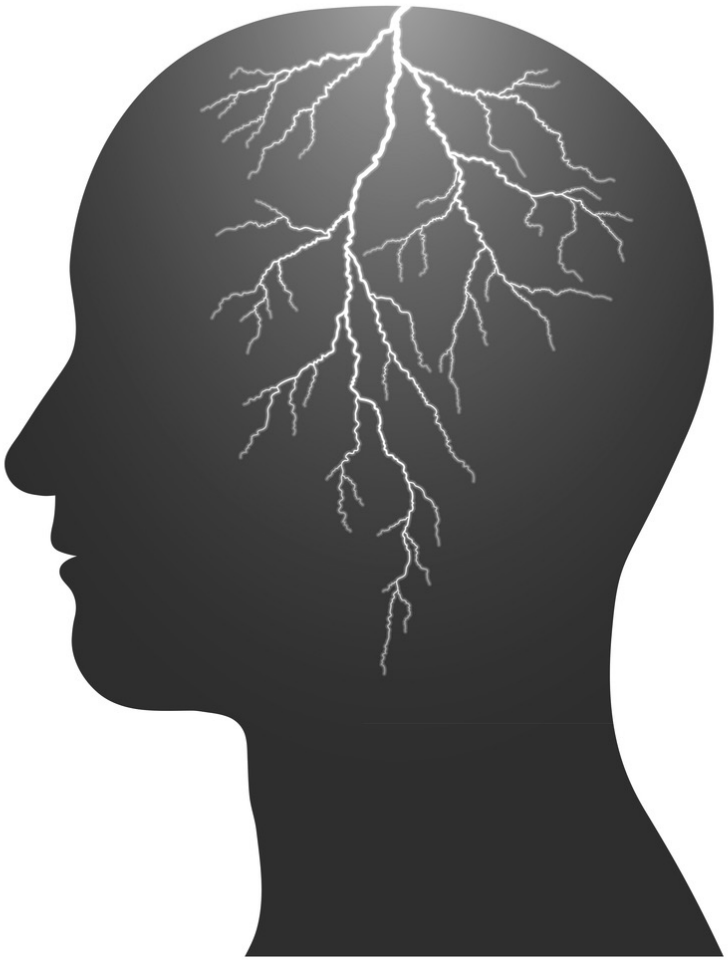
Long-term outcome 12-15 years after aneurysmal subarachnoid haemorrhage: a prospective cohort study



Erika Svanborg
Supervisor: Bengt Nellgård
Master thesis in Medicine
University of Gothenburg 2015

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ABSTRACT

Master Thesis, Programme in Medicine

Title: Long-term outcome 12-15 years after aneurysmal subarachnoid haemorrhage: a prospective cohort study

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Background: Aneurysmal subarachnoid haemorrhage (aSAH) is a severe disease with poor outcome. Few studies on long-term outcome exist. Therefore we initiated this outcome study, 12-15 years post-aSAH on a previously validated patient-cohort at admission and at 1-year.

Aim: To investigate long-term outcomes using the Glasgow Outcome Scale (GOS). We hypothesized to find 1) functional improvement > 1-year post-ictus, 2) increased long-term mortality in aSAH patients vs. matched controls, and 3) predictors of long-term favourable outcome (GOS 4-5).

Methods: We prospectively investigated data of patients admitted to the Sahlgrenska University Hospital (SU), 2000-2003. GOS, 12-15 years post-aSAH was validated by structured-telephone interviews and compared to previous GOS at 1-year follow-up. Mortality was analysed by Kaplan-Meier survival curves vs. age-, gender-, calendar year - and area-matched controls. Uni- and multivariable logistic regression analyses were applied to determine independent predictors of long-term favourable outcome.

Results: 158 aSAH-patients of 212 study candidates were included, with women 72.2% and mean age 55-years (SD 10.7). In a complete follow-up at 12-15 years post-aSAH, the 103 survivors (65.2%) were categorized: good recovery (39.9%, n=63), moderate disability (15.2%, n=24) and severe disability (10.1%, n=16). 55 had died at median 3.95 years (0.01-13.7). In the patient cohort 23.6% (n=30) improved GOS. There was a significant deterioration when dichotomized outcomes in unfavourable and favourable ($p=0.0002$). Age ($p>0.022$) and Hunt and Hess ($p<0.0008$) correlated to worse GOS at 12-15 years, but not gender, ($p=0.69$). aSAH-patients had 3.5 times increased mortality 12-15 years post-ictus vs. matched controls ($p<0.0001$). Patients with favourable outcome at 1-year (67.3%, n=101) had

the same survival probability as controls (p=0.27). The highest prognostic indicators of long-term favourable outcome were high GOS and low age at 1-year (AUC_{ROC}, 0.79).

Conclusions: Individual functional improvement occurred >1-year post-ictus. Patients with favourable outcome at 1-year had the same long-term life expectancy as the general population. High age and severe clinical status are risk factors for poor outcome. The best indicators of long-term favourable prognosis were GOS and age at 1-year follow-up.

Keywords: aneurysmal subarachnoid haemorrhage, functional outcome, Glasgow Outcome Scale, mortality, predictors

ABBREVIATIONS

ADL – Activity of Daily Living

aSAH – aneurysmal Subarachnoid Haemorrhage

AUC – Area Under the Curve

BI – Barthel Index

CSF – Cerebrovascular fluid

CVS – Cerebral Vasospasm

CT – Computed Tomography

CTA – Computed Tomography Angiography

DSA – Digital Subtractions Angiography

GCS – Glasgow Coma Scale

GOS – Glasgow Outcome Scale

GOSE – Glasgow Outcome Scale Extended

Hunt-Hess – Hunt and Hess scale

ISAT – International Subarachnoid Aneurysm Trial

LP – Lumbar Puncture

MRA – Magnetic Resonance imaging Angiography

mRS – modified Rankin Scale

NICU – Neuro-Intensive Care Unit

NIHSS – National Institute of Health Stroke Scale

OD – Odds ratio

RLS 85 – Reaction Level Scale

ROC – Receiver operator characteristic curve

SAH – Subarachnoid Haemorrhage

S-GOS 04 - Swedish version of Glasgow Outcome Scale

SMR - Standard Mortality Ratio

SU - Sahlgrenska University Hospital

WFNS – World Federation of Neurosurgical Surgeons Scale

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INTRODUCTION

The brain´s complexity distinguishes it from other organs. Similarly, brain insults have special characteristics, as it often contributes to both physical and psychological disabilities (1-3). Further, previous knowledge imply that recovery after brain insults, like one of the stroke entities aneurysmal Subarachnoid Haemorrhage (aSAH) have potential to improve over prolonged time (1, 4). Studies assessing outcome beyond 1-year are lacking and consequently late recovery following aSAH is poorly investigated (5-10). Thus long-term mortality and morbidity regarding aSAH-patients need to be further investigated (10, 11). Therefore we initiated this outcome study, 12-15 years after onset of the aSAH.

The present extended long-term study is established on a prospectively study cohort enrolled at Sahlgrenska University Hospital (SU), between October 2000 and December 2003 (12, 13). These aSAH-patients were consecutive included and thoroughly investigated both at admission and 1-year post-ictus. The 1-year follow-up included extensive neurological examination as well as outcome assessment by Glasgow Outcome Scale, Extended (GOSE), all performed by the same neurologist. It was particularly interesting to investigate the same study cohort 12-15 years after the insult, as this study population from West Sweden, was priory extensive evaluated and had received standardized treatment at SU.

Our hypotheses were:

1. Is it possible to detect functional improvement > 1-year post-aSAH.
2. Patients with aSAH have increased long-term mortality compared matched controls.
3. It is possible to detect predictors like age, gender and admission status at onset and/ or at 1-year post-aSAH and correlate them to long-term functional outcome.

BACKGROUND

Subarachnoid Haemorrhage (SAH) is a haemorrhage from a blood vessel within the subarachnoid space (13, 14). The major ethology is a ruptured, saccular intracranial aneurysm(s) (85%) at the base of the brain, from the circulus arteriosus Willisii and its branches (14, 15). SAH can also be induced by perimesencephalic haemorrhage (10%), a venous benign bleeding and other rare causes (5%) e.g. arterial dissection, cerebral arteriovenous malformations, septic aneurysm, cocaine abuse and trauma (16). Further, intracranial aneurysm develops with age and the rupture risk increase with size, particularly in the posterior circulation (17). However, a majority of all ruptured aneurysms are small (<10mm) and located in the anterior circulation (16, 18). The fact that multiple aneurysms may be detected in connection with the diagnosis of the aSAH (18), that de novo intracranial aneurysm may develop after the first insult (19), and that the risk of a new aSAH in survivors is 15 times higher compared with the general population (20), makes this devastating haemorrhagic stroke horrifying. Fortunately, the majority of all intracranial aneurysm, who appear in 2-5 % of adults in the general population, will never rupture (20, 21).

SAH accounts for a minority of all strokes (5%) (16, 21, 22). Although the average age at onset is lower (mean 55 years), the morbidity and mortality is substantial compared to intracerebral haemorrhage and ischemic stroke (4, 18, 23, 24). Whereas 12% of all aSAH-patients die immediately (25-27), more than 30% die within 1-month (24), 25-50% die within 6-months (28) and of survivors 30% remain dependent (14). Despite the bleak outcome, the current overall case-fatality rate of 30% (10-60%) has decreased with 17% since 1970s (24). In accordance the case-fatality rate in Sweden has reduced over the last three decades (27). However, the relatively young age at onset of the aSAH and the poor outcome, contribute to considerable loss of productive life years, in similar extent as that from ischemic stroke (23, 29).

The global incidence of aSAH is 9 per 100 000 person-year (18), though it varies in the world and within countries (18, 21). The incidence is much higher in Finland and Japan, approximately 20 per 100 000 person-year (21), and in Sweden it is higher in north (15.2 per 100 000 person-year) than in south (11.4 per 100 000 person-year). Hence the overall incidence in Sweden is 12.4 per 100 000 person-year (27). Further, the incidence of aSAH increase with female gender (1.3-1.6 times), age, non-white ethnicity, autosomal dominant polycystic kidney disease (ADPKD) and for a positive family history of aSAH (20, 21, 23,

27, 30, 31). Despite, that first-degree relatives of patients with aSAH have 3 to 7 times higher risk to suffer the same insult than the general population (32), the familial-aSAH accounts for a minority (10%) of all aSAH i.e. the majority are spontaneous-aSAH (33).

Further, independent modifiable risk factors for aSAH are current smoking (RR 2.2 95% CI 1.3-3.6), hypertension (RR 2.5 95% CI 2.0-3.1) and excessive alcohol intake (>150g per week) (RR 2.1 95% CI 1.5-2.8) (30, 34). Interestingly, it is suggested that hormone replacement therapy and hypercholesterolemia reduced the risk for aSAH (30). Thus, prevention of the devastating haemorrhagic stroke, with a heritable component is possible and for sure all aSAH-patients should stop smoking.

