continuously staffed with specialist nurses and anesthesiologists, and neurointensive care with multimodal monitoring including continuous intracranial pressure (ICP) and brain tissue oxygen (P_{btO2}) monitoring is provided.

All patients diagnosed with aSAH are considered eligible for aneurysm repair, except when the clinical examination or imaging reveal obvious and irreversible structural or ischemic brain damage, considered incompatible with survival by the neurosurgeon on call.

In cases with CT-verified hydrocephalus or clinical signs indicating elevated ICP, external ventricular drainage (EVD) is established immediately. EVD is also routinely established prior to endovascular treatment in Fisher grade 3 and 4 hemorrhages, prior to planned antiplatelet treatment. Patients with space occupying hematomas are operated immediately with hematoma removal and aneurysm repair. Otherwise, aneurysm repair is scheduled as soon as possible, but usually not between midnight and 8:00 a.m.

Middle cerebral artery (MCA) aneurysms are preferably treated with microsurgical clipping and vertebrobasilar (VB) aneurysms with endovascular coiling. Aneurysms in other locations or with challenging morphology are individually evaluated in a multidisciplinary team including both vascular neurosurgeon and interventionist. When stent-assisted coiling is performed, glycopeptide II/IIa receptor inhibitors are used during the procedure, with subsequent individualized acetyl salicylic acid and adenosine diphosphate inhibitors treatment closely monitored by platelet function tests.

Patients are evaluated by a rehabilitation medicine specialist before discharge. Patients assessed not to need specialized rehabilitation are discharged home or to the local hospital. Patients with cognitive dysfunction or neurological deficits are transferred to the university hospital's rehabilitation unit. Patients not expected to benefit from rehabilitation are transferred to the local hospital, and reassessed if they recover sufficiently.

Participants

This study included all patients admitted with aSAH during the years 2007 through 2019. Primary diagnosis was established with CT at the local hospitals.

Data source

Clinical quality register

We established a clinical quality register in 2006 and register data on all patients diagnosed with aSAH or treated for unruptured intracranial aneurysms. In 2020, a revised version was implemented and we retrospectively reviewed EHRs and completed data registration. The register is approved by the institutional data protection officer (file nr. 00001/07) and the Regional Committee for Medical and Health Research Ethics North (file nr. 72/2005), and does not require informed consent.

Identification of cases for the retrospective completion was based on a search in the EHR for the International Classification of Diseases, Tenth Revision code for subarachnoid hemorrhage (I60), the NOMESKO Classification of Surgical Procedures codes for surgical or endovascular treatment of an intracranial aneurysm (codes AAC00, AAC05, AAC10, AAC15, AAC99, AAW97B, AAY00B, AAY20B, AAY30B, AAQ61B) and the Norwegian Classification of Radiological Procedures codes for endovascular treatment of intracranial aneurysms (codes AAL00 and AAL99). Case ascertainment was done by analyzing EHRs and image findings. Registration required confirmation of aSAH with CTA, DSA, MR angiography (MRA) or intraoperatively. Cases with non-aneurysmal SAH due to arteriovenous malformations, perimesencephalic bleeding or trauma are not registered.

We retrieved all data from the register (06.05.2021).

Variables

Baseline characteristics and treatment variables

Baseline characteristics included age (years), gender (female or male), habitual modified Rankin scale (mRS) score, hypertension (yes; diagnosis or use of antihypertensive medication recorded in the EHR) and smoking habits (never, former, or current smoker with cut-off for former at one year after cessation). The method for repair of the aneurysm was categorized as surgical (clipping, trapping and wrapping), endovascular (coiling and/or stenting) or no repair.

Clinical condition at baseline, immediately after establishment of the diagnosis at the referring hospital or at the UNN, was assessed with the Hunt and Hess grading scale [11, 12]. For patients who were sedated and intubated before CT, the pre-intubation condition was registered. The amount of subarachnoid bleeding was quantified with the Fisher scale score [13]. The size of the ruptured aneurysm was measured in mm as the largest diameter captured on three dimensional CTA, MRA or DSA. Location was categorized based on the same images as anterior cerebral artery (ACA; anterior communicating artery and other segments of the ACA), MCA, posterior communicating artery (PCom), internal carotid artery (ICA; all internal carotid artery segments except PCom, including the ICA bifurcation), or VB.

