# Short- and long-term outcomes after aneurysmal subarachnoid hemorrhage

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To my family

## ABSTRACT

Aneurysmal subarachnoid hemorrhage (aSAH) is a sudden and devastating event with significant morbidity and mortality. The development of delayed cerebral ischemia (DCI) is a major contributor to the observed high morbidity. Prompt detection of these injuries remains a considerable challenge. This dissertation explores two approaches: heart rate variability (HRV) analysis and inflammatory biomarker evaluation. As an increasing number of patients survive the acute phase, it is crucial to understand the long-term post-SAH complications and sequelae experienced by patients.

HRV data and blood samples for inflammatory biomarkers were collected from patients during the acute phase. Correlations between these parameters and the development of DCI and overall outcome were investigated. Follow-up assessments at 1-, 3-, and 5 years post-hemorrhage were conducted via telephone interviews and self-assessment questionnaires.

In study I, altered HRV patterns indicating increased sympathetic activation were observed for the patient cohort, particularly those who developed DCI. However, the predictive value of HRV for DCI onset was limited. Patients who did not survive beyond the first year exhibited reduced HRV compared with survivors. Study II investigated the potential of five inflammatory biomarkers (TNF-α, IL-6, IL-1Ra ICAM-1, and CRP) in peripheral blood to predict DCI. No clear association was found between elevated levels of biomarkers and DCI development. However, patients with unfavorable outcomes had higher biomarker levels during the acute phase. Studies III and IV revealed that cognitive impairments, especially mental fatigue, persisted several years after the initial hemorrhage. Although many patients improved, approximately half continued to experience mental fatigue after 5 years. Further research is needed to refine prediction methods for the development of DCI. Follow-up assessments should extend several years after an aSAH and include broad assessment instruments focusing on cognitive outcomes, particularly mental fatigue.



**Keywords**: Aneurysmal subarachnoid hemorrhage, Delayed cerebral ischemia, Biomarker, Inflammation, Heart rate variability, Long-term outcome, Self-assessment, Cognitive impairments, Mental fatigue

# SAMMANFATTNING PÅ SVENSKA

Aneurysmal subaracknoidalblödning (aSAH) är en typ av stroke med ett, ofta plötsligt och akut, insjuknande då ett aneurysm, pulsåderbråck, i hjärnan brister. Ett typiskt symtom är så kallad ”åskknallshuvudvärk”. Vid blödningen ökar trycket inuti skallen vilket kan medföra risk för syrebrist i hjärnan. Detta utlöser en kaskad av reaktioner, som under de följande dagarna och veckorna kan leda till sekundära hjärnskador som utan behandling riskerar att bli permanenta. Dessa skador benämns delayed cerebral ischemia (DCI). Idag saknas effektiva metoder för att i tid varna för uppkomsten av DCI, särskilt hos patienter som är medvetslösa.

I två delarbeten av denna avhandling utforskas möjligheten att använda hjärtfrekvensvariabilitet (HRV) och analys av inflammatoriska biomarkörer i blodet för att tidigt upptäcka DCI. När kroppen utsätts för stress som vid en blödning i hjärnan minskar den naturliga variationen i hjärtrytmen. I den första studien analyserade vi HRV i korta intervall men ingen tydlig koppling kunde hittas mellan förändrad HRV och utvecklingen av DCI. Däremot hade de patienter som avled under det första året en minskad HRV. En akut blödning stimulerar kroppens inflammatoriska svar för att försöka förhindra och läka eventuella skador. I den andra studien fann vi inget tydligt samband mellan uppkomsten av DCI och de undersökta markörerna i blodet. Däremot kunde vi se att patienter med sämre utfall efter ett år hade högre nivåer av inflammatoriska markörer under den akuta fasen.

Aneurysmal SAH har en hög dödlighet och många av de överlevande patienterna har långvarigt bestående kognitiva besvär som ofta påverkar deras förmåga att återgå till sitt arbete, sin vardag och familjeliv. I de två sista delarbetena följdes patienterna med enkäter i upp till 5 år efter blödningen. Trots att många patienter återhämtat sig kroppsligt led en stor andel av dem av bestående kognitiva besvär. Mental trötthet var särskilt framträdande och studerades därför specifikt i delarbete 4. Trots att många patienter förbättrades över tid led fortfarande hälften av dem av mental trötthet efter 5 år. Fler studier behövs för att fortsätta identifiera och utveckla effektiva metoder för att förutsäga och förebygga utvecklingen av DCI efter aSAH. Vid uppföljning efter aSAH bör utvärdering av långvariga kognitiva besvär ingå, med särskilt fokus på mental trötthet.

# LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by Roman numerals.

I. Bjerkne Wenneberg S, Löwhagen Hendén PM, Oras J, Naredi S, Block L, Ljungqvist J, Odenstedt Hergès H. Heart rate variability monitoring for the detection of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage. *Acta Anaesthesiol Scand*. 2020; 64:945–952

II. Bjerkne Wenneberg S, Odenstedt Hergès H, Svedin P, Mallard C, Karlsson T, Adiels M, Naredi S, Block L. Association between inflammatory response and outcome after subarachnoid haemorrhage. *Acta Neurol Scand*. 2021; 143:195–205

III. Wenneberg S. B., Block, L., Sörbo, A., Naredi, S., Oras, J., Hendén, P. L., Ljungqvist, J., Liljencrantz, J. & Hergès, H. O. Long-term outcomes after aneurysmal subarachnoid hemorrhage: A prospective observational cohort study. *Acta Neurol Scand*. 2022; 146(5): 525-536

IV. Bjerkne Wenneberg S, Block L, Oras J, Löwhagen Hendén P, Liljencrantz J, Odenstedt Hergès H. Mental fatigue after aneurysmal subarachnoid hemorrhage. A prospective 5-year follow-up study. Manuscript. 2023.