The cardinal symptom of a ruptured intracranial aneurysm, is sudden (within seconds) severe headache "thunderclap-headache", often (2/3) associated with other symptoms e.g. depressed consciousness, acute confusional state, seizures, vomiting, oculomotor nerve palsy and neck stiffness (3-12 hours post-ictus) (35). The first investigation if SAH is clinically suspected is a non-contrast computed tomography (CT). CT scan is the golden standard for SAH diagnostic (18), and modern 3rd generation CT scan has a sensitivity of 97% to 100% to detect SAH, when performed by an experienced radiologist within 6 hour after onset of the headache (36). The most characteristic sign of SAH is the "crab of death" i.e. subarachnoid blood in the subarachnoid space/ basal cisterns (18). However, if the patient presents "thunderclap headache" and a negative CT scan a lumbar puncture (LP) is obtained, after minimum 6 hours post-ictus (16). Centrifugation followed by spectrophotometry of the cerebrospinal fluid (CSF) enables us to distinguish between SAH-blood (i.e. breakdown of erythrocytes to bilirubin, wavelength 456 nm) and a traumatic puncture (oxyhemoglobin, wavelength 415nm) (13, 37). Further, the aSAH diagnosis is followed by a CT angiography (CTA) involving contrast injection, easily obtained after the CT scan and enables 3D reconstruction of the intracranial vessels malformations (13, 14). Magnetic resonance imaging angiography (MRA) is an alternative to the CTA, but unsuitable in agitated patients and patients who need extensive monitoring (18), hence MRA is no emergency investigation for aSAH. Finally, digital subtractions angiography (DSA) is performed, an invasive investigation involving puncture of a major artery (often femoral artery) and contrast injection, facilitates detailed 3D mapping of the ruptured aneurysm(s) (13, 18).

Treatment routines of intracranial aneurysms and SAH at SU (neurosurgical department) follow a well-established standardized protocol, in agreement with The European Stroke Organisations guidelines (18). At admittance extended monitoring and general management are obtained, follow by the primary objective of the aSAH treatment, i.e. to occlude the ruptured aneurysm and prevent from re-bleeding (13). Re-bleeding is the most frightful early complication affecting 15 % of all patients within the first 24 hours (38, 39). Thus, Tranexamic acid (Cyklapron® i.v. 1g three times daily), a fibrinolysis inhibitor is administrated immediately after the diagnosis of SAH, until the ruptured intracranial aneurysm(s) is secured (13, 38). The occlusion is performed either by endovascular coiling or neurosurgical clipping, depending on factors such as patient age, comorbidity, aneurysm; size, localization and configuration, and is a decision taken in agreement between the neurosurgeon and the intervention neuroradiologist (13, 18). The major difference between the interventions is that clipping involves open craniotomy and brain manipulation (40). After occlusion of the ruptured aneurysm(s) Nimodipine, a calcium antagonist is administrated (infusion or orally for 10 days) to prevent delayed cerebral ischemia (cerebral vasospasm, CVS) and improve outcome. Further, acute hydrocephalus is treated (when needed) with an intra-ventricular catheter for CSF drainage. Intracranial haemorrhage is removed at initial surgical or if extensive. Conservative treatment i.e. no active aneurysmal intervention (the aneurysm is left untreated) is applied in 2-4% cases (13). Among those approximately one third die within 6 months (18). Finally, patients are cared and monitored in specialised Neuro-Intensive Care Units (NICU), followed by rehabilitation at neuro-rehabilitation centres (13, 41, 42).

Our aim was not to compare aneurysmal treatment interventions i.e. endovascular coiling vs. neurosurgical clipping, although a current published study (2015) need to be commented. Molyenux et al. (43) performed a large, randomized, multicentre, 18-year follow-up study (International Subarachnoid Aneurysmal Trial, ISAT) comparing the interventions among patients equally acceptable for coiling vs. clipping. They reported significantly reduced mortality and independency at 10-years post-aSAH for patients allocated to coiling. Thus, the beneficial outcome favouring coiling is in line with the current management routines. As endovascular coiling is the dominant treatment strategy since the introduction during the1990s (40) and represents 50-80% of current aSAH interventions (13).

Despite the fact that aSAH management have improved during the last three decades e.g. imaging techniques, Nimodipine administration and coiling technics (18, 24, 27)

complications frequently occur after aSAH such as re-bleeding, acute hydrocephalus, CVS (typically day 3-14 post-ictus) and seizures (18, 41). More, at admission the most important factor related to outcome is the neurological condition, particularly the level of consciousness. Other prognostic factors are; age, location of the ruptured aneurysm and the amount of extravasated blood seen on CT scans (18, 44). Further, the recovery following aSAH vary considerably, as some patients obtain favourable recovery with mild sequelae, and other become totally dependent in every day life (2, 39). aSAH-survivors frequently receive both physical/neurological disabilities e.g. hemiparesis, dysphasia and hemianopia and psychological disabilities i.e. cognitive deficits and personality change, of these psychological disabilities have a major impact on functional outcome (2, 3, 6). However, recovery may occur over prolonged time (8), especially physical sequel, while psychological recovery is suggested to occur earlier, within 12 months (1). Although there are many opinions considering the endpoint of recovery following aSAH and consequently it needs to be further investigated (39, 45, 46).

Admission assessment

Several rating scales exist at admission to assessing the initial clinical condition and the severity of SAH-patients e.g. Glasgow Coma Scale (GCS), Reaction Level Scale 85 (RLS85), World Federation of Neurological Surgeons scale (WFNS), Hunt and Hess scale (Hunt-Hess) and The Fischer scale (13, 47). Hunt-Hess, is a validated five-grading scale established on the level of consciousness, headache, neck stiffness and focal neurological deficits, often dichotomized in favourable (Hunt-Hess 1-3) and unfavourable (Hunt-Hess 4-5) grades (48). The scale is frequently used at admission, despite criticized for the subjective parameters and poor outcome discrimination (47, 49).

Outcome assessment and S-GOS 04 questionnaire

There are several outcome measurements e.g. Glasgow Outcome Scale (GOS), GOSE, modified Rankin Scale (mRS, 0-6), National Institute of Health Stroke Scale (NIHSS, scale of focal neurological deficits) and Barthel Index (BI, 0-100, rating scale of activity of daily living, ADL) (13). We further address GOS and GOSE, especially the former as it was used to investigate long-term functional outcome of aSAH survivors (1, 2). Description of the five-point GOS and eight-point GOSE are given in appendix, table A1.

GOS and GOSE are validated outcome measurements after traumatic brain injuries and non-traumatic brain insults including aSAH. The scales are frequently applied worldwide and recommended to use in clinical trials (11, 46, 49-51). However, it is important to emphasize that GOS and GOSE scores indicate overall functional outcome including physical/ neurological deficits and psychological deficits (1, 2). In this master thesis we have used the term "functional" to describe overall functional outcome after aSAH. Further, GOS and GOSE focus on how the injury influence major area of life without receiving detailed information concerning the deficits and symptoms (51). Thus, the outcome measures only reflect the effect of the brain insult and not pre-existing injuries or chronic conditions (46).

The five-point GOS is a hierarchical scale stratified into following five outcome categories: 1) death 2) persistent vegetative state 3) severe disability 4) moderate disability and 5) good recovery (1). Patients in a vegetative state are unconscious i.e. lack function in the cerebral cortex. Severe disability represents patients, who are conscious, but dependent, i.e. need assistance in daily life. Patients assigned moderate disability are independent in daily life, but disabled i.e. posttraumatic signs are present. Good recovery implicates patients capable of resuming normal life even though minor neurological and psychological deficits exist (1, 2, 7, 12, 46). However, to allow a more sensitive rating of conscious patients the eight-point extended GOS (GOSE) was developed (2, 51).

The eight-point GOSE is identical to the five-point GOS expect for further outcome categories, as the upper three GOS categories (3-5) are subdivided into "better" and "worse" (2). Although, it has been reported that GOSE increase the inter-observer reliability with favourable agreement for GOS (92%) vs. (78%) (51, 52).

Further, GOS and GOSE can be dichotomized in unfavourable outcome (GOS 1-3, GOSE 1-4) i.e. death and independent status and favourable outcome (GOS 4-5, GOSE 5-8) i.e. independent status. This division is beneficial for statistical calculations, applied in this master thesis (2).

To obtain practical and reliable outcome assessment after traumatic brain injuries and non-traumatic brain insults guidelines and a standard well-specified questionnaire has been developed (51). Further, a Swedish version of GOS, S-GOS 04 has been established in accordance with Wilson et al. guidelines. The questionnaire protocol, S-GOS 04 was used in

this master thesis, shown in appendix. S-GOS 04 covers following areas: 1) independence at home 2) independence outside the home (shopping and traveling) 3) employability (work or study) 4) social and leisure activities and 5) interpersonal relationship (family and friendship). In addition there are equal questions concerning pre-injury status. Accordingly, this makes it possible to distinguish between disability caused by the brain insult from pre-existing injuries or chronic diseases (1, 12).

Timing for outcome assessment frequently occurs at 3- or 6-months post-aSAH (3, 9, 53). Despite, Anderson et al. (46) have pointed out that later outcome evaluation at 12- and 24-months post-ictus is more reliable. Further, as already mention there are many opinions considering the endpoint of recovery and consequently the most appropriate time for outcome assessment is frequently discussed. Thus, so far no standardized time for outcome evaluation has been established (45, 46). Consequently, outcome after aSAH needs to be further investigated, especially a decade after the insult, as few studies exist. Thus, this prospectively cohort study 12-15 years post-aSAH may contribute to increased knowledge of functional recovery and mortality for this patient group.

AIM

The primary aim of this master thesis was to investigate long-term morbidity and mortality after aSAH, utilizing GOS and relate these results to Kaplan-Meier survival curves. Further, we wanted to investigate the possibility to detect functional improvement with respect to previous GOS assessments at 1-year for the same patient cohort. Although, we address aneurysm treatment strategies our objective was not to compare treatment paradigms. Finally, we analysed long-term overall mortality and did not investigate the actual death cause.

METHODS

Ethics

The present study was approved by the ethic committee at University of Gothenburg, approval number S 161-00 and complying to the Helsinki Declaration. Informed consent was obtained from patient or next-of kin at admittance to the SU after receiving both oral and written information. A supplement request for this long-term follow-up study was made and approved.

Patients

The present long-term cohort is established from prospectively collected data of consecutive aSAH-patients admitted to the NICU at SU, Gothenburg, Sweden between October 2000 and December 2003. The study design and characteristics of patients have previously been detailed described by Karin Nylén and Ludvig Zoltán Csajbók (12, 13). In this extended prospectively long-term follow-up study-patients were consecutively enrolled when fulfilling the inclusion criteria's:

- NICU admittance < 48 hours after the aSAH
- Confirmed intracranial ruptured aneurysm by intra-arterial angiography, DSA, CTA or intra-operated detected
- Residing in Sweden for outcome assessment
- Informed consent obtained from the patient or next-of-kin

Further inclusion criteria was:

- GOSE assessment at 1-year to explore change in long-term functional outcome.

Thus patients were excluded when not fulfilling above inclusion criteria and if more than one aSAH was verified during the inclusion period, October 2000 to December 2003.

Data collection

We reviewed the following prospectively collected data: date of aSAH onset i.e. day 0 the day of initial severe aSAH symptoms prior arrival to NICU at SU (12), admission date to NICU, gender, admission status evaluated with Hunt-Hess (1-5) and WFNS (1-5), outcome assessments including NIHSS and BI. WFNS, NIHSS and BI are not further evaluated in this study of the aSAH cohort of patients at 12-15 years post-ictus. Further, functional outcome at

1-year, according to the eight-point GOSE was assessed after the long-term outcome data was collected i.e. the current examiner was blinded to previous GOSE-results. Furthermore, we noted aneurysmal treatment strategy either by endovascular coiling, neurosurgical clipping, both interventions (coiling and clipping) or conservative treatment. Age at onset was calculated from birthdate to day 0 (approximated to whole year, cut-off at 6 months). Finally, data regarding the incidence of lifetime aSAH admitted to NICU at SU was collected through records (dead patients) or by telephone-interviews at 12-15 years follow-up (long-term survivors).