Time from admission to aneurysm repair (if performed) was categorized as <6 hours, ≥6<24 hours, ≥24<48 hours, and ≥48 hours. The use of EVD, implantation of a permanent cerebrospinal fluid shunt during the first hospital admission, rebleeding (any time after ictus) prior to aneurysm repair (clinically evident and verified by imaging or intraoperatively), and the presence of radiologically confirmed hydrocephalus within the first week were dichotomized as yes or no. The length of stay in the ICU and the total length of stay during the first admission was counted in days. Vasospasm was assessed with CTA or transcranial doppler (TCD), and categorized as 1) not present, 2) TCD- or CTA-confirmed without symptoms or 3) present with neurologic deficits. Vasospasm treatment was categorized as 1) standard (nimodipine orally or intravenously (iv)), 2) treatment with vasopressor iv, and 3) vasopressor and endovascular treatment (intraarterial nimodipine administration and/or balloon dilatation and/or stent placement).

Procedure related complications for patients treated with aneurysm repair were registered as hemorrhage (yes; intracerebral hematoma or new SAH occurring during the surgical or endovascular procedure), vessel occlusion (yes; ischemia caused by a prolonged or permanent occlusion of a blood vessel or the development of an embolus during the procedure) and surgical site infection.

The general medical complications registered during the hospitalization were epilepsy (yes; one or more epileptic seizure verified with electroencephalography or treated with antiepileptic medication), cerebral infarction (yes; persistent imaging-confirmed ischemic lesion in the brain not caused by the surgical or endovascular procedure), other infection (yes; infections at other locations than the operation wound (e.g.

pneumonia or urinary tract infections)), venous thromboembolism (yes; imaging confirmed lung embolism or deep vein thrombosis) and cardiac complications (yes; dysrhythmia or cardiac arrest).

Outcomes

The main outcome measure was functional status assessed with the modified Rankin scale (mRS) [14] at discharge and after three and 12 months. We dichotomized the outcome as favorable (mRS scores 0-2) or unfavorable (mRS scores 3-6). Mortality (mRS score 6) was defined as death of any cause. The exact time point for registration of the outcome data could vary moderately depending on the timing of scheduled follow-ups at the UNN and local hospitals.

Statistical methods

Statistical analyses were performed with SPSS version 27.0 (IBM Corporation, NY, USA). The distribution of continuous data was analyzed with the Shapiro-Wilks test, histograms and Q-Q-plots. Normally distributed data are presented with means and standard deviations and skewed data with medians and ranges or inter-quartile ranges (IQR). We compared means between independent groups with the independent samples t-test and medians with the Mann-Whitney U-test. Categorical variables are presented as frequencies and percentages. Between groups comparisons of proportions were done with Pearson's Chi-squared test or Fisher's exact test (when $n \leq 5$ in one or more cells). Time trends for incidence rate in annual case load and aneurysm repair modality were analyzed with Poisson regression, and time trends for differences in outcomes between groups with binary logistic regression. P-levels < 0.05 were considered significant. We used binary univariate and multivariate regression to identify variables associated with an unfavorable outcome. Odds ratios (OR) are reported with 95 % confidence intervals (CI).

Results

We included 332 patients. Figure 1 shows the total number of cases and aneurysm repair modality per year. The mean annual number of cases was 26 (range 16-38) and the mean crude incidence rate was 5.4 per 100,000 person-years. There was a moderate not significant (p=0.71) reduction in the annual number of cases and a significant (p=0.032) decrease in incidence by 3.1 % (95 % CI 0.3 – 5.9) per year. The number transferred from a local hospital was 220 (66 %) and the median day post bleeding for transfer was 0 (IQR 0-2).