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# ABBREVIATIONS

| | |
|---|---|
| ADL | Activity of Daily Living |
| ANS | Autonomic Nervous System |
| aSAH | Aneurysmal Subarachnoid Hemorrhage |
| BBB | Blood-Brain Barrier |
| CRP | C-Reactive Protein |
| CBF | Cerebral Blood Flow |
| cEEG | Continuous Electroencephalogram |
| CNS | Central Nervous System |
| CPP | Cerebral Perfusion Pressure |
| CSF | Cerebrospinal Fluid |
| CT | Computed Tomography |
| CTA | Computed Tomography Angiography |
| CTG | Cardiotocography |
| DAMP | Danger Associated Molecular Patterns |
| DCI | Delayed Cerebral Ischemia |
| DSA | Digital Subtraction Angiography |
| ECG | Electrocardiogram |
| EBI | Early Brain Injury |
| EVD | External Ventricular Drainage |
| FSS | Fatigue Severity Scale |
| GOSE | Glasgow Outcome Scale Extended |
| GCS | Glasgow Coma Scale |
| HF | High Frequency |
| H&H scale | Hunt and Hess scale |
| HRV | Heart Rate Variability |
| ICAM-1 | Intercellular Adhesion Molecule-1 |
| ICP | Intracranial Pressure |
| IL-1Ra | Interleukin-1 Receptor Antagonist |
| IL-6 | Interleukin-6 |
| LF | Low Frequency |
| LiSat-11 | Life Satisfaction Questionniare-11 |
| LOCi | Loss of Consciousness at ictus |
| MFS | Mental Fatigue Scale |
| MPAI-4 | Mayo-Portland Adaptability Inventory-4 |
| MoCA | Montreal Cognitive Assessment |
| MRI | Magnetic Resonance Imaging |
| NPi | Neurological Pupil index |
| NICU | Neurological Intensive Care Unit |

| | |
|---|---|
| PNS | Parasympathetic Nervous System |
| RMSSD | Root Mean Square of Successive Differences |
| SNS | Sympathetic Nervous System |
| STDRR | Standard Deviation of RR intervals |
| TCD | Transcranial Doppler |
| TNF- α | Tumor Necrosis Factor Alpha |
| WFNS | World Federation of Neurological Surgeons |

# DEFINITIONS IN SHORT

| | |
|---|---|
| Early Brain Injury (EBI) | Occurs within the first 72 hours after a hemorrhage. It has a complex pathophysiological etiology, including global cerebral edema, cerebral metabolic distress, inflammation, platelet activation, and cortical spreading depolarizations. Loss of consciousness is an indicator of EBI, and both are associated with unfavorable outcomes [1-3]. |
| Delayed Cerebral Ischemia (DCI) | As defined by Vergouwen et al. 2010 [4].<br>*Clinical deterioration caused by DCI*<br>"Focal neurological impairment (e.g., hemiparesis, aphasia, or apraxia) or a decrease of at least 2 points on the GCS. This should last > 1 hour is not immediately apparent after aneurysm occlusion and cannot be attributed to the aneurysm occlusion or other causes by means of clinical assessment, radiology, or laboratory studies".<br><br>*Cerebral infarction caused by DCI*<br>"The presence of cerebral infarction on CT or MR scan of the brain within 6 weeks, not present on the CT or MR scan between 24 and 48 h after early aneurysm occlusion and not attributed to other causes such as surgical clipping or endovascular treatment." |

# 1 INTRODUCTION

The ancient Greeks, including Hippocrates and his followers, believed that the brain was the center of all emotions and higher functions and that our spirit was held in the blood [5]. They thought that illness was an imbalance or excess of the human body's "four fluids", one of which was blood. Thus, disturbance of blood flow, or "spirit," to the brain would result in disease [5]. A stroke (then referred to as apoplexy) was described as an event of sudden onset that could render a patient aphasic and often caused severe impairments of motor and sensory functions [6]. In many cases, it was observed that patients with a stroke experienced prodromal symptoms such as dizziness, headaches, or confusion. Although the symptoms were accurately described, the term "stroke" did not appear until the late 1500s, likening it to a "stroke by God's hand." [6]. A lot of advancements in the care of stroke patients have taken place since, but it is still a devastating disease, often affecting the patients for years afterward.

"*It is impossible to cure a severe attack of apoplexy and difficult to cure a mild one."*

– Hippocratic Aphorism

*Patient case report*

*Ann-Marie is a 58-year-old woman residing outside of Göteborg. She maintains a full-time position at a clothing store and leads an active family life. Although she has a history of smoking from an early age and high blood pressure, she generally considers herself in good health. However, she woke up on a Monday with a mild headache and took paracetamol before heading to work. While at work, she suddenly experienced an intense thunderclap headache. In addition, she lost control of her right arm and leg and, ultimately, her consciousness. Upon her arrival at the local hospital, Ann-Marie had regained consciousness and the sensitivity on her right side but was drowsy. A computed tomography (CT) scan of her brain revealed considerable bleeding caused by the rupture of a bulge on a blood vessel, or an aneurysmal subarachnoid hemorrhage (aSAH). Additionally, the ventricles in the brain were widened. Ann-Marie was transferred to the neurointensive care unit (NICU) at the Sahlgrenska University Hospital to receive neurosurgical treatment.*

*Ann-Marie was sedated, and the aneurysm was repaired by packing it with a small bundle of wire, a minimally invasive procedure known as endovascular coiling. A small catheter was placed to drain the excessive intraventricular fluid. Subsequently, she was awakened and stayed in the NICU for close monitoring. Ann-Marie slowly recovered and was thankful to start careful mobilization, although she felt exhausted and experienced daily headaches.*

*On day 7, her headaches worsened, and she experienced episodes of sudden sleepiness. A routine ultrasound of Ann-Marie's brain vessels indicated an increased blood velocity. The following day, she began to experience numbness in her right arm and leg and difficulty in finding the correct words when speaking. A new CT scan revealed a narrowing of two major brain blood vessels and a small area where brain infarction was suspected. This complication, known as delayed cerebral ischemia, is common and feared following an aSAH. With treatment, Ann-Marie's symptoms gradually improved over the following days. However, she continued to experienced headaches, significant fatigue, and weakness in her right side upon returning to the local hospital.*

*During a follow-up visit one year later, Ann-Marie continued to experience daily headaches and profound fatigue, sleeping between 12-16 hours per day. She became sensitive to bright light and sound, leading to her confinement at home on most days. Her right side remained weaker, impacting her balance, and necessitating a walking aid. She could not return to work and harbored concerns that she may never be able to do so owing to her persistent fatigue and other symptoms. Ann-Marie and her family remained shocked by the sudden and profound change and worried that life might never be the same again.*

## 1.1 STROKE AND SUBARACHNOID HEMORRHAGE

A stroke is a sudden disruption of blood flow, which can either permanently or temporarily disturb the brain's oxygen supply [7]. Since the brain is a highly oxygen-dependent organ, tissue damage occurs rapidly, resulting in neurological impairments. Strokes can be classified into two main types: ischemic and hemorrhagic. Hemorrhagic strokes can be divided into intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH) [1,7]. This thesis will focus on the short- and long-term outcomes following an aneurysmal subarachnoid hemorrhage (aSAH).