Outcomes

We prospectively investigated long-term functional outcomes and mortality with the five-point GOS (1) and Kaplan-Meier survival curves.

Functional status

GOS at 12-15 years post-aSAH, concerning long-term survivors were obtained by structured-telephone interviews, according to the validated S-GOS 04 questionnaire protocol (shown in appendix), with the patient, next-of kin or the patient´s caretaker. The interviews were performed between: August 31, 2015 to October 10, 2015 after verifying that the patient was alive according to the Swedish death registry. Patients unavailable by phone were contacted through mail correspondence, then by a telephone interview. Further, one examiner, not involved in the acute care of the patients, blinded to GOSE-results at 1-year, performed all the interviews, applying guidelines i.e. used a standard written protocol followed by GOS assessment (51). In addition, the interviewer obtained instructions by Ingrid Eiving (present neurointensive nurse at SU, previously assessing functional outcome at 1-year). As described in the introduction, the eight-point GOSE is identical to five-point GOS, except for further outcome categories of conscious patients (2). Thus, we could calculate previous GOSE values (1-8) at 1-year to GOS scores (1-5) at 12-15 years post-ictus. Finally, the functional outcome scale was dichotomized in unfavourable (GOS 1-3) and unfavourable (GOS 4-5) outcomes, in agreement with previous investigations (12, 13).

Long-term GOS change was calculated among survivors with assessed GOS scores at 1-year and at 12-15 years. Accordingly, we could analyse functional outcome over time. Change in

functional outcome was defined as a decrease or increase in at least one outcome category (1-5) or change between unfavourable (GOS 1-3) and favourable (GOS 4-5) outcomes.

Mortality

The aim of this master thesis was to analyse long-term overall mortality/ survival i.e. the death from any cause. Thus, we did not investigate death cause and consequently did not obtain death certificates. However, deceased patients were identified until August 3, 2015 by search in the Swedish death registry and death date was noted. According to an inclusion period between October 2000 and December 2003, long-term aSAH survivors were assessed between 12 and 15 years post-aSAH. Survival probabilities were analysed for; 1) the entire study cohort, starting at aSAH onset and 2) subgroups stratified for age (younger <55years, older >55years), gender and treatment strategy (coiling vs. clipping). Further, we investigated survival probabilities for aSAH survivors at 1-year concerning GOS values (3-5) and dichotomized outcomes in unfavourable (GOS 2- 3) and favourable (GOS 4-5). Deaths in the study cohort were compared to (when appropriate) age, gender, calendar year and area (West Sweden) matched-controls from the Statistical Institute Sweden (SCB) (54).

Statistical methods

Professional statistics assistance (Statistiska Konsultgruppen, Gothenburg, Sweden) was used to obtain the statistical analyses. The statistical analyses were performed with SAS, System Version 9.4 (SAS Institute, Inc, Cary, NC, USA). Further, all significance tests were two-sided and conducted at the 5% significance level. Sample size calculation to detect a difference have previous been performed and were therefore not repeated for this long-term follow-up study (41). The distribution of variables is given as mean, standard deviation (SD), median, minimum and maximum for continuous variables (age) and as number percentage for categorical variables (ordered and dichotomous). For comparison between two groups Mantel-Haenszel Chi Square Exact was used for ordered categorical variables (GOS 1-5 and Hunt-Hess 1-5), Mann-Whitney U-test for continuous variables and Fischer´s exact test for dichotomous variables (gender, age group, coil vs. op. and unfavourable vs. favourable outcome). Spermans´s rank correlation coefficient (r_s) was used for all correlation analyses. Change over time in ordered categorical variables and dichotomous variables, was analysed with Sign test.

Kaplan-Meier survival curves were estimated to analyse overall survival and the end-point being time to death by any cause. The survival analyses were done until August 3, 2015. Patients alive after time to long-term follow-up were censored. We calculated Kaplan-Meier survival curves for the entire study cohort, stratified for age, gender and treatment starting at onset of the aSAH and at 1-year according to GOS values and dichotomized outcomes in unfavourable and favourable. We plotted simulated age, gender, calendar year and area-matched normal population survival curves when appropriate. Log-rank test was used for comparison between survival curves. In order to calculate Hazard Ratio with 95% confidence interval (CI) a Cox proportional hazard regression model was performed.

Standard mortality ratios (SMRs) were calculated to quantify the increase or decrease in mortality for the entire cohort and subgroups compared to age, gender, calendar year and area-matched controls. Observed person-year and observed deaths were calculated for the entire study-cohort from the time of the insult and according to outcome assessments, from 1-year post-aSAH. The expected numbers of deaths were obtained by multiplication of number of observation years in each cell (based on age, gender, calendar year with probability of death in this cell in West of Sweden), data from SCB, summered up over all cells. SMRs with exact 95% CI and p-values using Poisson-distribution from observed and expected number of deaths.

In order to select predictors of long-term favourable outcome (GOS 4-5) univariable logistics regression analysis was applied to each predictor. Further, to select independent predictors of long-term favourable outcome significant predictors in the univariable analysis were entered into a multivariable stepwise logistic regression analysis. The results from the logistic regression analyses are given as Odds Ratio (OR) with 95% CI and p-values. The goodness of fit in the multivariable logistic regression is given as area under the receiver operator characteristic curve (AUC_{ROC}).

RESULTS

Patients

During the inclusion period (Oct 2000-Dec 2003) 212 consecutively patients admitted to NICU at SU were initial candidates to be study participants, of those 158 fulfilled the inclusions criteria's. Accordingly, 54 patients were excluded: 4 patients admitted to NICU >48 hours, ruptured aneurysm was not proven in 40 patients (no aneurysm verified by intra-arterial angiography, DSA or CTA in 32 cases and angiography was not performed in 8 cases), informed consent was not obtained or was withdrawn in 8 cases, 1 patient was not residing in Sweden and 1 patient was initially included twice due to two aSAH insults during the inclusion´s period, therefore we excluded the second insult. Consequently, 158 patients remained and constitute the study population of this master thesis.

Baseline characteristics of all aSAH patients and stratified for age (cut-off median age), gender, Hunt-Hess (1-5) and treatment strategy i.e. endovascular coiling vs. neurosurgical clipping are presented in table 1. Accordingly, the study population consisted of 114 women (72.2%) and 44 men (27.8%), mean age at onset of the haemorrhage was 55 years (SD 10.7) and median age 56 years (range 20-81 years). Further, we observed that men were significant younger (p=0.030) than women at onset of the haemorrhage. Mean age for men was 52.8 (SD 9.9) and for women 56.2 (SD 10.9). Furthermore, there was a significant difference (p=0.036) between gender and Hunt-Hess with favourable grading i.e. less severe aSAH at admission for men. Endovascular coiling was the dominant aneurysmal intervention applied in 111 patients (70.3%). Operation with neurosurgical clipping was performed in 40 cases (25.3%), 3 patients (1.9%) underwent both coiling and clipping to occlude the aneurysm(s). Conservative treatment i.e. no active aneurysmal intervention was implemented in 4 cases (2.5%).

Further, we identified six patients (3.8%) (3 men and 3 women), with two insults during their lifetime admitted to NICU at SU, of those 5 had multiple aneurysms and 2 patients are still living (2 women).

Table 1. Baseline characteristics of all aSAH-patients and stratified for age group and gender.

		By age group			By gender		
Variable	**Total Population (n=158)**	**<55 years at onset (n=72)**	**≥55 years at onset (n=86)**	**p-value**	**Male (n=44)**	**Female (n=114)**	**p-value**
Gender							
Male	44 (27.8%)	26 (36.1%)	18 (20.9%)		44 (100.0%)		
Female	114 (72.2%)	46 (63.9%)	68 (79.1%)	0.052		114 (100.0%)	
Age at onset	55.2 (10.7) 56 (20; 81) n=158	45.8 (6.7) 47 (20; 54) n=72	63.2 (5.9) 62 (55; 81) n=86		52.8 (9.9) 52 (34; 74) n=44	56.2 (10.9) 58.5 (20; 81) n=114	0.030
Treatment							
Coil	111 (70.3%)	48 (69.6%)	63 (76.8%)		32 (76.2%)	79 (72.5%)	
Op	40 (25.3%)	21 (30.4%)	19 (23.2%)	0.41	10 (23.8%)	30 (27.5%)	0.81
Coil + Op	3 (1.9%)						
Conservative	4 (2.5%)						
Hunt and Hess							
1	29 (18.7%)	18 (26.1%)	11 (12.8%)		14 (31.8%)	15 (13.5%)	
2	47 (30.3%)	22 (31.9%)	25 (29.1%)		12 (27.3%)	35 (31.5%)	
3	44 (28.4%)	14 (20.3%)	30 (34.9%)		11 (25.0%)	33 (29.7%)	
4	25 (16.1%)	10 (14.5%)	15 (17.4%)		5 (11.4%)	20 (18.0%)	
5	10 (6.5%)	5 (7.2%)	5 (5.8%)	0.12	2 (4.5%)	8 (7.2%)	0.036

For categorical variables n (%) is presented. For continuous variables Mean (SD) / Median (Min; Max) / n= is presented.
For comparison between groups Fisher´s Exact test was used for dichotomous variables and the Mantel-Haenszel Chi Square Exact test was used for ordered categorical variables and the Mann-Whitney U-test was used for continues variables. Coil, endovascular coiling. Op, neurosurgical clipping. P-values, coiling vs. clipping is presented. Hunt-Hess, favourable 1-3, poor 4-5, missing, n=3.

Outcomes

Functional outcomes according to GOS at 1-year (n=150) and at 12-15 years (n=158) post-aSAH, and mortality for the entire study cohort (n=158) until August 3, 2015 are shown in table 2. Thus, GOS results at 1-year were missing for 8 patients and no patient was in vegetative state (GOS 2) at any time.

Table 2. Functional outcomes by GOS scores and dichotomized in unfavourable and favourable outcomes at 1-year and at 12-15 years post-aSAH. Mortality from onset of the insult to the long-term follow-up is presented.

	GOS		Mortality
Variable	1-year post-aSAH (n=150)	12-15 years post- aSAH (n=158)	Total deaths (n=55)
GOS scores			
1 (dead)	23 (15.3%)	55 (34.8%)	
3 (severe disability)	26 (17.3%)	16 (10.1%)	
4 (moderate disability)	62 (41.3%)	24 (15.2%)	
5 (good recovery)	39 (26.0%)	63 (39.9%)	
Dichotomized outcomes			
Unfavourable (GOS 1-3)	49 (32.7%)	71 (44.9%)	
Favourable (GOS 4-5)	101 (67.3%)	87 (55.1%)	
Mortality			
Deaths within the first 30 days			15 (9.5%)
Deaths between 30 days and 1-year			8 (5.1%)
Deaths between 1-year and 12-15 years			32 (20.3%)
Time to death (years)			4.84 (4.84) 3.95 (0.01; 13.71) (n=55)

For categorical variables n (%) is presented. For continuous variables Mean (SD) / Median (Min; Max) / n= is presented.
GOS scores at 1-year, missing n=8. No one obtained GOS 2 (vegetative state) at any time.