279 (84 %) cases underwent aneurysm repair, 158 (47.5 %) with endovascular techniques and 121 (36.4 %) with microsurgical clipping, while 53 (15.9 %) did not. In the endovascular group, 148 (93,7 %) were coiled and 2 (1.3 %) stented, while 5 (3.2 %) were treated with a combination of coils and stents. The proportions undergoing surgical repair (p=0.040) and no repair (p=0.049) decreased significantly compared to the reference category (endovascular repair).

Table 1 shows baseline characteristics for all patients and stratified by the method for aneurysm repair. The patients were 216 (65.1%) females and 116 (34.9 %) men with median age 59 (range 15-92) years. Table 2 shows management and complications and table 3 the multivariate analysis.

Patients who were treated with aneurysm repair were significantly younger (p<0.001), had smaller aneurysms (p<0.001), lower Hunt and Hess grade (p<0.001) and less severe bleeding (p<0.001) assessed with the Fisher scale than those who did not receive such treatment.

There were no statistically significant differences in baseline characteristics between patients who underwent surgical and endovascular repair, except from the expected skewness in the distribution of aneurysm location (table 1). A significantly higher proportion of endovascularly treated patients had hydrocephalus at admittance (p=0.004), and they were more frequently treated with EVD (p= 0.020) and shunt (p=0.004) (table 2). The length of stay and days in the ICU did not differ between the groups (p=0.446 and p=0.444, respectively).

Table 2 shows that 49 (17.6%) patients experienced a procedure related complication. There were no statistically significant differences between patients treated endovascularly and surgically. Cardiac complications were more frequent in patients treated endovascularly (p=0.015), but there were no significant differences in other general complications between the groups. Patients who did not receive aneurysm repair had more cerebral infarctions (p=0.021), other infections (p=0.023) and cardiac complications (p=0.010).

Figure 2A shows outcomes at discharge and after three and 12 months for all patients. The case fatality rate was 16.0% at discharge, and the overall mortality was 21,4 % at three months and 23.8% at 12 months. The proportion with a favorable outcome increased from 36.1% at discharge to 48.5% at 3 months, and further to 51.5% at 12 months. The proportion with moderately severe or severe disability (mRS scores 4-5) decreased from 30.5% at discharge to 3.9% at 12 months. There was no significant time trend in the risk for an unfavorable outcome (OR 0.95 per year, 95 % CI 0.906 - 0.998) and the case fatality rate was stable during the study period.

Figure 2B shows subgroup analysis for the patients who received aneurysm repair. The case fatality rate was 4.7% at discharge, and the overall mortality was 9,3 % at three months and 11.8% at 12 months. The proportion with a favorable outcome increased from 42.3% at discharge to 56.6% at 3 months, and further to 59.9% at 12 months. The proportion with mRS scores 4-5 decreased from 34.1% at discharge to 4.3% at 12 months. There was no significant time trend in the risk for an unfavorable outcome (OR 0.97 per year, 95 % CI 0.946 - 1.002) and the case fatality rate was stable during the study period.

Subgroup analysis for the patients who did not receive aneurysm repair showed case fatality rates of 75.5 % at discharge, with an overall mortality of 84.9 % at three months and 86.8 % at 12 months.

Table 3 shows multivariate analysis of predictors of an unfavorable outcome at 12 months. For the univariate analysis, please see https://www.ahajournals.org/journal/str. In multivariate analysis, higher age (OR 1.050 per year increase, 95% CI 1.024 - 1.077), any procedure related complication (OR 1.330, 95% CI 1.163 - 1.522), higher Hunt and Hess grade (OR 1.354 per step, 95% CI 1.076 - 1.703), higher Fisher scale score (OR 1.815 per step, 95% CI 1.157 - 2.846) and higher habitual mRS score (OR 2.270 per step, 95% CI 1.258 - 4.098) were independent predictors of an unfavorable outcome at 12 months.