*Figure 1. Ruptured aneurysm. Illustration by Alexander and Laura Bjerkne Wenneberg*

### 1.1.1 EPIDEMIOLOGY OF ANEURYSMAL SUBARACHNOID HEMORRHAGE

Among all strokes, SAH constitutes 2-7%. A ruptured intracranial aneurysm is the cause of 85% of all spontaneous SAH or aneurysmal SAH (aSAH), while 15% may have other etiologies [8]. Women have a higher risk of experiencing an aSAH than men [9]. Patients with an aSAH have a relatively young onset age, on average 62 years in Sweden, compared with 75 years for patients with an ischemic stroke, the most prevalent stroke category (Riksstroke 2021). Consequently, an aSAH leads to a substantial loss of productive years and years with quality of life [1]. The improved management of risk factors, including hypertension and a reduction of smoking, has led to a decreased prevalence of aSAH over the last decades, with a current global incidence of 6-9/100 000 person-years. A decline in case fatality has been observed with improving surgical and medical management; however, mortality and morbidity remain high [1,10,11]. Despite half of the patients regaining an independent life, up to 75% have significant long-lasting neurological impairments [8,12].

### 1.1.2 CLINICAL PRESENTATION

When an aneurysm ruptures, blood rushes from the artery into the subarachnoid space, raising the intracranial pressure (ICP) and subsequently decreasing the cerebral perfusion pressure (CPP) and cerebral blood flow (CBF) [13]. The subarachnoid space is normally filled with only cerebrospinal fluid (CSF). However, after an aSAH, blood mixes with the CSF and interferes with its normal drainage via the lymphatic and glymphatic systems, further affecting the ICP [14]. Headache is a common symptom, although only around 2% are caused by a hemorrhage [15]. The hallmark symptom of an aSAH is a sudden onset thunderclap headache described by patients as “the worst headache of my life.” Additional symptoms range from mild nausea, vomiting, and neck pain to neurological deficits, altered levels or loss of consciousness, and seizures [16,17]. Many patients report transient prodromal symptoms, including headaches, several days or weeks prior to the event. These are symptoms of a “sentinel bleed” or a minor bleed before an aneurysmal rupture [18].

## 1.1.3 DIAGNOSTICS

If an aSAH is suspected, patients should undergo a non-contrast computed tomography (CT) scan [19]. The sensitivity is almost 100% for the first 24 hours after the event; however, it declines over time and approaches 60% after 1 week [2]. A lumbar puncture with CSF spectrophotometry can be considered if the CT is inconclusive or negative for an aSAH, and the suspicion remains [20]. After an aSAH is diagnosed on CT, a computed tomographic angiography (CTA) or a digital subtraction angiography (DSA) is performed to determine the aneurysm location, its size, and appropriate treatment modality [21]. Although DSA is a more invasive procedure, diagnostics and treatment can be achieved simultaneously [22].

The clinical condition of patients with an aSAH on admission to the hospital varies from awake with minimal headache to deeply unconscious. Neurological status is commonly assessed using the Glasgow Coma Scale (GCS), a clinical tool providing a structured and efficient mean of evaluating the level of consciousness in individuals with an acute disease or injury [23].

*Table 1. The Glasgow Coma Scale.*

| BEHAVIOR | RESPONSE |
|---|---|
| Eye Opening Response  | 4. Spontaneously<br>3. To speech<br>3. To pain<br>1. No response |
| Verbal Response  | 5. Oriented to time, person, and place<br>4. Confused<br>3. Inappropriate words<br>2. Incomprehensible sounds<br>1. No response |
| Motor Response  | 6. Obeys command<br>5. Moves to localized pain<br>4. Flex to withdraw from pain<br>3. Abnormal flexion<br>2. Abnormal extension<br>1. No response |

Additional evaluation is typically performed using the World Federation of Neurological Surgeons (WFNS) grading scale, which incorporates the GCS score and any focal motor deficits [24].

*Table 2. The World Federation of Neurological Surgeons scale*

| Grade | GCS | Motor deficit |
|---|---|---|
| 1 | 15 | Absent |
| 2 | 14-13 | Present |
| 3 | 14-13 | Present or absent |
| 4 | 12-7 | Present or absent |
| 5 | 6-3 | Present or absent |

*GCS; Glasgow Coma Scale*

The modified Fisher grading scale is used to classify the hemorrhage's appearance on CT scans and stratify the risk of developing vasospasm [25].

*Table 3. The Modified Fisher scale*

| Grade | Radiological presentation | Risk for vasospasm |
|---|---|---|
| 1 | Thin SAH (< 1 mm). No IVH | Low risk |
| 2 | Thin SAH (< 1 mm). IVH present | Moderate risk |
| 3 | Thick SAH (> 1 mm). No IVH | High risk |
| 4 | Thick SAH (> 1 mm). IVH present | Very high risk |

*SAH; Subarachnoid Hemorrhage, IVH; Intraventricular Hemorrhage*

Furthermore, the Hunt and Hess (H&H) scale is used to predict mortality rates based on the severity of the patient's clinical condition [26].

*Table 4. The Hunt and Hess scale*

| Grade | Clinical presentation |
|---|---|
| 1 | Mild headache, normal mental status, no neurological deficits |
| 2 | Severe headache, normal mental status |
| 3 | Somnolent, confused, mild nerve deficits |
| 4 | Stupor, moderate to severe motor deficits |
| 5 | Coma |

## 1.1.4 TREATMENT

After diagnosing an aSAH, patients are preferably transferred to high-volume centers (> 35 cases/year) for further treatment, including aneurysm securement [27]. In West Sweden, with a population of 1,7 million, approximately 100 patients/year are admitted to the neurological intensive care unit (NICU) at the Sahlgrenska University Hospital for neurosurgical treatment.

The initial management is focused on minimizing the risk of rebleeding and medically managing extreme variations in blood pressure [28]. Short-term antifibrinolytic therapy before aneurysm securement was previously recommended; however, the 2023 American Heart Association/American Stroke Association Guidelines do not recommend routine antifibrinolytic therapy [19,29]. Aneurysms are secured either via endovascular intervention or surgically, preferably within 24 hours [30,31]. After aneurysm securement, patients are closely monitored, often in an ICU setting, regarding hemodynamics, respiration, fluid balance, electrolyte status, and temperature and for the development of secondary complications [1].

Nimodipine, a calcium channel antagonist which blocks extracellular calcium flow, is administered prophylactically to all patients [32-34]. Its potential neuroprotective actions include reducing vasospasm, inhibiting cortical spreading depolarizations, decreasing microthromboemboli occurrence, and enhancing fibrinolytic activity [35].

## 1.1.5 SECONDARY COMPLICATIONS

Both neurological and systemic complications of an aSAH can arise immediately after the initial hemorrhage or after several days or weeks. Neurological complications include rebleeding, loss of consciousness at ictus (LOCi), early brain injury (EBI) seizures, hydrocephalus, and delayed ischemic injuries (DCI) [2,36-39].