Functional status

GOS at 1-year; a major of the study cohort, 62 patients (41.3%) had moderate disability (GOS 4) at 1-year follow-up. 26 patients (17.3%) assigned severe disability (GOS 3) i.e. were dependent in every day life. Favourable outcome (GOS 4-5) was identified in 101 patients (67.3%). Further, GOS at 1-year stratified for age (p=0.57), gender (p=0.30) and treatment strategy: coiling vs. clipping (p=0.76) did not show any significantly difference (shown in appendix, table A2).

GOS was validated in all 103 survivors (65.2%) at 12-15 years post-aSAH i.e. complete long-term follow-up. Outcome categories (GOS 3-5) were obtained by telephone-interviews from: patient (n=83), patient + next-of kin (n=1), patient + caretaker (n=1), only next-of kin (n=12), next of-kin + caretaker (n=3), and only caretaker (n=3). The majority of the study cohort, 63 patients (39.9%) had good recovery (GOS 5) at 12-15 years post-aSAH. Moderate disability (GOS 4) was noted in 24 patients (15.2%). 16 patients (10.1%) had severe disability (GOS 3). Further, unfavourable outcome (GOS 1-3) was detected in 71 patients (45.9 %) and favourable outcome (GOS 4-5) was noted in 87 patients (55.1 %) at 12-15 post-ictus.

GOS assessments at long-term follow-up stratified for age, gender, treatment and admissions status (Hunt-Hess 1-5) are presented in table 3. There was no significant difference between gender and GOS values at 12-15 years post-aSAH (p=0.69). Further, a significant correlation regarding older age at onset and worse functional outcome was detected (p=0.024, r_s -0.18). There was a significant difference between aneurysmal intervention and GOS scores (p=0.029), favouring clipping over coiling. Finally, poor Hunt-Hess (4-5) was significantly correlated with worse functional outcome at 12-15 years post-ictus (p=0.0008, r_s-0.27).

Table 3. GOS scores at 12-15 years post-aSAH stratified for age, gender, treatment and admission status.

Variable	1 (n=55)	3 (n=16)	4 (n=24)	5 (n=63)	p-value
Gender					
Male	16 (29.1%)	7 (43.8%)	3 (12.5%)	18 (28.6%)	
Female	39 (70.9%)	9 (56.3%)	21 (87.5%)	45 (71.4%)	0.69
Age at onset	59.2 (10.6) 59.0 (32.0; 81.0) n=55	52.5 (9.3) 51.5 (34.0; 66.0) n=16	50.6 (7.6) 51.0 (39.0; 67.0) n=24	54.2 (11.2) 56.0 (20.0; 76.0) n=63	0.024
Coil/Op					
Coil	44 (88.0%)	9 (56.3%)	15 (62.5%)	43 (70.5%)	
Op	6 (12.0%)	7 (43.8%)	9 (37.5%)	18 (29.5%)	0.029
Hunt and Hess					
1	6 (10.9%)	1 (6.7%)	5 (21.7%)	17 (27.4%)	
2	14 (25.5%)	5 (33.3%)	4 (17.4%)	24 (38.7%)	
3	18 (32.7%)	7 (46.7%)	8 (34.8%)	11 (17.7%)	
4	10 (18.2%)	2 (13.3%)	5 (21.7%)	8 (12.9%)	
5	7 (12.7%)	0 (0.0%)	1 (4.3%)	2 (3.2%)	0.0008

For categorical variables n (%) is presented. For continuous variables Mean (SD) / Median (min; Max) / n = is presented.
For comparison between groups the Mantel-Haenszel Chi Square Exact test was used for dichotomous variables and Spearman´s rank correlation test was used for continuous and ordered categorical variables. Coil, endovascular coiling. Op, neurosurgical clipping. Hunt-Hess, favourable 1-3, poor 4-5, missing n=3.

GOS change from 1-year to 12-15 years post-aSAH, stratified for GOS scores (3-5) and dichotomized in unfavourable and favourable outcomes, only including survivors at 1-year (n=127) are summarized in table 4 and illustrated in figure 1. Whereas 23 patients died within 1-year they are not considered regarding GOS change over long-time. As mentioned earlier no patient estimated vegetative state (GOS 2) at any time i.e. change in functional outcome consider conscious patients at 1-year follow-up.

Concerning GOS scores (3-5), 31 patients (24.4%) died between 1-year and 12-15 years post-aSAH. A major patient population, 59 patients (46.5%) obtained equal outcome category at 1-year and at 12-15 years. Further, 38 patients (29.9%) obtained a reduced outcome category. Approximately one forth (23.6%), 30 patients improved GOS scores over long-time.

Although changed in GOS categories were estimated between 1-year and 12-15 years post-aSAH there was not a significant difference between decreased and increased GOS scores (p=0.40). Further, when dichotomizing patients into unfavourable (GOS 1-3) and favourable (4-5) outcome a significant decreases in outcome was noted (p=0.0002). As result of that 22 patients (17.3%) relocated from favourable to unfavourable outcome and 3 patients (2.4%) relocated from unfavourable to favourable outcome i.e. from dependency to independency.

Table 4. GOS change from 1-year to 12-15 years post-aSAH, only including survivors at 1-year follow-up (GOS 3-5).

Variable	1-year follow up (n=127)	12-15 years follow up (n=127)	Change from 1-year to 12-15 years follow-up		p-value
GOS scores					
1	0 (0.0%)	31 (24.4%)			
3	26 (20.5%)	14 (11.0%)	Decrease	38 (29.9%)	
4	62 (48.8%)	21 (16.5%)	Equal	59 (46.5%)	
5	39 (30.7%)	61 (48.0%)	Increase	30 (23.6%)	0.40
Dichotomized outcomes			Decrease	22 (17.3%)	
Unfavourable (GOS 1-3)	26 (20.5%)	45 (35.4%)	Equal	102 (80.3%)	
Favourable (GOS 4-5)	101 (79.5%)	82 (64.6%)	Increase	3 (2.4%)	0.0002

For categorical variables n (%) is presented. For comparison over-time, Sign test was used for categorical variables. GOS scores: 1=dead, 3=severe disability, 4=moderate disability, 5=good recovery.

Detailed description of changes in functional outcomes within each GOS category among the 127 survivors at 1-year to 12-15 years are depicted in figure 1. Concerning the 26 patients having severe disability (GOS 3) at 1-year, the majority, 16 patients (62%) died, 7 patients (27%) remained at the same outcome level, and 3 patients (12%) improved to good recovery (GOS 5) i.e. relocated from dependency to independency. Further, of those 62 patients assigned moderate disability (GOS 4) at 1-year a minority, 14 patients (22%) decreased outcome scores: 7 patients died and 7 patients trans located to severe disability (GOS 3). 21 patients (34%) had equal functional outcome level and the majority, 27 patients (44%) improved to good recovery (GOS 5). Finally, of those 39 patients having good recovery (GOS 5) at 1-year, an excessive majority, 31 patients (79%) remained at the same functional level over long-time. Approximately one fifth, 8 patients (21%) died.

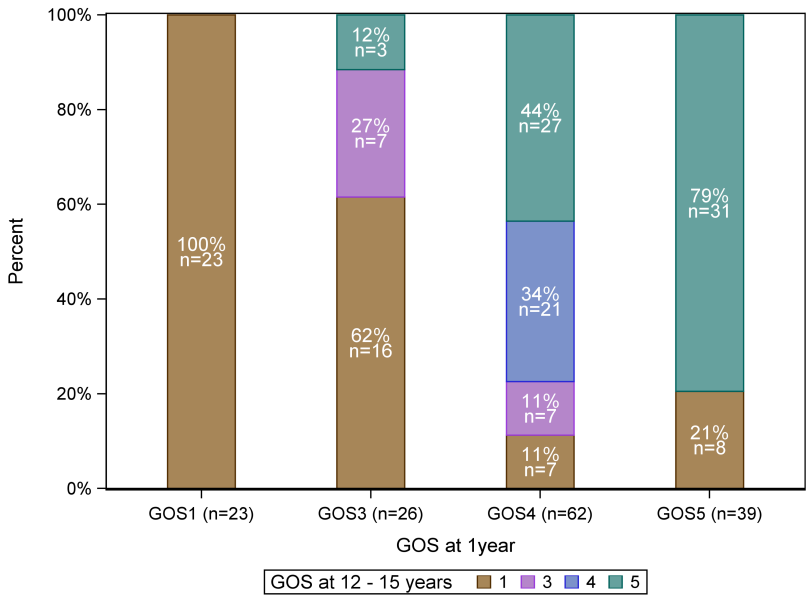

Figure 1. GOS change among the 127 aSAH survivors at 1-year to 12-15 years and deaths within 1-year. Staples represent GOS at 1-year and colours GOS at 12-15 years. GOS 1=dead, GOS 3=severe disability, GOS 4=moderate disability and GOS 5=good recovery.

In addition, we analysed GOS change between 1-year and 12-15 years stratified for age and gender (shown in appendix, table A3 and A4). Age dichotomized in two groups, cut-off median age: younger (<55 years, n=64) and older (≥55 years, n=71) patients did not significant influence change in GOS, neither in GOS scores (p=0.73) nor dichotomized outcomes in unfavourable and favourable (p=0.45). Further, there was no significant difference between gender and change in GOS scores or dichotomized outcomes (adjusted p for age and Hunt-Hess: p=0.057 and p= 0,47 respectively).

Mortality

The distribution of death rates within long-term follow-up (until August 3, 2015) is listed in table 2. Accordingly, of all 158 aSAH-patients enrolled in this study, 55 patients (34.8%) died during the long-term follow-up period, median 3.95 years (range 0.01-13.7 years) post-ictus. Thus, we identified 15 deaths (9.5%) within the first 30 days, 8 patients (5.1%) died between 30 days and 1-year and 32 patients (20.3%) died between 1-year and time for long-term follow-up (last death occurred July 30, 2015). Consequently, 103 aSAH survivors (65.2%) were identified. The survival time was mean 13.3 years (range 11.6-14.8 years) post-aSAH, depending on when the patient was included between October 2000 and December 2003.

Kaplan-Meier survival curves of all aSAH patients (n = 158) and stratified for GOS, age, gender and treatment strategy are presented in figures 2-6. SMRs are shown in appendix, table A4 and A5. In the Kaplan-Meier survival curves censured observations i.e. long-term survivors (n=103) are visualized with vertical lines. The cumulative survival probability is represented on the y-axel and numbers at risk indicated on the x-axel at six time points.

Figure 2. Illustrates survival curves of all aSAH patients (n=158) from onset of the insult to long-term follow-up compared to age, gender, calendar year and area-matched controls. There was a statistically significant increased mortality for aSAH-patients; SMR 3.50 (95 % CI 2.6–4.6, p<0.0001) compared matched controls.

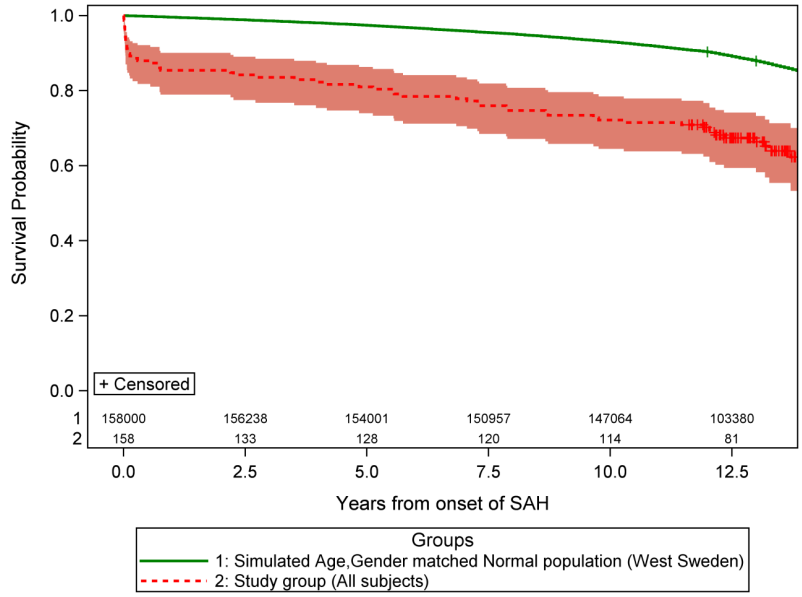

Figure 2. Kaplan-Meier survival curves of all aSAH-patients (n=158) compared to matched controls. 95 % CI is plotted and censured observations i.e. long-term survivors (n=103) indicated with vertical lines.