Discussion

Key results

The main findings in this unselected population-based cohort of aSAH cases were that 51.5% reached a favorable outcome (mRS scores 0-2), and that the overall mortality was 23.7%. after 12 months. Only a small proportion (3.9%) remained severely disabled (mRS scores 4-5). The proportion who underwent aneurysm repair was 84%, and in this group, the proportion with a favorable outcome was 59.9% and the mortality was 11,8 % after 12 months.

Interpretation

Overall, these results are satisfactory, especially in a low-volume neurosurgical center serving a sparsely populated rural region with long pre- and inter-hospital transport distances.

A review with meta-analysis of population-based prospective cohorts published between 1973 and 2002 reported a median case fatality rate of 44.4% in Europe, and the proportion with a favorable outcome was

55% [3]. Lovelock and co-workers reviewed seven population-based studies of time-trends conducted between 1980 and 2005, and meta-analysis showed that unadjusted case-fatality rates declined by 0.9% per year [4]. The most recent rates ranged between 18 and 43%. A population-based single center study in northeast England reported outcomes for patients treated between 2005 and 2010. The case fatality rate was 19.2%, and 56.5% of men and 61.1% of women had a favorable outcome after three months [6]. The nationwide Swiss SOS reported patients treated between 2009 and 2014. The case fatality rate was 22.1% and 58.8% achieved mRS scores of 0-2 after 12 months [5]. The Danish Stroke registry reports 30-day case fatality rates ranging from 18% in 2017 to 23% in 2019 [7].

Huang and Lai analyzed nationwide patient administrative data for Australia from 2008-2018 [15]. The 30-day case fatality rate was 26.7%. An analysis of Norwegian patient-administrative data for 2008-2014 reported case fatality rates of 22% at 30 days and 37% at 12 months [16]. A recent analysis of data for 2017 from the Nationwide Inpatient Sample in the USA reported in-hospital mortality rates of 21.2 % for urban teaching and 33.4 % for rural hospitals [9].

Summarized, the case fatality rates reported after year 2000 range from 18 to 43% and the proportion with a favorable outcome from 51 to 61%. The case fatality rate (16% at discharge) and one-year overall mortality (23,7%) in the present study is in the lower part and the proportion of patients with a favorable outcome in the group undergoing aneurysm repair (59.9%) in the upper part of these ranges.

Few studies detail the proportion of patients not undergoing aneurysm repair. In the present study it was 16%, and these patients were older and had more severe SAH. As expected, the mortality was very high (86.8% at 12 months). The Danish Stroke registry reported that 13% did not receive aneurysm repair in 2019. Corresponding figures based on patient-administrative data from Australia and Norway were 34 and 36%, respectively [15, 16].

The crude incidence rate was 5.4 per 100 000 person-years, which is lower than reported from previous Norwegian population-based cohort studies (5.7 - 12.0 per 100 000 person-years) [16, 17]. Some studies have reported decreasing rates, both globally [2] and in Norway [16, 18], but these results are not consistent [15]. The present study indicates a decline. The proportion receiving endovascular aneurysm repair increased in accordance with present guidelines [19].

The American Heart Association Stroke Council defines hospitals treating >35 aSAH cases per year as high-volume centers [19]. Our mean annual number of cases (n=26) was lower. An analysis of data from the Nationwide Inpatient Sample in the USA for the years 2002-2010 confirmed the association between high patient volume and lower mortality, and indicated that this association did not plateau until hospitals were treating more than 100 cases per year[8]. However, we found no relationship between caseload and mortality in a study of patient administrative data from Scandinavian hospitals [20]. The present study confirms that satisfactory outcomes can be achieved in low-volume institutions, and indicates that a reasonable balance between timely access to treatment and hospital volume has been found. Despite being rural and low-volume, the UNN is a teaching hospital with a broad range of specialized support in neurointensive care, neuroradiology and neurophysiology available. Norwegian healthcare is also relatively amply resourced with regard to equipment and financial capability. Further, there was no turnover among the four specialist (two neurosurgeons and two interventionists) who treated patients during the study period. These factors may have contributed to results comparable with higher volume institutions. However, ongoing decline in the incidence and further sub-specialization caused by new endovascular techniques may challenge this in the future.