The elevation of ICP with a decrease in CPP stimulates catecholamine release with sympathetic activation and consequently induces the risk of widespread secondary complications throughout the body [8,40]. These complications include cardiopulmonary failure, fluid status and electrolyte balance disruptions resulting from hormonal alterations, and the development of infections [2,41,42].

### 1.1.5.1 EARLY BRAIN INJURY AND LOSS OF CONSCIOUSNESS AT ICTUS

Approximately 40% of patients with an aSAH experience LOCi [3]. It occurs due to the increase in ICP and decrease in CPP that appear after aneurysm rupture leading to a transient loss or decrease of CBF and oxygen delivery [3,43]. LOCi have been associated with radiographic cerebral edema and is thought to be a potential marker of EBI [43]. During the first few hours and days after the initial hemorrhage, a cascade of reactions contributes to the development of EBI. This includes microcirculation disruption, micro thrombosis, blood-brain barrier (BBB) break-down, cortical spreading depolarizations, and activation of inflammatory pathways [44-46]. Changes and injuries triggered during the EBI phase are thought to play an important role in the development of secondary ischemic injuries [47]. Studies have reported a significant correlation between LOCi, the development of EBI, and unfavorable outcomes [3,48,49].

### 1.1.5.2 DELAYED CEREBRAL ISCHEMIA

Delayed neurological deterioration due to impending cerebral ischemia is a feared complication affecting approximately 30% of the patients post-aSAH [50]. Typically, DCI develops within the first 14 days following the initial hemorrhage, peaking in incidence at day 7 [51]. Previously, vasospasm was considered the main reason for the development of DCI. However, studies have found that pharmacological resolution of large vessel vasospasm did not improve outcomes after aSAH [52]. Moreover, it was observed that cerebral infarction resulting from DCI often occurred outside the regions affected by vasospasm. Furthermore, DCI can occur in patients with minimal or no

angiographic evidence of vasospasm. These findings suggest the involvement of factors beyond cerebral vasospasm [53-56]. The pathophysiology of DCI development encompasses various causes, including micro and macro circulatory vasospasm, micro thrombosis, cortical spreading depolarizations, BBB dysfunction, and inflammation [54,57-59].

In this thesis, a definition of DCI proposed by Vergouwen et al. in 2010 to unify terminology for both clinical and research purposes has been used [4]. The definition can be found under Definitions in short, page xvii .

#### 1.1.5.3 TREATMENT OF DELAYED CEREBRAL ISCHEMIA

Historically, the treatment and prevention of cerebral vasospasm and DCI were mainly vasodilatory or vasoactive strategies to optimize cerebral perfusion and prevent permanent brain injury. The "triple H" therapy involved inducing hypertension, hypervolemia, and hemodilution [60-62]. Owning to the development of adverse effects, mainly cardiopulmonary, current recommendations include only pharmacologically induced hypertension if DCI symptoms are observed [19,63].

Several pharmacological strategies have been tested in studies, including endothelin-1 receptor antagonists (Clazosentan), phosphodiesterase enzyme-3 inhibitors (Cilostazol), free radical scavengers (Tirilazad), statins (Simvastatin), and magnesium sulfate. However, convincing evidence of significant patient outcome improvement remains inconclusive [28,64,65].

Therefore, in current practice, if symptoms do not recede or respond to induced hypertension or if cerebral perfusion disruption is radiologically verified, angioplasty or intra-arterial vasodilator infusion can be considered the next step in rescue therapies [29,66].

#### 1.1.5.4 CURRENT METHODS FOR THE DETECTION OF DELAYED CEREBRAL ISCHEMIA

Currently, no optimal method for monitoring impending ischemia stands alone; with the diagnosis found through a combination of several different measures, each has its own drawbacks and considerations [67].

- *Clinical assessments*

Neurological examinations evaluating cognitive and motor function changes and overall neurological status are the basis of current DCI monitoring. However, the ischemic injuries might already be manifested when the neurological symptoms are discovered, [68]. Neurological examinations are even more challenging or impossible in patients with altered consciousness or those under sedation [69,70]. Sedated patients may be examined during wake-up trials, but as this may adversely affect ICP with the risk of aggravation of brain oxygenation it should be carefully performed [50,71].

- *Transcranial Doppler*

Transcranial Doppler (TCD) measures the blood velocities of the middle cerebral artery (MCA) or anterior cerebral artery (ACA). Mean flow velocities of > 120 cm/s is considered indicative of vasospasm. An increase in velocity of 50 cm/s/24 h or a cut-off velocity of > 200 cm/s are warnings signs warranting further diagnostics [29]. TCD is non-invasive and allows for dynamic surveillance by repeated measurements; however, it is observer-dependent and impossible to conduct in all patients because of differing cranial anatomies. TCD has been demonstrated to have high predictivity of DCI; however, increasing blood flow velocity secondary to other reasons, including hyperdynamic circulation, hyperemia, and arterial stenosis, cannot always be differentiated [50,72,73].

- *Pupillometry*

Pupillometry measures pupillary reactivity under different conditions and stimuli. The neurological pupil index (NPi) quantifies changes in pupillary size, constriction velocity, latency, and dilation velocity [50]. Changes in the NPi are considered to reflect the balance of the ANS influencing the visuomotor pathways; however, these changes are observed in direct injuries to the

oculomotor nerve or indirect brain injuries as well. The NPi has been demonstrated to decrease before clinical manifestations of ischemic injuries and might supplement TCD [74].

- *Continuous electroencephalogram.*

Continuous electroencephalogram (cEEG) may serve as a sensitive tool for detecting metabolic deterioration and disrupted neuronal activity after decreased CBF. Changes in cEEG observed in association with DCI include differences in alpha wave variability and reduction in alpha-to-delta ratio. Continuous EEG generates large amounts of data requiring manual reviewing and high levels of interpreter knowledge. Furthermore, this method is sensitive to disturbances and artifacts that can arise, especially in awake patients [75,76].

- *Radiology*

Cerebral CT angiogram and CT perfusion provides detailed visualization of cerebral blood vessels and surrounding tissues [77,78]. However, they are only diagnostics tools. Catheter-based angiography remains the gold standard for the possibility of a modality combining diagnostic capabilities and simultaneous treatment interventions, [29,50]. Nonetheless, this is a more invasive procedure with attendant risks of blood vessel perforation and bleeding. Even though radiological monitoring offers more precise diagnostics, these procedures involve transporting patients, sometimes in critical conditions, using ionized contrast agents, and increased radiation exposure.