Figure.3 illustrates long-term survival probability of all aSAH-patients still alive at 1-year (n = 127) dichotomized in unfavourable (GOS 3) and favourable (GOS 4-5) outcomes compared to age, gender, calendar year and area-matched controls, respectively. Thus, survivors at 1-year dichotomized into unfavourable outcome (n = 26) had statistically significant increased mortality compared to the matched controls, SMR 4.27 (95 % CI 2.4-6.9, p < 0.0001). This increased mortality was not observed in patients with favourable outcome (n = 101) at 1-year, SMR 1.4 (95 % CI 0.78 – 2.3, p = 0.27). Further, there was a significant difference between patients with favourable and unfavourable outcomes (log rank p<0.0001) Hazard Ratio = 0.16 (0.08; 0.32).

In addition, we investigated the correlation between GOS score (3-5) at 1-year and long-term survival probability. There was a significant correlation between worse GOS value at 1-year and increased mortality (log rank p=0.0003). As mention above and depicted in figure 3 patients assigned GOS 3 (unfavourable outcome, n=26) had significantly increased mortality than matched controls SMR 4.27 (95% CI 2.44-6.93 p<0.0001). This evaluated mortality was not significant for patients with GOS 4 and 5, SMR 1.38 (95% CI 0.56-2.85, p=0.49) and SMR 1.39 (95% CI 0.60-2.73, p=0.45), respectively.

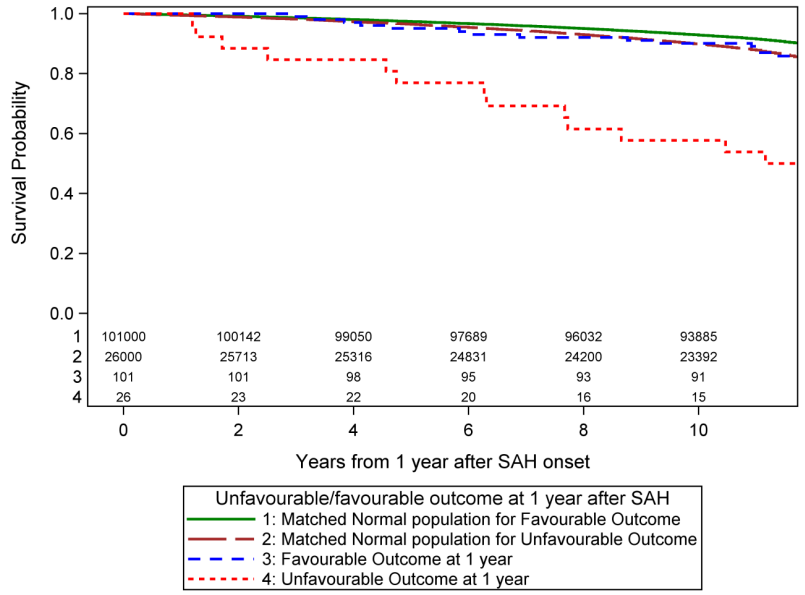

Figure 3. Kaplan-Meier survival curves divided in unfavourable (GOS 3) and favourable (GOS 4-5) outcomes at 1-year compared to respective matched controls.

Survival curves stratified for two age groups are depicted in figure 4. There was a significant difference between younger (<55 years) and older (≥55 years) aSAH-patients (log rank p=0.012). Further, both younger and older patients had significantly increased mortality compared to matched controls, SMR 7.09 (95 % CI 4.13 – 11.35, p<0.0001 and SMR 2.86 (95 % CI 2.02 – 3.92, p<0.0001), respectively.

Comparison of survival curves according to gender did not show significant difference (log rank p=0.75), shown in figure 5. Further, both men (n=44) and women (n=114) had approximately 3.5 times higher mortality than matched controls. The increased mortality was significant both for men SMR 3.45 (95% CI 1.97-5.60, p<0.0001) and women SMR 3.53 (95% CI 2.51-4.82, p<0.0001).

Survival curves in patients who underwent endovascular coiling (n=111) and neurosurgical clipping (n=40) are presented in figure 6. There was a significant different survival probability between the interventions (log rank p=0.0089), favouring surgical treatment. Further, patient treated with coiling had a significant increased mortality than matched controls SMR 3.69 (95% CI 2.68-4.95 p<0.0001). The evaluated mortality was not significant for an operative treatment strategy, SMR 1.67 (95% CI 0.61-3.63, p=0.31).

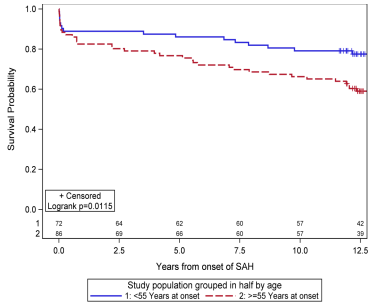

Figure 4. Survival curves according to two age groups: <55 vs. ≥55 years.

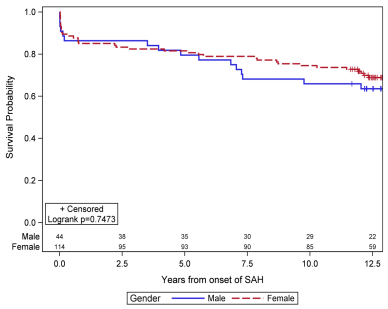

Figure 5. Survival curves according to gender.

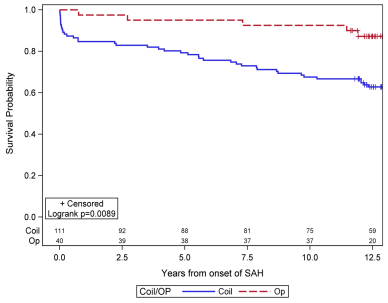

Figure 6. Survival curves according to treatment: coiling vs. clipping.

Prediction of long-term favourable outcome

The results concerning predictors of long-term favourable outcome (GOS 4-5) from onset of the aSAH are shown in appendix, table A7. Hence, univariable significant predictors of favourable outcome at 12-15 years post-ictus were low age; OR per ten year 0.66, p=0.0095 and low Hunt-Hess; OR per ten year 0.66, p=0.0057. In the multivariate model both, age adjusted OR 0.68 and Hunt-Hess adjusted OR 0.68 were included, AUC_{ROC}: 0.67 (95% CI 0.58-0.76).

Predictors of long-term favourable outcome at 1-year follow-up are presented in appendix, table A8. Thus, univariable significant predictors of favourable outcome at 12-15 years post-aSAH were low age; OR per ten year 0.62, p=0.012, high GOS at 1-year; OR 4.88, p<0.0001 and favourable outcome at 1-year; OR 27.5, p<0.0001. In the multivariate model both age adjusted OR 0.57, and GOS at 1-year adjusted OR 5.02 were included, AUC_{ROC}: 0.79 (95% CI 0.71-0.88). Further, no predictive values were shown for gender (univariabale p=0.25 and 0.17) and treatment strategy (univaraible p=0.098 and 0.41) at neither time-point.

DISCUSSION

In this prospectively study cohort, conducted on 158 aSAH-patients admitted to NICU at SU between October 2000 and December 2003 outcome was investigated 12-15 years post-ictus. We focused on long-term morbidity and mortality, validated by GOS. We found that individual functional improvement occurred between 1-year and 12-15 years after the haemorrhage. Although at cohort level deterioration was noted. Further, we detected that GOS assessment at 1-year was a useful predictor of long-term mortality and functional outcome. Thus, patients with favourable outcome (i.e. independency) at 1-year follow-up had the same long-term life expectancy as the general population, while patients with unfavourable outcome (i.e. dependency) had >4 times increased mortality than similar matched controls. More, the best indicators of long-term favourable prognosis were high GOS scores and low age at 1-year follow-up. Finally, high age and severe clinical status, but not gender, were risk factors for poor outcome.

Initially, we discovered that our patient-cohort had similar characteristic's concerning; age (55.2 years), gender (72.2% female), clinical admission status (77.4% Hunt-Hess 1-3) vs. others (7-9, 18, 24, 27, 49, 55). When scrutinizing our material we observed that male patients were younger (52.8 years) than female (56.2 years), in accordance with previous studies (4, 24, 56). Further, we detected that female patients were admitted in worse clinical condition (higher Hunt-Hess) than male patients. These results comply with Koffijberg et al. (27) reported higher case fatality rate within the first 28 days in women (32.5%) than in men (30.5%). Conclusively, women seem to be older and in a more severe condition than men at University Hospital admission. The dominant aneurysmal treatment of the patients was endovascular coiling (70.3%), in agreement with the therapy trend during the 2000s, favouring coiling over clipping (13, 24). Further, approximately one third (32.7%) was assigned unfavourable outcome at 1-year i.e. dead or dependency, as reported in larger studies (49, 57). In conclusion, our study cohort of 158 aSAH patients has similar characteristics as other studies, indicating that our results may be generally applicable.

Hypotheses

Hypothesis 1 – functional improvement

Our first hypothesis was that it possible to detect functional improvement >1-year post-aSAH. Our results demonstrated that long-term functional recovery is possible in conscious patients at 1-year, either by increased GOS scores and/ or change from unfavourable to favourable outcome i.e. from dependency to independency. A forth (23.6%) of the 127 survivors at 1-year increased their functional recovery, primarily from moderate disability to good recovery. Further, in the 26 patients with unfavourable outcome i.e. severe disability at 1-year, approximately 12% improved and relocated to good recovery. In addition, we detected that 1-year survivors with good recovery, either stayed at the same functional level or died similarly as matched healthy controls. Conclusively, our findings show that recovery following aSAH is a long-term dynamic process as deterioration and improvement occurred between 1-year and 12-15 years post-ictus and the incidence of recovery was greatest of those with moderate disability at 1-year. Hence, the endpoint of functional outcome is beyond 1-year post-aSAH.

The possibility of long-term recovery is in agreement with other studies (8, 9). Thus, Wilson et al. (9) investigated clinical improvement within a period of 3-years, by mRS in poor-grade aSAH patients (Hunt-Hess 4-5). They observed that 19% of the 75 available patients improved at least one mRS grade between 1- and 3-years post-ictus. However, few studies have investigated long-term clinical outcomes beyond 10-years. The only previous study found was Grebbe et al. (8) analysing functional outcomes by mRS and quality of life (QoL) with the short form 36 (SF-36) and visual analogue scale (VAS) at 5-years and 12.5-years post-aSAH and compared the results with previous follow-up investigations at 4- and 18-months. The authors found functional improvement between 4-months and 5-years in 55.5% (29 of 52 patients), but no further recovery to 12.5-years, although increased QoL. This prospective study has some limitations. Firstly, it is a relative small cohort, as only 52 patients was available at the 5-years follow-up and secondly, 5 patients were lost to long-term follow-up. Contrary, the probability to detect functional recovery is higher in our prospective long-term follow-up study, among the 127 survivors at 1-year. As all 103 patients still living at 12-15 years post-ictus were structured interviewed according to GOS. Thus, we identified individual long-term functional recovery in 30 patients (23.6%) and of those 3 patients (2.3%) relocated from severe disability to good recovery from 1-year to 12-15 years after the aSAH.