Limitations

This study assumes all aSAH cases admitted alive to local hospitals in the study region were transferred to the regional neurosurgical center. We cannot preclude deviations from this routine, as deaths in local hospitals were not registered. An ignorable proportion of patients were probably transferred to other neurosurgical centers, e. g. when extreme weather conditions obstructed flights. We did not have access to data about pre-hospital deaths, but consider it likely that Norway's extensive and advanced pre-hospital emergency service ensures that the proportion of patients not reaching hospital alive is comparably low. These factors could, however, cause selection bias. Further, the register we retrieved data from was updated retrospectively, and there could be weaknesses in the case-ascertainment procedure. This could cause information bias. Cause of deaths at 3 and 12 months was not obtained, and in patients with good outcomes at discharge and/or major comorbidity, deaths not related to aSAH must be expected. We are therefore restricted to reporting overall mortality at 3 and 12 months.

Generalizability

This study was conducted in a very large rural region with a well-funded single payer public health system and a comprehensive air-ambulance system. The results may not be generalizable to other rural settings with sparser resource availability.

Conclusions

We report satisfactory outcomes after treatment of aSAH in a low-volume teaching hospital neurosurgical department serving a rural population in Northern Norway. A favorable outcome (mRS scores 0-2) was reached for 51.5% of the patients at 12 months, and the overall mortality was 23.7%. This indicates a reasonable balance between timely access to treatment and hospital case volume.

Acknowledgments

For contributions to the statistics performed in this study, we would like to express our appreciation to Tom Wilsgaard for valuable help. We are also grateful to Eva Jacobsen, Torgrim Vorren and Radoslav Bajic, who have performed many of the endovascular procedures in the study period.

Sources of funding

MVI is a medical student and a participant in the student research program at the UiT. She has received a research fellowship from the UiT. TI has received research grants from the Norwegian Health Association and the Northern Norway Regional Health Authority.

Disclosures

None.

Supplemental materials

Table I. Univariate analysis of predictors for outcome.

References

1. Abd-Allah F, Abdulle AM, Abera SF, Abu-Raddad LJ, Adetokunboh O, Afshin A, Aggarwal R, Agrawal A, Aichour I, Akseer N, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: A systematic analysis for the global burden of disease study 2016. *Lancet*. 2017;390:1211-1259
2. de Rooij NK, Linn FHH, van der Plas JA, Algra A, Rinkel GJE. Incidence of subarachnoid haemorrhage: A systematic review with emphasis on region, age, gender and time trends. *J Neurol Neurosurg Psychiatry*. 2007;78:1365-1372
3. Nieuwkamp DJ, Setz LE, Algra A, Linn FHH, de Rooij NK, Rinkel GJE. Changes in case fatality of aneurysmal subarachnoid haemorrhage over time, according to age, sex, and region: A meta-analysis. *Lancet Neurol*. 2009;8:635-642
4. Lovelock CE, Rinkel GJ, Rothwell PM. Time trends in outcome of subarachnoid hemorrhage: Population-based study and systematic review. *Neurology*. 2010;74:1494-1501
5. Schatlo B, Fung C, Stienen MN, Fathi AR, Fandino J, Smoll NR, Zumofen D, Daniel RT, Burkhardt J-K, Bervini D, et al. Incidence and outcome of aneurysmal subarachnoid hemorrhage: The swiss study on subarachnoid hemorrhage (swiss sos). *Stroke*. 2020;52:344-347
6. Hamdan A, Barnes J, Mitchell P. Subarachnoid hemorrhage and the female sex: Analysis of risk factors, aneurysm characteristics, and outcomes. *J Neurosurg*. 2014;121:1367-1373
7. Damgaard DV, P; Johnsen, S. P; Rasmussen, T. S; Koldborg, L; Madsen, C. M; Brandes, A; Brynningsen, P. K; Mikkelsen, R; Jeppesen, M; Ebbesen, B. H; Christensen, H; Wienecke, T; Modrau, B; Stavngaard, T; Hauerberg, J; Munthe, S; Ingeman, Annette; Hundbord. H., H; Chousa, M, G; Øster, I. Årsrapport 2019. *Dansk Apopleksiregister*. 2019
8. Pandey AS, Gemmete JJ, Wilson TJ, Chaudhary N, Thompson BG, Morgenstern LB, Burke JF. High subarachnoid hemorrhage patient volume associated with lower mortality and better outcomes. *Neurosurgery*. 2015;77:462-470