The timely detection of impending ischemia in patients post-aSAH remains a significant challenge, especially in sedated patients or those with altered levels of consciousness, where conducting regular neurological examinations are often difficult. Research on exploring more precise detection methods, including identifying potential biomarkers, both physiological and in blood samples, for the detection of DCI is actively ongoing.

# 1.2 BIOMARKERS FOR THE DETECTION OF SECONDARY COMPLICATIONS AND OUTCOMES

In this thesis, we examined two distinct types of biomarkers with potential clinical applications to detect DCI and predict outcomes. First, we explored heart rate variability (HRV), which may signal imbalances in the autonomic nervous system (ANS). Secondly, we investigated serum biomarkers indicative of the inflammatory process following an aSAH.

## 1.2.1 HEART RATE VARIABILITY AND THE AUTONOMIC NERVOUS SYSTEM

The brain-heart axis is the intricate interaction between the nervous and cardiovascular systems [79]. The ANS, part of the peripheral nervous system, regulates various body functions, including heart rate, blood pressure, and respiration, in response to incoming signals. It comprises the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS) [80]. The PNS rapidly affects heart rate beat-to-beat, while the SNS has a slower and longer-lasting impact. Even at rest, a balance between the SNS and PNS results in a slight though detectable variation in inter-beat intervals, which can be measured via an electrocardiograph as changes in R-to-R intervals or heart rate variability [80,81]. HRV monitoring for clinical use began during the 1960s when Hon and Lee noted that before fetal distress caused a decrease in the heart rate, a change was perceptible in the length of inter-beat intervals [82]. Subsequently, cardiotocography (CTG) was developed, and the first commercial CTG fetal monitor was released in 1968 [83]. CTG is now widely used as the standard approach for fetal monitoring [82]. Thus, HRV analysis can non-invasively detect imbalances in the ANS and over the past decades, HRV analysis has expanded to multiple medical fields, including neurology. A low HRV has been found to be an indicator and predictor of complications, adverse outcomes, and mortality [68,84-87].

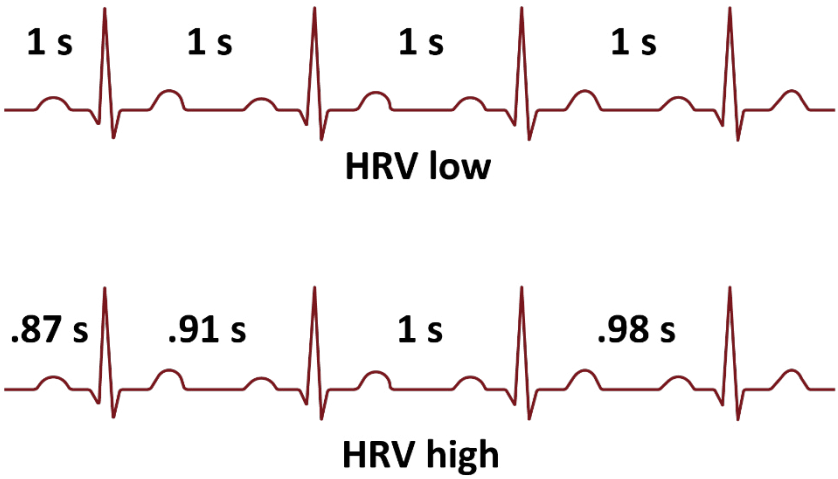



*Figure 2. Heart rate variability (HRV). The top ECG example exhibits 1-second intervals between each successive beat, indicative of a reduced HRV. In contrast, the second ECG exhibits minor variations in the temporal intervals between successive beats, thereby illustrating an elevated HRV.*

## 1.2.2 ANALYZING HEART RATE VARIABILITY

The European Society of Cardiology and the North American Society of Pacing and Electrophysiology developed guidelines for standards of measurement of HRV in 1996 [88]. Depending on the recording length, different physiological factors dominate the HRV registrations. For longer registrations, often 24 hours, circadian rhythms, the renin-angiotensin system, and metabolism are involved. For shorter registrations, ≤5 minutes, the rapid changes in SNS and PNS are reflected [89]. While HRV can be analyzed in several domains, time- and frequency are the most common.

*Table 5. Heart rate variability parameters*

| HRV parameters | Unit | Description | Physiologic correlates |
|---|---|---|---|
| Time-domain | | | |
| SDRR | ms | The standard deviation of the RR intervals | Reflects components responsible for the heart rate variability |
| RMSSD | | The square root of the mean squared difference of successive RR intervals | Reflects mainly the vagally mediated changes in the heart rate variability |
| Frequency-domain | | | |
| LF | $ms^2$ | The power within the low frequency (LF; 0.04-0.15 Hz) band of the RR interval tachogram | Reflects both the sympathetic and parasympathetic parts of the ANS |
| nLF | nu, normalized units | LF/(LF+HF+VLF) | |
| HF | $ms^2$ | The power within the high frequency (HF; 0.15-0.40 Hz) band of the RR interval tachogram | Reflects the parasympathetic parts of the ANS |
| nHF | nu, normalized units | HF/(LF+HF+VLF) | |
| LF/HF | Ratio | The LF/HF quota | Reflects the sympathovagal balance |
| VLF | $ms^2$ | The power within the very low frequency (VLF; 0-0.04 Hz) band of the RR interval tachogram | Thermo- regulatory mechanisms, changes in peripheral chemoreceptor activity, and fluctuations in the renin-angiotensin system (RAAS) |
| Total power | | VLF+HF+LF | Reflects the activity in the sympathetic and the parasympathetic parts of the ANS |

*SNS; Sympathetic nervous system, PNS; parasympathetic nervous system, STDRR; Standard Deviation of RR intervals, RMSSD; Root Mean Square of Successive Differences, LF; Low Frequency, HF; High Frequency, VLF; Very Low Frequency, ms; milliseconds, Hz; Hertz. Adaptation from: Bjerkne Wenneberg, S.B. et al. Acta Anaestiol Scand, 2021. Creative Commons BY 4.0 License*

*Time domain*

Time-domain measurement of HRV involves analyzing RR interval variations, which represent the time between consecutive heartbeats. This approach provides an overall assessment of ANS activity. Two commonly used time-domain measurements are the standard deviation of RR intervals (SDRR) and the square root of the mean squared difference of successive RR intervals (RMSSD). The SDRR reflects the overall HRV, while the RMSSD primarily focuses on the short-term components of HRV, providing insights into rapid fluctuations in heart rate. Time-domain analyses are relatively straightforward to compute; however, they may be sensitive to artifacts, thereby necessitating careful processing of the HRV data [88,90,91].