We observed that recovery following aSAH is a long-term dynamic process, in accord with other investigations (7, 9). Whereas similar proportion deteriorated and improved GOS scores over time; 29.9% and 23.6%, significant decrease in outcome was only detected when dichotomizing outcome into unfavourable and favourable. In agreement with Svensson et al. (7) we identified highest recovery potential in those who were found to have moderate disability at 1-year.

When scrutinizing age and gender we identified that younger (<55years) and older (≥55years) conscious patients at 1-year recovered similarly over long-time. This observation is in line with Wilson et al. (9) who reported that aSAH patients <65years had higher potential for improvement beyond 6 months, although not beyond 1-year, than those >65years of age. When investigating gender, our results demonstrated that men and women have comparable probability for functional improvement beyond 1-year, in accord with Wilson et al. (9). However, the influence of age and gender of long-term functional recovery need to be investigated further in larger patient cohorts.

To conclude, we found that long-term functional improvement is possible at the individual level, both in independent and dependent patients at 1-year. One forth improved GOS scores and in those having severe disability, 12% relocated to favourable outcome between 1-year and 12-15 years post-ictus. Patients with moderate disability at 1-year have the highest potential to further recovery. Although at cohort level deterioration was detected when dichotomizing patients into unfavourable and favourable outcome. Conclusively, our results demonstrate that outcome assessment may be appropriate beyond 1-year, as long-term recovery is possible. Thus giving the patient, their families and caregivers important knowledge.

Hypothesis 2 – mortality

Our second hypothesis was that patients with aSAH have increased long-term mortality compared matched controls. We found this hypothesis to be true as aSAH-patients had 3.5 times higher long-term mortality compared to the control population. Further, the mortality in aSAH-patients 12-15 years post-ictus was 35%. However, surprisingly, our results demonstrated that survivors at 1-year with favourable outcome i.e. independency had similar survival probability as age-, gender-, calendar year- area-matched controls, while patients

with unfavourable outcome i.e. dependency had 4.3 times excess mortality than the control population. Conclusively, the long-term mortality is increased in patients with aSAH vs. matched controls. However, the novel finding in this study is that patients with favourable functional outcome at 1-year follow-up had the same long-term life expectancy as the general population.

The long-term mortality of 35% is in line with other studies (10, 49, 55, 58, 59). Contrary to our results, Wermer et al. (59) prospectively study, found that independent patients at 1-year had reduced survival probability compared to a matched control population. The study by Wermer and co-workers, though larger (n=752) has several limitations. Their patients were only surgical treated and they had an earlier inclusion-period; 1985 to 2001 when new treatments i.e. endovascular coiling was introduced during the 1990s (24, 40). Thus, our results with an inclusion-period between 2000 and 2003 and with the majority (70%) being coiled may be more generally applicable.

We investigated long-term mortality including confounding factors like age, gender and treatment strategy at onset of the aSAH. We found that younger (<55 years), independent of gender, had favourable survival probability than older (≥55 years) patients. This is not surprising and in agreement with several studies (10, 18, 24, 27, 47, 49, 60). The striking enhanced mortality for younger (<55years) patients, approximately 7 times, may be explained by the fact that younger healthy individuals have lower yearly mortality. Further, as already mention, gender did not influence long-term mortality, previous demonstrated (10, 24). Interestingly, our results suggest beneficial long-term survival probability for neurosurgical clipping over endovascular coiling, opposed to larger multicentre, randomized studies (e.g. ISAT and Barrow Ruptured Aneurysm Trial, BRAT) (43, 61). However, these results must be interpreted with caution, as aneurysms in the posterior circulation is difficult and hazardous to secure and is if possible/ often endovascular treatment of choice (18). Further, patients in this study were not randomized to treatment paradigms.

Finally, it is relevant to know whether long-term morbidity and mortality have improved with the established treatment routines at SU over the past. This includes CT angiography, Nimodipine administration, improved intensive care and endovascular coiling techniques. The appreciations of these new procedures/ treatments have reduced both morbidity and mortality during the past three decades (11, 24). For instance Naval et al. (11) observed that functional

outcomes after aSAH estimated 30-120 days post-discharge by dichotomized GOS in favourable (GOS 4-5) have improved in the decade of 2001 to 2009 (71.5%) compared to 1991 to 2001 (65.2%). In accord with these result Nieuwkamp et al. (24) stated in a meta-analysis that case-fatality rates have decreased with 17% between 1973 and 2000. In addition, a Swedish retrospective study in >18000 aSAH-patients between1987 to 2002 reported that both the incidence and case-fatality rates have decreased over time (27). Conclusively, as the treatment routines (according to the standardized protocol) at SU are similar since early 2000s we can conclude that the management of aSAH-patients in our study cohort probably has contributed to beneficial outcomes compared to previous treatment paradigm.

In summary, life expectancy is reduced in aSAH survivors independent of gender. Further, our results demonstrate that independent patients i.e. dichotomized in favourable outcome at 1-year have similar survival probability compared to age-, gender-, calendar year-, area-matched controls. Therefore, we speculate that patients with unfavourable outcome at 1-year should have periodical intermittent follow-ups as individual recovery is possible to occur over long-time. Finally, the financial applications of our research may be great.

Hypothesis 3 – outcome prediction

To facilitate management decision and as a consequent of that current admission scales (GCS, RLS 85, Hunt-Hess, WFNS, Fischer scale) are claimed to poorly predict outcome (13, 47) we investigated predictors of long-term favourable outcome i.e. independency. We found independent significant predictors of long-term favourable outcome at onset of the haemorrhage; low age, low Hunt-Hess grade and at 1-year; low age, high GOS scores and favourable outcome. The best indicators of long-term favourable prognosis were GOS and age at 1-year follow-up.

As mentioned, the prognostic accuracy was greatest for GOS at 1-year combined with age, as AUC_{ROC} in the multivariate model was 0.79 (95% CI 0.71-0.88). In addition, GOS scores and dichotomized outcome in favourable (i.e. independency) were separately moderate/ strong significant predictors of long-term favourable outcome, as AUC_{ROC} was similar (0.74, $p<0.0001$). Interestingly, Rosen et al. (49) in a large multicentre study among 3567 aSAH patients compared their created grading scale with the WFNS. They demonstrated favourable prognostic accuracy for their scale (AUC_{ROC} 0.78 vs. 0.74, $p<0.05$). Hence, the prognostic

accuracy that we demonstrated for GOS at 1-year together with age is greater and maybe useful to add in clinical practice to facilitate clinical decisions.

Further, low age and low Hunt-Hess grade were significant independent predictors (separately and together) of long-term favourable outcome, although the prognostic value was poor. AUC_{ROC} in the multivariate model including age and Hunt-Hess at admission was 0.67 (95% CI 0.58-0.76). Concerning age, the prognostic value were poor both at admission and at 1-year (AUC_{ROC} 0.62, p=0.019 and p=0.016). The negative association with increasing age at admission and outcome has previously been demonstrated (27, 47, 49, 60), though the prognostic value beyond 1-year is questioned in agreement with our findings. For instance Wilson et al. (9) observed that age <65years was not associated with clinical improvement after 1-year. Further, Hunt-Hess predictive value should be interpreted with caution, even if it has been associated with outcome (9, 47, 49). Firstly our results indicate poor prognostic value and secondly the admission scale has been criticized for high inter-observer variability and poor outcome discrimination (47, 49). Accordingly, age and Hunt-Hess predictive value of long-term favourable outcome need to be further investigated.

Furthermore, no predictive values were shown for gender, previously reported (9, 49) and treatment strategy (coiling vs. clipping) at admission or at 1-year, in accord with (9).

In conclusion, among the variables found to be independent predictors of favourable outcome at 12-15 years after the insult, GOS scores and favourable outcome at 1-year were the strongest predictors and the best indicators of long-term favourable prognosis were GOS and age at 1-year follow-up. As described in the introduction, GOS is a current useful tool worldwide in outcome assessment, despite most frequently used within the first 6 months (1, 3, 9, 13, 53). Our findings suggest that GOS is a valuable outcome tool at 1-year and consequently may an appropriate complement in clinical practice.

Methodological considerations

Strengths

The major strength of this single centre prospectively cohort study was the complete long-term follow-up, 12-15 years after the aSAH. All the 103 survivors were structured-telephone interviewed, according to validated GOS and mortality was demonstrated for the entire study

cohort. Further, all interviews were performed by the same (trained) examiner, blinded to previous GOSE results at 1-year and had not been involved in the acute care of the patient in agreement with current guidelines (51). In addition, the standardized questionnaire protocol (S-GOS 04) made the results valuable i.e. received high inter- and intra-observer agreement (46). Further, in accordance with the detailed follow-up at 1-year (performed by the same neurologist), we could compare functional outcome between 1- and 12-15 years post-aSAH. Another strength was that we could evaluate management routines of this particular patient cohort, as our patient cohort is from the same geographical area (West Sweden), have received management at NICU at SU according to an established protocol. Finally, we adjusted for age, gender, calendar year and geographical area (West Sweden) and used matched controls in all our analyses.

Limitations

Limitations consider GOS assessment should be acknowledged. Firstly, it is subjective outcome assessment and therefore combined with inter- and intra-observer variability (46, 62, 63). However, this is an issue of all rating scales. As mention above we tried to prevent uncertainty, by adopting guidelines for the interviews (51), and applied a validated standard questionnaire (S-GOS 04). Further, GOS has been criticized to be insensitive and emphasizing physical rather than cognitive and emotional deficits (45, 46, 52). Hence, we may have oversight the actual improvement beyond 1-year and neglected psychological deficits that have a major impact on functional outcome (1). Further, pre-existing injuries/diseases and naturally aging have might confounding GOS rating. Further, I would suggest adaption of the S-GOS 04 to a more appropriate questionnaire for long-term outcome estimation, as the question concerning employability was inconsistent in this aging population. Finally, outcome assessment based on direct patient contact (as the 1-year follow-up) would have been desirable (46). Although hard to achieve, for instance appointment attendance may contribute to high incidence of dropouts.

Other limitations need to be considered. We have probably underestimated the accurate mortality, as the most severe patients, outside downtown Gothenburg, do not reach the University Hospital (12, 13). Our results demonstrated 9.5% deaths within the first 30 days, in contrary to Koffjiberg et al. (27) retrospectively study in Sweden reporting 31.7% case-fatality rate within the first 28 days. Although, mortality rates based on retrospectively

collected data are associated with uncertainty. In addition, case-fatality rates vary considerable between medical centres in the world (10% to 60%) (24, 39). Further, selection bias may have skewed our results comparing the interventions; coiling vs. clipping. As already mention, coiling have been restricted to poor surgical candidates e.g. patients with greater medical comorbidities and increased age that may prevent generalising our findings (13). Finally, we did not adjust for modifiable risk factors for aSAH such as smoking, hypertension and excessive alcohol intake (30, 34). However, we adjusted for age, gender, calendar year and area.