9. Neifert SN, Martini ML, Hardigan T, Ladner TR, MacDonald RL, Oermann EK. Trends in incidence and mortality by hospital teaching status and location in aneurysmal subarachnoid hemorrhage. *World Neurosurg*. 2020;142:e253-e259

10. Statistics Norway. Population and area (m) 2007-2020. https://www.ssb.no/en/statbank/table/11342/. Accessed July 13, 2021.

11. Hunt WE, Hess RM. Surgical risk as related to time of intervention in the repair of intracranial aneurysms. *J Neurosurg*. 1968;28:14-20

12. Report of world federation of neurological surgeons committee on a universal subarachnoid hemorrhage grading scale. *J Neurosurg*. 1988;68:985-986

13. Fisher CM, Kistler JP, Davis JM. Relation of cerebral vasospasm to subarachnoid hemorrhage visualized by computerized tomographic scanning. *Neurosurgery*. 1980;6:1-9

14. Rankin J. Cerebral vascular accidents in patients over the age of 60. Ii. Prognosis. *Scott Med J*. 1957;2:200-215

15. Huang H, Lai LT. Incidence and case-fatality of aneurysmal subarachnoid hemorrhage in australia, 2008–2018. *World Neurosurg*. 2020;144:e438-e446

16. Øie LR, Solheim O, Majewska P, Nordseth T, Müller TB, Carlsen SM, Jensberg H, Salvesen Ø, Gulati S. Incidence and case fatality of aneurysmal subarachnoid hemorrhage admitted to hospital between 2008 and 2014 in norway. *Acta Neurochir (Wien)*. 2020;162:2251-2259

17. Müller TB, Sandvei MS, Kvistad KA, Rydland J, Håberg A, Vik A, Gårseth M, Stovner LJ. Unruptured intracranial aneurysms in the norwegian nord-trøndelag health study (hunt): Risk of rupture calculated from data in a population-based cohort study. *Neurosurgery*. 2013;73:256-261

18. Lindekleiv HM, Njølstad I, Ingebrigtsen T, Mathiesen EB. Incidence of aneurysmal subarachnoid hemorrhage in norway, 1999–2007. *Acta Neurol Scand*. 2011;123:34-40

19. Bederson JB, Connolly ES, Batjer HH, Dacey RG, Dion JE, Diringer MN, Duldner JE, Harbaugh RE, Patel AB, Rosenwasser RH. Guidelines for the management of aneurysmal subarachnoid hemorrhage a statement for healthcare professionals from a special writing group of the stroke council, american heart association. *Stroke*. 2009;40:994-1025

20. Lindekleiv H, Mathiesen EB, Forde OH, Wilsgaard T, Ingebrigtsen T. Hospital volume and 1-year mortality after treatment of intracranial aneurysms: A study based on patient registries in scandinavia. *J Neurosurg*. 2015;123:631-637

Figure Legends

Figure 1. Time trends for annual caseload and treatment modalities

Figure 2. Distribution of outcomes

Distribution of outcomes (percentages) assessed with the modified Rankin scale (mRS) at discharge, and after 3 and 12 months for all patients (A) and for patients who received aneurysm repair (B).