*Frequency domain*

Frequency domain analysis measures the different oscillation ranges of the HRV signal [92]. The different frequency areas of the HRV signal represent which components of the ANS is dominating. Software programs are utilized to analyze R-R intervals from HRV registrations, creating tachograms by plotting intervals in milliseconds (ms) against time. Subsequently, Fourier transformation is employed to separate and identify the cosine curves representing the main signal, plotted based on their frequencies and amplitudes to visualize different frequency domains. Previous studies on the blockade of the PNS using anti-cholinergic medication or the SNS through stellate ganglion block have demonstrated a frequency-based representation of the components of the ANS [93,94]. Two main spectral components are usually calculated for analyses of short, 5-minute intervals: low frequency (LF) and high frequency (HF) [88]. The HF is thought to reflect the PNS and the LF, both PNS and SNS. A calculated ratio between LF and HF indicate the balance between the SNS and PNS, with a higher value representing a sympathetic dominance or parasympathetic withdrawal.

### 1.2.3 HEART RATE VARIABILITY AND STROKE

HRV has been explored as a possible biomarker for the changes and dysregulation in the ANS seen after a stroke, linking to post-stroke outcomes and mortality [95-97]. In 2011, Chen et al. found an imbalance with higher sympathetic tone in patients with an ischemic stroke than in non-stroke controls. Moreover, they found a significant lowering of the HRV parameters, VLF (very low frequency), LF, and HF with a higher LF/HF ratio [98]. A difference in autonomic dysregulation has also been revealed to depend on the affected brain hemisphere and lesion location, with the right and left hemispheres relating to sympathetic tone and parasympathetic tone, respectively [99-101]. In 2015, Kanai et al. detected differences depending on stroke etiology, with atherosclerosis causing a lowering of parasympathetic activity and an elevation of sympathetic activity compared with lacunar infarctions. Possible reasons might be the different sizes of the lesions or various underlying risk factors [102]. Long-term impairment of autonomic dysfunction with reduced HRV has also been shown to correlated with outcome and mortality several years after the stroke [97].

### 1.2.4 HEART RATE VARIABILITY AND ANEURYSMAL SUBARACHNOID HEMORRHAGE

It was noted in the 1950s that patients with cerebral hemorrhages developed post-ictal ECG changes [103]. Several decades later, research regarding the relationship between changes in HRV and post-aSAH secondary complications and outcomes emerged. In 2003, Kawahara et al. demonstrated a change in frequency domain parameters in patients after an aSAH, with rather contradictory results, including elevation of blood catecholamines during the acute phase and lowering of the LF/HF ratio and elevation of HF [104]. In 2009 Su et al. found that an increased LF/HF ratio during the first 3 days post-hemorrhage was related to the development of symptomatic vasospasm, cerebral infarction, neurogenic pulmonary edema, or death within the first week [87]. Furthermore, changes in HRV have been demonstrated to be an independent variable in predicting in-hospital mortality and associated with the development of reversible stress cardiomyopathy [85,86]. In 2014, Schmidt et al. used continuous ECG data from the first 48 hours post-hemorrhage as baseline values and compared it to HRV data from the day preceding the onset of DCI

or a nosocomial infection. Differences in both time- and frequency domains before the development of these secondary complications were found [105]. In 2019, Megjhani et al. demonstrated a lowering of time-domain parameters and a higher LF/HF ratio in patients who developed cardiac complications without signs of coronary artery insufficiency after an SAH. These findings suggest an ANS imbalance, with augmentation of sympathetic activity or lack of augmentation of vagal activity in patients after an aSAH [106].

*Figure 3. Heart rate variability device used for study I.*

## 1.2.5 INFLAMMATION AND ANEURYSMAL SUBARACHNOID HEMORRHAGE

Inflammation is a complex and multifaceted response to endogenous or exogenous stimuli, including pathogens, cellular components, or toxic compounds [107]. Inflammatory processes may be involved in the development of an aneurysm; however, in this thesis, the focus is on the inflammatory responses after an aneurysm ruptures [108]. The role of the immune system and neuroinflammation has gained increased attention as part of the development of complications following an aSAH, such as EBI, and DCI, and unfavorable outcomes [109-111]. Inflammatory reactions are initiated to limit the injury and promote the healing of wounded tissue and damaged cells. However, inflammation may contribute to inverse processes leading to tissue injury and secondary complications instead [57,112]. In critical conditions such as an aSAH, the innate inflammatory response is believed to be pathologically prolonged, further increasing the risk of developing CNS injuries [113,114]. Thus, the probable dual role, being both harmful and beneficial to the brain, contribute to the difficulty of studying post-aSAH inflammatory complications [115].

## 1.2.6 THE INFLAMMATORY PROCESS IN ANEURYSMAL SUBARACHNOID HEMORRHAGE

The breakdown and degradation products of red blood cells include hemoglobin, methemoglobin, oxyhemoglobin heme, and hemin, which act as danger-associated molecular patterns, DAMPs [116]. In addition, other types of DAMPs may be released from injured cells secondary to ischemia following an aSAH. DAMPs bind to pattern-recognition receptors on cell surfaces and stimulate intracellular pathways with the transcription of pro-inflammatory genes and release of cytokines, further initiating and stimulating the inflammatory cascade [117-120]. Normally, the BBB comprising endothelial cells, basal lamina, and astrocytes connected by tight junctions provides physical protection from peripherally circulating pathogens and immune cells, only allowing specific molecules to pass. The inflammatory response after an aSAH triggers the upregulation of specific cell adhesion molecules, CAMs, including intercellular adhesion molecule 1 (ICAM-1) on the vascular endothelium, thus recruiting peripheral innate immune cells, macrophages, neutrophils, and lymphocytes to enter the subarachnoid space [54,112]. Furthermore, damage to the

BBB causes disruptions of the protective barrier, allowing a more uncontrolled entrance of peripheral cells into the CNS [121-123]. Several studies have identified biomarkers, including cell adhesion proteins, neuron and astrocyte proteins, cytokines, and extracellular matrix molecules, as potential markers in predicting DCI development and unfavorable outcomes [122,124-127]. However, no conclusive evidence has emerged to support their routine use in clinical settings.