Further studies

In future, when performing extensive long-term follow-ups after aSAH, it would be desirable with more frequent time-points for outcome estimation, to specify when improvement occurs. Further, neuropsychiatric testing should be a consideration, especially of those in the upper functional outcome categories (GOS 4-5). Concerning our study cohort, I would suggest continual follow-ups of young (<55 years) aSAH-patients to analyse the mortality compared to matched controls. In addition, it would be interesting to continue to follow the unfavourable (GOS 3) study cohort to investigate if long-term recovery is possible to occur beyond 15-years. Further, for comparison of long-term outcome between medical centres in Sweden and according to the high incidence of aSAH in the north (27), an extended follow-up in this geographical area would be valuable. Finally, we have investigated the overall long-term mortality i.e. the actual death causes remain to be examined. In addition the correlation with modifiable risk factors such as hypertension, smoking and excessive alcohol consumption (30, 34) and long-term outcome persist to be further investigated.

CONCLUSIONS

- Functional improvement was possible at the individual level between 1 and 12-15 years post-aSAH. Both concerning increased GOS scores and relocation from dependent (GOS 3) to independent (GOS 4-5) status. The majority of long-term recovery appeared in patients with moderate disability at 1-year and in patients with good recovery, a majority (79%) stayed at the same functional outcome level over long-time.
- Patients with aSAH had independent of gender 3.5 times increased mortality as the general population. Although, patients with favourable outcome at 1-year had the same long-term life expectancy compared to matched controls, while dependent patients had 4.3 times excess mortality.
- GOS was a validated tool at 1-year to predict long-term favourable outcome at 12-15 years post-aSAH. The best indicators of long-term favourable prognosis were GOS and age at 1-year follow-up.
- High age and low Hunt-Hess grade, but not gender, were risk factors of long-term poor outcome.

Medical relevance

Our findings indicate that GOS at 1-year may be a valuable tool in clinical practice to predict long-term prognosis, both concerning mortality and functional status. As patients with favourable outcome at 1-year had the same long-term life expectancy as the general population and of those, younger patients had the greatest possibility to an independent status 12-15 years post-aSAH. While patients with severe disability at 1-year had enhanced mortality, but at individual level recovery is possible over time. Thus, a better functional status may be possible to obtain with rehabilitation. Conclusively, GOS long-term predictive value may be a complement to facilitate clinical decision-making and enable comparison of outcome between medical centres.

POPULÄRVETENSKAPLIG SAMMANFATTNING

Subarachnoidalblödning (SAH) är en undergrupp av stroke som oftast (85 %) beror på ett brustet pulsåderbråck s.k. aneurysm lokaliserat på skallbotten som medför att blod sprids utanför hjärnan. Denna hjärnblödning har vi studerat. Det mest karakteristiska symtomet för insjuknandet i en aneurysmal subarachnoidalblödning (aSAH) är plötslig, intensiv huvudvärk. Övriga kännetecken för aSAH är att den företrädvis drabbar medelålders kvinnor, är vanligare i norra än i södra Sverige, samt är associerad med hög sjuklighet och dödlighet. Komplikationer uppkommer ofta, varav den mest fruktade är en efterföljande blödning. Därför är det viktigt att omedelbart sluta det brustna aneurysmet på en neurokirurgisk klinik. Oftast (50-80%) sker det med röntgenledd teknik då aneurysmet packas med platinaspiraler s.k. coils via inträde från ett blodkärl i ljumsken. Det andra alternativet är en omfattande operation som involverar ingrepp via skallbenet och hjärnan för att sluta aneurysmet med en metall-klämma s.k. clip. Därefter krävs fortsatt intensivvård och rehabilitering.

Trots den dåliga prognosen är återhämtning efter aSAH möjlig över tid. Dagens forskning är däremot inte överens om över hur lång tid förbättringen kan fortgå. Dessutom är följderna mer än tio år efter hjärnblödningen bristfälligt studerat. Därför initierade vi denna studie, 12-15 år efter insjuknandet i aSAH baserat på en studiegrupp från Västra Götalandsregionen som insjuknat mellan 2000-2003 och behandlas på Sahlgrenska Universitetssjukhuset.

För att studera det långsiktiga utfallet efter aSAH telefonintervjuade vi alla levande patienter baserat på ett validerat och strukturerat frågeformulär, Glasgow Outcome Scale (GOS). Därmed kunde vi gradera patienternas funktionsstatus (1-5). Avlidna efter hjärnblödningen identifierades genom sökning i dödsregistret. Slutligen analyserades data av statistiska experter.

Vi fann att individuell förbättring var möjlig mer än ett år efter aSAH, men på gruppnivå skedde framförallt en försämring. Vi upptäckte att patienter med bra funktionsstatus vid ett år efter hjärnblödningen hade samma förväntade överlevnad som övriga befolkning, medan svårt funktionsnedsatta patienter hade en påtaglig ökad dödlighet. Vidare fann via att den långsiktiga prognosen påverkades av åldern, men inte kön.

Våra upptäckter kan vara användbara för vårdpersonal för att få en vägledning om patienternas långsiktiga prognos. Där de med en ettårsuppföljning, innefattande gradering av funktionsstatus enligt GOS kan få en indikation om vilka patienter som behöver ökad rehabilitering och tätare uppföljning för att förhoppningsvis förbättras. Därmed gynnas patienter, anhöriga och samhället.

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APPENDICES

Assessment tool: GOS and S-GOS 04 questionnaire

Table A1. GOS and GOSE description.

	GOS	GOSE	Definition
P	1	1	Death
O	2	2	Vegetative state
O	3	3	Lower severe disability
R	3	4	Upper severe disability
G	4	5	Lower moderate disability
O	4	6	Upper moderate disability
O	5	7	Lower good recovery
D	5	8	Upper good recovery

Dichotomized outcomes in unfavourable (GOS 1-3, GOSE 1-4) and favourable (GOS 4-5, GOSE 5-8).

S-GOS 04-questionnaire, pages 1 and 2

S-GOS 04 formulär

Underlag: *möte* ☐ *tel* ☐ *j-txt* ☐ *typ* ___ *sign av*____
Pat ☐ *anh* ☐ *vän* ☐ *datum*_____

Patient _____
P-nummer _____
Aktuellt tel. nr. till pat _____

Ifylld av_____Datum _____

Alla patienter kontrolleras mot folkbokföringen.
Datum:_____ sign_____

Avliden, datum:_____ ☐ A

Inte kontaktbar "vegetativt tillstånd" — Inte kontaktbar innebär att patienten inte kan lyda en enkel uppmaning, inte säga enstaka ord och inte följa med blicken. Patienten kan ibland öppna och röra ögonen, dock utan meningsfull blickkontakt. För att säkert fastställa att ett s k vegetativt tillstånd föreligger krävs en neurologisk specialundersökning (jfr Jennett, B., Plum F. Lancet, 1972, i, 734). ☐ B

Ringa in ett svar för varje fråga.

Beroende av annan persons hjälp i hemmet varje dygn för dagliga aktiviteter? Dagliga aktiviteter innefattar: tvätta sig, ta på sig rena kläder och laga mat. För att kunna klara sig själv minst ett dygn måste patienten klara detta utan påminnelser och måste kunna lämnas ensam på natten. Patienten skall dessutom kunna tillkalla hjälp vid mindre missöden i hemmet. Dock behöver patienten vanligtvis inte klara sig helt själv.	Ja oftare än var 8:e tim	Ja glesare än var 8:e tim	Nej		
Kan själv klara inköp? Klara inköp utan hjälp innebär: att kunna planera, sköta betalning och anpassa sig till omgivningen.		Nej	Ja		
Kan själv klara lokala resor? Klara lokala resor utan hjälp innebär: att kunna köra själv eller använda allmänna transportmedel. Taxi/färdtjänst är OK om de själva kan beställa bil och instruera föraren.		Nej	Ja		
Klarar normalt förvärvsarbete (el studier) som tidigare ? Patienten arbetade inte före skadan pga: pensionär ☐ långtidsarbetslös ☐ annat:_____			Nej	Ja deltid	Ja full tid
Har normalt socialt liv och fritidsaktiviteter?			Nej eller sällan	Ja men mindre än hälften så ofta som tidigare	Ja mer än hälften så ofta som tidigare	Ja helt som tidigare
Personlighetsförändringar som lett till störningar i familjen eller med vänner? T ex lättuppbrusande, oroliga, okänsliga för andras reaktioner, humörsvängningar, nedstämdhet & oresonlighet.			Ja ständigt och ohanterligt	Ja en el flera ggr per vecka men hanterligt	Ja hanterligt och färre än 1 gång per vecka	Nej
Finns det pga hjärnskadan några andra problem som påverkar dagligt liv? Ange vilka:_____ _____					Ja	Nej

OBS! Man måste även fråga om hur det var **före skadan** för att kunna bedöma hur väl patienten återhämtat sig: **fyll i baksidan** →

S-GOS 04 är en svensk version av Glasgow Outcome Scale (GOS, Jennett & Bond 1975) utvecklad av Stålhammar och Starmark 1990 (Stålhammar et al 1990, Svensson & Starmark 2002) och 2004 reviderad och anpassad av Ljungqvist och Stålhammar (Ljungqvist et al 2004) till kriterierna i Extended GOS (Wilson et al 1998). S-GOS 04 kan användas för att beskriva sena följder efter akuta hjärnskador i 5 eller 8 kategorier enligt GOS 1975 respektive Extended GOS 1998.
För att få en tillförlitlig bedömning bör man dels ha tillägnat sig den särskilda handledningen för S-GOS 04 dels ha övat på typfallen. Patientintervjuerna kan ske vid personligt möte eller via telefon. För att få en så säker uppfattning som möjligt om hur patienten mår och vad han/hon kan klara så bör man överväga intervju även med närstående. Patientens egen mening om sin förmåga kan vara missvisande. De olika kategorierna i S-GOS 04 är benämnda A – H. A: död. Kategori B (ej kontaktbar/vegetativt tillstånd) måste fastställas med en neurologisk specialistundersökning. För att bestämma om till vilken av kategorierna C – H en kontaktbar patient kan höra ställer man de ovan angivna frågorna. Ringa in det som gäller. OBS, alla frågorna måste besvaras!
Den kategori patienten skall tillhöra enligt S-GOS 04 bestämmes av den lägsta nivå som markerade svar anger.

S-GOS bla sept-05.ppt 2004-11-06 04:50 ©Ljungqvist & Stålhammar 2004

Före skadan gällde följande.
Ringa in ett svar för varje fråga.

Beroende av annan persons hjälp i hemmet varje dygn för dagliga aktiviteter?	Ja oftare än var 8:e tim	Ja men glesare än var 8:e tim	Nej			Nej
Kunde själv klara inköp?		Nej	Ja			Ja
Kunde själv klara lokala resor?		Nej	Ja			Ja
Klarade normalt förvärvsarbete (el studier)? Arbetade inte före skadan: pensionär ☐ långtidsarbetslös ☐ annat:			Nej	Ja deltid	Ja full tid	
Hade normalt socialt liv och fritids-aktiviteter?			Nej eller sällan	Ja men inte så ofta	Ja nien inte lika mycket som andra	Ja i normal omfattning
Hade personlighetsförändringar som lett till stömingar i familjen eller med vänner?			Ja ständigt och ohanterligt	Ja en el flera ggr per vecka men hanterligt	Ja hanterligt och färre än en gång per vecka	Nej
Fanns det några andra problem som påverkade dagligt liv? Ange vilka:					Ja	Nej

Har besvär av annan skada: nej ☐ ja ☐ _____ Ep efter skada: nej ☐ ja ☐

*Litteratur: Wilson et al, J Neurotrauma 1998; 15:573-585; Svensson & Starmark, J Rehab Med 2002; 34: 251-259. © Ljungqvist & Stålhammar 2004

Stratified GOS at 1-year, table A2

Table A2. GOS scores at 1-year post-aSAH stratified for age, gender and treatment.