Tables

Table 1. Baseline characteristics

		Aneurysm repair				
	Total (n=332)	Surgical (n=121)	Endovascular (n=158)	p-value (surgical versus endovascular)	None (n=53)	p-value (repair versus none)
Age, years, median (range)	59 (15 – 92)	56 (15 – 79)	58 (18 – 85)	0.428	67 (34 – 92)	<0.001
Sex (women)	216 (65.1)	84 (69.4)	101 (63.9)	0.336	31 (58.5)	0.274
Hypertension	124 (37.3)	39 (32.2)	62 (39.2)	0.227	23 (43.4)	0.321
Smoking				0.352		<0.001
Never	78 (23.5)	22 (18.2)	37 (23.4)		19 (35.8)	
Former	56 (16.9)	19 (15.7)	23 (14.6)		14 (26.4)	
Current	177 (53.3)	76 (62.8)	87 (55.1)		14 (26.4)	
Missing	21 (6.3)	4 (3.3)	11 (7.0)		6 (11.3)	
Hunt and Hess grade on admission				0.890		<0.001
1	109 (32.8)	44 (36.4)	62 (39.2)		3 (5.7)	
2	78 (23.5)	32 (26.4)	38 (24.1)		8 (15.1)	
3	45 (13.6)	19 (15.7)	20 (12.7)		6 (11.3)	
4	33 (9.9)	13 (10.7)	17 (10.8)		3 (5.7)	
5	67 (20.2)	13 (10.7)	21 (13.3)		33 (62.3)	

Fisher scale score				0.122		<0.001
1	13 (4.0)	3 (2.5)	9 (5.7)		1 (1.9)	
2	47 (14.6)	24 (19.8)	23 (14.6)		0 (0)	
3	61 (18.9)	18 (14.9)	37 (23.4)		6 (11.3)	
4	211 (65.5)	76 (62.8)	89 (56.3)		46 (86.8)	
Aneurysm size, mm, mean ± SD	7.5 ± 5.4	6.9 ± 3.4	6.6 ± 3.2	0.433	11.7 ± 10.6	<0.001
Aneurysm location				<0.001		0.051
ACA*	112 (34.8)	27 (22.3)	75 (47.5)		10 (18.9)	
MCA†	101 (31.4)	80 (66.1)	3 (1.9)		18 (34.0)	
ICA‡	23 (7.1)	6 (5.0)	13 (8.2)		4 (7.5)	
PCom§	53 (16.5)	5 (4.1)	39 (24.7)		9 (17.0)	
VB∣∣	43 (13.4)	3 (2.5)	28 (17.7)		12 (22.6)	

Table 1.

*ACA; anterior cerebral artery, †MCA; middle cerebral artery, ‡ICA; internal carotid artery, §PCom; posterior communicating artery, ∣∣VB; vertebrobasilar artery.

Values represent number of patients (%) unless stated otherwise.

Table 2. Management and complications

		Aneurysm repair				
	Total (n=332)	Surgical (n=121)	Endovascular (n=158)	p-value (surgical versus endovascular)	None (n=53)	p-value (repair versus none)
Time from admission to aneurysm repair	N= 279	N=121	N=158	0,412	n.a.	
< 6 hours	87 (31.2)	34 (28.1)	53 (33.5)			
≥6 < 24 hours	160 (57.3)	69 (57.0)	91 (57.6)			
≥ 24 < 48 hours	13 (4.7)	7 (5.8)	6 (3.8)			
≥ 48 hours	19 (6.8)	11 (9.1)	8 (5.1)			
Rebleeding (prior to aneurysm repair, n= 279)	19 (5.7)	5 (4.1)	5 (3.2)	0.751	9 (17.0)	< 0.001
Hydrocephalus	164 (49.4)	45 (37.2)	86 (54.4)	0.004	33 (62.3)	0.041
EVD*	178 (53.6)	59 (48.8)	99 (62.7)	0.020	20 (37.7)	0.011
Shunt	93 (28.0)	28 (23.1)	62 (39.2)	0.004	3 (5.7)	< 0.001
Vasospasm				0.455		0.005
None	226 (68.1)	82 (67.8)	98 (62.0)		46 (86.8)	
TCD/CTA† without symptoms	39 (11.7)	16 (13.2)	20 (12.7)		3 (5.7)	
Neurologic deficit	67 (20.2)	23 (19.0)	40 (25.3)		4 (7.5)	