## 1.2.7 STUDIED INFLAMMATORY BIOMARKERS

From among the several inflammatory biomarkers linked to poor outcomes and DCI development after aSAH, this thesis focuses on the following five: tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6, IL-1-receptor antagonist (IL-1Ra), intercellular adhesion molecule 1 (ICAM-1), and C-reactive protein (CRP)[125,128-132]

### 1.2.7.1 TUMOR NECROSIS FACTOR-ALPHA

Tumor necrosis factor-alpha is a pro-inflammatory cytokine produced by various immune cells, including macrophages, T-cells, and natural killer cells. It has multifaceted effects depending on the target cell, including stimulating the expression of adhesion molecules, chemokines, and other inflammatory cytokines and recruiting immune cells to the site of inflammation. Elevated levels of TNF- α and its receptors in serum and CSF have been associated with poor outcomes in several studies; however, its relation to DCI development is unclear [129,133-135].

### 1.2.7.2 INTERLEUKIN-1 RECEPTOR ANTAGONIST

Interleukin-1 receptor antagonist is produced by many cells, including monocytes, macrophages, and fibroblasts. It is a competitive inhibitor of the pro-inflammatory cytokine interleukin-1 (IL-1) and blocks the effect of IL-1 by binding to the same signaling receptor [136,137]. Mathisen et al. noted higher IL-1Ra concentrations in patients with unfavorable outcomes on days 3–10 post-aSAH, suggesting that this marker might reflect the severity of the initial hemorrhage [138]. The administration of IL-1Ra has been found to have neuroprotective effects in various models of cerebral ischemia, suggesting it could be a potential treatment for reducing inflammation and improving outcomes in patients after aSAH [139].

#### 1.2.7.3 INTERLEUKIN-6

Interleukin-6 is one of the most studied inflammatory biomarkers after aSAH. It has pro- and anti-inflammatory effects depending on its activation and downstream receptor binding [140]. Stimuli, including infections, traumatic tissue damage, and chronic pain, induce IL-6 secretion [125,128,141]. Owning to the ambiguous effects of IL-6 and its non-specific origin, determining its exact correlation to complications after an aSAH has proved difficult. In 1993, Mathiesen et al. demonstrated elevated Il-6 levels in CSF after aSAH [142]. In a recent review, Simon et al. pointed out that several studies have reported positive findings associating elevated levels of IL-6 in CSF and serum with DCI development and unfavorable outcomes [143].

#### 1.2.7.4 INTERCELLULAR ADHESION MOLECULE-1

Intercellular adhesion molecule-1 is a transmembrane glycoprotein found on cerebral endothelial cells, and its expression is upregulated in response to inflammatory cytokines, including IL-1, IL-6, and TNF- α [144,145]. Mack et al. found significantly elevated ICAM-1 levels in post-aSAH serum samples and further reported a higher association between ICAM-1 and poor outcomes [146]. Contrarily, Rasmussen et al. did not find an association between several biomarkers, including ICAM-1, and DCI development or poor outcomes [134].

#### 1.2.7.5 C-REACTIVE PROTEIN

C-reactive protein is a pentameric acute-phase reactant protein predominantly synthesized in the liver, with its production primarily stimulated by IL-6 [147]. CRP can bind to pathogens and damaged cells, facilitating their identification for subsequent clearance. Several studies have identified elevated CRP levels after aSAH and associated higher levels with unfavorable outcomes [148-151] and DCI [150,152]. However, as CRP is elevated in response to many inflammatory conditions, it is a more unspecific biomarker; thus, distinguishing the effect of an aSAH and secondary complications becomes difficult [153].

# 1.3 OUTCOME AFTER ANEURYSMAL SUBARACHNOID HEMORRHAGE

With improving survival rates for patients after an aSAH and the relatively young onset age, many live with the consequences for a significant part of their lives. Approximately one-third of the patients after an aSAH experience severe disabilities and are functionally dependent [154,155]. In addition, apart from neurological deficits, cognitive impairments are found to be present in 40-70 % of survivors [156-159]. Post-aSAH neurological injuries are often more diffuse, affecting multiple areas of the brain and having a wide array of symptoms and sequelae, including memory, attention, and language impairments [160-162]. Therefore, even among patients with good functional outcomes, significant cognitive impairments can affect their ability to fully return to work, daily life, and quality of life [159]. As these complications may be subtle and difficult to fully grasp, they are often under-detected [163]. It is therefore important to identify the areas where patients after an aSAH might find it more challenging to direct rehabilitation and support measures provided during the acute phase and after their discharge home or to a care facility [162]. As pointed out by Lindner et al., there is a gap in knowledge regarding the longitudinal clinical trajectory after the acute phase, especially regarding long-term outcomes for patients after an aSAH [164].

## 1.3.1 ASSESSING OUTCOME AFTER ANEURYSMAL SUBARACHNOID HEMORRHAGE

Several neurophysiological tests are used in clinical and research settings to assess functional and cognitive outcomes after aSAH [165-167]. Some of these are self-assessment questionnaires that include the patient's perspective on their health status and well-being. They provide valuable information on the impact of the condition on the patient's daily life and help to evaluate rehabilitation interventions. However, a large discrepancy may exist between functional outcome measures and the patient's self-assessed outcomes [168,169]. In the studies included in this thesis, the Glasgow Outcome Scale Extended (GOSE) was used for grading the functional outcomes, and the Life Satisfaction Questionnaire-11 (LiSat-11), Mayo-Portland Adaptability Inventory-4

(MPAI-4), and the Mental Fatigue Scale (MFS) for patients' self-assessment of sequelae [170,171].

#### 1.3.1.1 FUNCTIONAL OUTCOME

The GOSE, a widely used outcome measure in clinical research and practice, was primarily developed to assess patients after brain injuries, specifically traumatic brain injury, [171]. It evaluates the functional outcome and level of independence across various domains of daily living, such as physical, cognitive, emotional, and social functioning. The scale ranges from death (1 point) to good recovery (8 points), with higher scores indicating better outcomes and higher levels of independence. The scale is presented in Table 8, page 47. The modified Rankin Scale (mRS) developed for assessing outcomes after cerebrovascular accidents, primarily ischemic stroke, is another commonly used outcome measure [172,173]. The scale comprises seven ordinal categories ranging from 0 to 6, with 0 indicating no symptoms and 6 representing death.

#### 1.3.1.2 LIFE SATISFACTION QUESTIONNAIRE-11

The Life Satisfaction Questionnaire-11 is a self-reporting questionnaire used to assess patients' satisfaction through one global item, "Life as a whole," and 10 domain-specific items [174]. The items consider different aspects such as physical health, psychological health, vocational situation, financial situation, leisure activities, and partner relationships. The LiSat-11 has been used in studies investigating life satisfaction after stroke, polio, traumatic spinal cord injury, and TBI [174-176].