Variable	1 (n=23)	3 (n=26)	4 (n=62)	5 (n=39)	p-value
Gender					
Male	6 (26.1%)	9 (34.6%)	10 (16.1%)	16 (41.0%)	
Female	17 (73.9%)	17 (65.4%)	52 (83.9%)	23 (59.0%)	0.57
Age at onset	57.0 (11.7) 57.0 (32.0; 75.0) n=23	58.8 (10.1) 59.0 (34.0; 79.0) n=26	53.8 (8.2) 54.5 (38.0; 68.0) n=62	55.4 (13.9) 58.0 (20.0; 81.0) n=39	0.30
Coil/Op					
Coil	17 (94.4%)	16 (61.5%)	40 (64.5%)	33 (89.2%)	
Op	1 (5.6%)	10 (38.5%)	22 (35.5%)	4 (10.8%)	0.76

For categorical variables n (%) is presented. For continuous variables Mean (SD) / Median (min; Max) / n = is presented.
For comparison between groups the Mantel Haenszel Chi Square Exactest was used for ordered categorical variables.
GOS at 1-year n=150. Coil, endovascular coiling. Op, neurosurgical clipping.

Stratified GOS change over long-time, table A3-4

Table A3. GOS at 1-year and at 12-15 years and change in GOS by age group: <55yeras vs. ≥55 years, only including survivors at 1-year.

	<55 Years at onset (n=64)		≥55 Years at onset (n=71)		
Variable	**n (%)**	**p-value within group**	**n (%)**	**p-value within group**	**p-value between groups**
GOS scores at 1-year					
3	8 (14.3%)		18 (25.4%)		
4	31 (55.4%)		31 (43.7%)		
5	17 (30.4%)		22 (31.0%)		0.45
GOS scores at 12-15 years					
1	9 (14.1%)		23 (32.4%)		
3	9 (14.1%)		7 (9.9%)		
4	16 (25.0%)		8 (11.3%)		
5	30 (46.9%)		33 (46.5%)		0.069
Change in GOS scores: 1 to 12-15 years					
Decrease	11 (19.6%)		27 (38.0%)		
Equal	32 (57.1%)		27 (38.0%)		
Increase	13 (23.2%)	0.84	17 (23.9%)	0.17	0.18
Change in Outcomes: 1 to 12-15 years					
Decrease	7 (12.5%)		15 (21.1%)		
Equal	49 (87.5%)		53 (74.6%)		
Increase	0 (0.0%)	0.016	3 (4.2%)	0.0075	0.67

For categorical variables n (%) is presented. For comparison between groups the Mantel-Haenszel Chi Square Exact test was used for ordered categorical variables. For comparison within groups Sign test was used. GOS 1=dead, GOS 3=severe disability, GOS 4=moderate disability and GOS 5=good recovery. GOS at 1-year consider survivors, n=127, missing n=8. Change in GOS scores and dichotomized outcomes: unfavourable (GOS 3) vs. favourable (GOS 4-5) are presented.

Table A4. GOS at 1-year and at 12-15 years and change in GOS by gender, only including survivors at 1-year.

	Male (n=38)		Female (n=97)			
Variable	**n (%)**	**p-value within group**	**n (%)**	**p-value within group**	**p-value between groups**	**Adjusted p-value***
GOS scores at 1-year						
3	9 (25.7%)		17 (18.5%)			
4	10 (28.6%)		52 (56.5%)			
5	16 (45.7%)		23 (25.0%)		0.40	0.90
GOS scores at 12-15 years						
1	10 (26.3%)		22 (22.7%)			
3	7 (18.4%)		9 (9.3%)			
4	3 (7.9%)		21 (21.6%)			
5	18 (47.4%)		45 (46.4%)		0.55	0.18
Change in GOS scores: 1 to 12-15 years						
Decrease	12 (34.3%)		26 (28.3%)			
Equal	18 (51.4%)		41 (44.6%)			
Increase	5 (14.3%)	0.14	25 (27.2%)	1.00	0.22	0.057
Change in Outcomes: 1 to 12-15 years						
Decrease	8 (22.9%)		14 (15.2%)			
Equal	26 (74.3%)		76 (82.6%)			
Increase	1 (2.9%)	0.039	2 (2.2%)	0.0042	0.48	0.47

For categorical variables n (%) is presented. For comparison between groups the Mantel-Haenszel Chi Square Exact test was used for ordered categorical variables. For comparison within groups Sign test was used.
*) Adjusting for age at onset and Hunt-Hess using Logistic regression.
GOS 1=dead, GOS 3=severe disability, GOS 4=moderate disability and GOS 5=good recovery. GOS at 1-year consider survivors, n=127, missing n=8. Change in GOS scores and dichotomized outcomes: unfavourable (GOS 3) vs. favourable (GOS 4-5) are presented.

Standard mortality ratios, table A5-6

Table A5. SMRs for the entire study cohort at onset of the aSAH according to age group, gender, admission status and treatment compared to age, gender, calendar year and area matched-controls.

Label	**Number of observations**	**Observed person years**	**Observed deaths**	**Expected deaths**	**SMR value**	**95% CI**	**p-value**
All aSAH patients	158	1633.4	55	15.70	3.50	2.64 - 4.56	<.0001
Age <55 years at onset	72	802.6	17	2.40	7.09	4.13 - 11.35	<.0001
Age ≥55 years at onset	86	830.9	38	13.30	2.86	2.02 - 3.92	<.0001
Male	44	442.6	16	4.64	3.45	1.97 - 5.60	<.0001
Female	114	1190.8	39	11.06	3.53	2.51 - 4.82	<.0001
Hunt and Hess 1	29	348.0	6	2.44	2.46	0.90 - 5.35	0.076
Hunt and Hess 2	47	528.3	14	7.14	1.96	1.07 - 3.29	0.030
Hunt and Hess 3	44	438.9	18	3.99	4.51	2.67 - 7.13	<.0001
Hunt and Hess 4	25	228.0	10	1.81	5.53	2.65 - 10.18	<.0001
Hunt and Hess 5	10	54.8	7	0.25	27.57	11.09 - 56.81	<.0001
Coil	111	1123.9	44	11.94	3.69	2.68 - 4.95	<.0001
Op	40	480.3	6	3.60	1.67	0.61 - 3.63	0.31

Op, neurosurgical clipping. Hunt-Hess favourable 1-3, poor 4-5, missing, n=3.

Table A6. SMRs according to unfavourable and favourable outcomes and GOS scores (3-5) at 1-year post-aSAH compared to age, gender, calendar year and area matched-controls.

Label	Number of observations	Observed person years	Observed deaths	Expected deaths	SMR value	95% CI	p-value
Favourable outcome (GOS 4-5)	101	1180.2	15	10.82	1.39	0.78 - 2.29	0.27
Unfavourable outcome (GOS 3)	26	227.8	16	3.75	4.27	2.44 - 6.93	<.0001
GOS 3 (severe disability)	26	227.8	16	3.75	4.27	2.44 - 6.93	<.0001
GOS 4 (moderate disability)	62	738.2	7	5.06	1.38	0.56 - 2.85	0.49
GOS 5 (good recovery)	39	442.0	8	5.77	1.39	0.60 - 2.73	0.45

Predictors of long-term favourable outcome, table A7-8

Table A7. Prediction of long-term favourable outcome at onset of the aSAH.

				Univariable*			Multivariable**	
Variable	n missing	Value	n (%) of event	OR (95%CI) Unfavourable favourable outcome at 12-15 years after aSAH	p-value	Area under ROC-Curve (95%CI)	OR (95%CI) Unfavourable favourable outcome at 12-15 years after aSAH	p-value
Gender	0	**Male**	21 (47.7%)					
		Female	66 (57.9%)	1.51 (0.75-3.03)	0.2508	0.54 (0.47-0.61)		
Age at onset (OR per 10 years)	0	**20-<51**	34 (65.4%)					
		51-<61	34 (59.6%)					
		61-81	19 (38.8%)	0.66 (0.48-0.90)	0.0095	0.62 (0.53-0.71)	0.68 (0.49-0.94)	0.0194
Coil/ Op	7	**Coil**	58 (52.3%)					
		Op	27 (67.5%)	1.90 (0.89-4.05)	0.0982	0.56 (0.49-0.63)		
Hunt and Hess	3	**1**	22 (75.9%)					
		2	28 (59.6%)					
		3	19 (43.2%)					
		4	13 (52.0%)					
		5	3 (30.0%)	0.66 (0.50-0.89)	0.0057	0.63 (0.54-0.71)	0.68 (0.51-0.91)	0.0103

P-values, OR and Area under ROC-curve are based on original values and not on stratified groups. OR is the ratio for an increase of the predictor of one unit.
*) All tests are performed with univariable logistic regression**.**
**) Multivariable logistic regression model including age at onset and Hunt and Hess grade.
Area under ROC-curve with 95% CI for multivariable model = 0.67 (0.58-0.76).
Coil, endovascular coiling. Op, neurosurgical clipping. Hunt-Hess, favourable 1-3 and poor 4-5.

Table A8. Prediction of long-term favourable outcome at 1-year post-aSAH.

				Univariable*			Multivariable**	
Variable	**n missing**	**Value**	**n (%) of event**	**OR (95%CI) Unfavourable favourable outcome at 12-15 years after aSAH**	**p-value**	**Area under ROC-Curve (95%CI)**	**OR (95%CI) Unfavourable favourable outcome at 12-15 years after aSAH**	**p-value**
Gender	0	**Male**	21 (55.3%)					
		Female	66 (68.0%)	1.72 (0.80-3.72)	0.1652	0.56 (0.47-0.64)		
Age at onset (OR per 10 years)	0	**20-<51**	34 (73.9%)					
		51-<60	27 (64.3%)					
		60-81	26 (55.3%)	0.62 (0.43-0.90)	0.0118	0.62 (0.52-0.72)	0.57 (0.36-0.90)	0.0155
Coil/Op	2	**Coil**	58 (61.7%)					
		Op	27 (69.2%)	1.40 (0.63-3.10)	0.4115	0.53 (0.45-0.61)		
GOS scores at 1-year	8	**3**	3 (11.5%)					
		4	48 (77.4%)					
		5	31 (79.5%)	4.88 (2.50-9.52)	<0.0001	0.74 (0.65-0.84)	5.02 (2.52-9.99)	<0.0001
Unfavourable/favourable outcome at 1-year	8	**Unfavourable Outcome**	3 (11.5%)					
		Favourable Outcome	79 (78.2%)	27.52 (7.56-100.21)	<0.0001	0.74 (0.66-0.81)		

P-values, OR and Area under ROC-curve are based on original values and not on stratified groups. OR is the ratio for an increase of the predictor of one unit.
*) All tests are performed with univariable logistic regression.
**) Multivariable logistic regression model including age at onset and GOS at 1-year.
Area under ROC-curve with 95% CI for multivariable model = 0.79 (0.71-0.88).
Coil, endovascular coiling. Op, neurosurgical clipping. GOS 3=severe disability, GOS 4=moderate disability and GOS 5=good recovery. Dichotomized outcomes in unfavourable (GOS 3) and favourable (GOS 4-5).