Vasospasm treatment (patients with vasospasm, n= 106)				0.007		0.201
Standard	68 (64.2)	22 (56.4)	39 (65.0)		7 (100)	
Pressor	30 (28.3)	17 (43.6)	13 (21.7)		0 (0)	
Pressor and endovascular	8 (7.5)	0 (0)	8 (13.3)		0 (0)	
Days in ICU‡, median (range)	1 (0-35)	1 (0-21)	2 (0-35)	0.444	1 (0-29)	0.828
Length of stay, median (range)	11 (0-36)	11 (0-36)	13 (2-35)	0.446	3 (0-35)	<0.001
Procedure related complications						
Hemorrhage	21 (7.5)	11 (9.1)	10 (6.3)	0.386	n.a.	
Vessel occlusion	26 (9.3)	7 (5.8)	19 (12.0)	0.076	n.a.	
Surgical site infection	2 (0.7)	2 (1.7)	n.a.	0.187	n.a.	
General medical complications						
Epilepsy	21 (6.3)	7 (5.8)	11 (7.0)	0.692	3 (5.7)	1.000
Cerebral infarction	64 (19.3)	32 (26.4)	28 (17.7)	0.079	4 (7.5)	0.021
Other infection	141 (42.5)	49 (40.5)	77 (48.7)	0.171	15 (28.3)	0.023
VTE§	10 (3.0)	3 (2.5)	6 (3.8)	0.736	1 (1.9)	1.000
Cardiac	19 (5.7)	1 (0.8)	11 (7.0)	0.015	7 (13.2)	0.010

Table 2.

[*]EVD; external ventricular drainage, [†]TCD/CTA; transcranial doppler/ CT angiography, [‡]ICU; intensive care unit, [§]VTE; venous thromboembolism.

Procedure related complications: For patients who received aneurysm repair.

Values represent number of patients (%) unless stated otherwise.

Table 3. Multivariate analysis of predictors for outcome

	Total (n = 299)	Favorable (mRS 0-2) (n = 171, 57.2 %)	Unfavorable (mRS 3-6) (n = 128, 42.8 %)	Adjusted OR (95 % C.I.)
Age, years median (IQR*)	59 (49 – 67)	56 (47 – 64)	65 (55 – 73)	1.050 (1.024 – 1.077)
Any procedure related complication	43 (14.4)	19 (44.2)	24 (55.8)	1.330 (1.163 – 1.522)
Hunt and Hess grade				1.354 (1.076 – 1.703)
1	92 (30.8)	73 (79.3)	19 (20.7)	
2	70 (23.4)	47 (67.1)	23 (32.9)	
3	39 (13.0)	20 (51.3)	19 (48.7)	
4	32 (10.7)	11 (34.4)	21 (65.6)	
5	66 (22.1)	20 (30.3)	46 (69.7)	
Fisher scale score				1.815 (1.157 – 2.846)
I	12 (4.0)	10 (83.3)	2 (16.7)	
II	44 (14.7)	37 (84.1)	7 (15.9)	
III	54 (18.1)	43 (79.6)	11 (20.4)	
IV	189 (63.2)	81 (42.9)	108 (57.1)	
Habitual mRS† score				2.270 (1.258 – 4.098)

0	263 (88.0)	158 (60.1)	105 (39.9)	
1	19 (6.4)	12 (63.2)	7 (36.8)	
2	10 (3.3)	1 (10.0)	9 (90.0)	
3	5 (1.7)	0 (0)	5 (100.0)	
4	2 (0.7)	0 (0)	2 (100.0)	
Favorable (0-2)	292 (97.7)	171 (58.6)	121 (41.4)	
Unfavorable (3-6)	7 (2.3)	0 (0)	7 (5.5)	

Table 3.

*IQR; interquartile range, †mRS; modified rankin scale score.

Values represent number of patients (%) unless stated otherwise.