#### 1.3.1.3 THE MAYO-PORTLAND ADAPTABILITY INVENTORY-4

The Mayo-Portland Adaptability Inventory-4 is a broad assessment instrument covering all the components of the International Classification of Functioning, Disability, and Health (ICF), a framework for describing and organizing information on functioning and disability [177]. It comprises 29 items assessing different domains of functioning, such as emotion, behavior, social adjustment, and community integration. It has been used in outpatient settings to evaluate patients after a stroke and TBI [178].

#### 1.3.1.4 THE MONTREAL COGNITIVE ASSESSMENT

The Montreal Cognitive Assessment (MoCA) is another instrument used to screen for cognitive impairments [179]. It evaluates various cognitive domains, executive functions, memory, language, visuospatial abilities, and orientation

after cerebrovascular events, including ischemic stroke. However, the MoCA requires in-person administration, requiring greater resources and logistics.

## 1.3.2 FATIGUE AND MENTAL FATIGUE AFTER ANEURYSMAL SUBARACHNOID HEMORRHAGE

Among the various sequelae patients experience after an aSAH, fatigue has emerged as the most prominent symptom, affecting up to 90% of the patients [180]. It is a debilitating long-term sequela, impacting the patient's work ability and social and family life [181]. However, despite its high prevalence with implications for both short- and long-term outcomes, the understanding of post-aSAH fatigue remains limited [182]. Currently no known effective treatment methods, pharmacological nor therapeutical, are available [183]. A contributing challenge is that fatigue is commonly assessed as a single entity; however, it can be classified into two distinct types, namely physical fatigue, and mental fatigue [184,185]. Notably, mental fatigue has been found to be independently associated with unfavorable outcomes following aSAH [186]. Although, mental fatigue has no established standard definition to date, it is described as difficulty initiating and sustaining mental tasks, often accompanied by other symptoms such as irritability, anxiety, depression, and stress sensitivity [181]. Furthermore, the specific pathophysiology of mental fatigue development post-aSAH is complex, multidimensional, and poorly understood [187]. Therefore, further studies are needed to facilitate and improve patient rehabilitation and outcomes.

### 1.3.2.1 ASSESSING FATIGUE AND MENTAL FATIGUE

The multifaceted and subjective nature of fatigue renders it challenging to measure and quantify objectively; however, several self-assessment questionnaires exist. Nevertheless, it is difficult to find a questionnaire covering all aspects of fatigue [188].

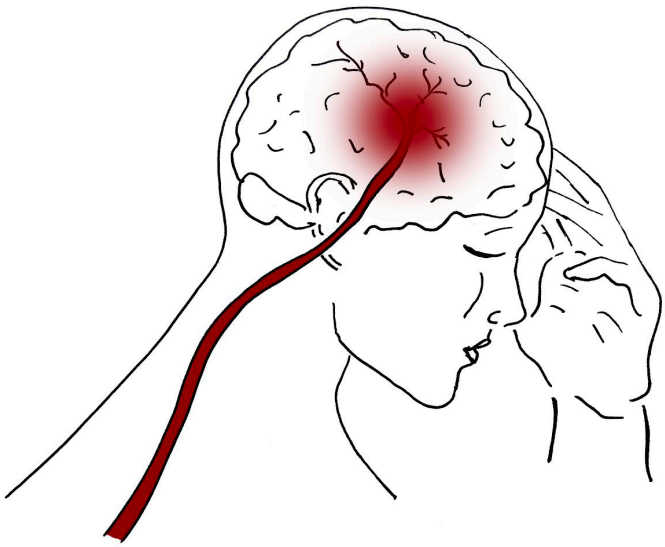
### 1.3.2.2 THE FATIGUE SEVERITY SCALE

The Fatigue Severity Scale (FSS) is a widely used self-report instrument in clinical and research settings to assess the severity and impact of fatigue on patients' lives. It comprises nine items that evaluate the subjective experience of fatigue across physical, cognitive, and psychosocial domains. Additionally,

it assists in evaluating to which degree fatigue interferes with daily functioning [189]. However, it does not assess the mental fatigue aspect separately.

#### 1.3.2.3 THE MENTAL FATIGUE SCALE

The Mental Fatigue Scale comprises 15 items regarding the mental aspects of fatigue, including cognitive and sensory symptoms, and evaluating their intensity, frequency, and duration. It was initially developed as a multidimensional self-reporting questionnaire for assessing mental fatigue in patients after brain injuries; however, it is now used for follow-up in various diagnoses [190,191]. It has a maximum score of 42, and a cut-off of > 10.5 indicates the presence of mental fatigue [192].



# 2 AIMS

## 2.1 THE OVERALL AIMS

- To investigate whether biomarkers can be used to detect or predict DCI after aSAH
- To explore longitudinal long-term outcomes after aSAH

## 2.2 SPECIFIC AIMS

**Study I**

- To investigate if HRV monitoring can be used to detect or predict incipient ischemia
- To explore if HRV parameters differ between patients developing DCI or those who do not
- To analyze whether HRV could be related to 1-year outcome

**Study II**

- To investigate whether unfavorable 1-year outcome can be predicted by analyzing TNF-α, IL-6, IL-1Ra, ICAM-1, and CRP
- To investigate whether the development of DCI can be predicted by analyzing levels of TNF-α, IL-6, IL-1Ra, ICAM-1, and CRP

**Study III**

- To evaluate long-term outcomes up to 3 years after an aSAH
- To assess dynamics in recovery after an aSAH
- To relate outcomes to patient characteristics and complications during the acute phase.

**Study IV**

- To determine the prevalence, severity, and dynamics of mental fatigue at 1, 3, and 5 years after aSAH
- To identify whether demographic characteristics and secondary complications after aSAH were associated with an increased risk of developing mental fatigue

# 3 PATIENTS AND METHODS

## 3.1 APPROVALS AND REGISTRATION

All the included studies were prospective and observational and adhered to the Declaration of Helsinki. Ethical approval was granted by the Regional Research Ethics Committee of Gothenburg, Sweden. The first ethical approval (053-15) permitted the collection of continuous HRV data and biobank storage of blood samples for later analysis. Patient characteristics and events during the acute phase for up to 10 days would be registered. The outcome was planned to be measured after 1 year using the GOSE and three questionnaires. A supplementary permit (T 213-18) was approved in April 2018 for an extended analysis of systemic inflammatory markers, including IL-6, IL-1Ra, TNF-alfa, and ICAM-1, with the Luminex technique. Furthermore, an extension of the outcome period up to 3- and 5 years post-ictus was accepted.

## 3.2 PATIENT POPULATION, STUDIES I-IV

This thesis was based on a patient cohort aged ≥18 treated for an aSAH in the NICU at the Sahlgrenska University Hospital, Göteborg, from May 2015 to October 2016. The aneurysms were verified on digital subtraction angiography. Exclusion criteria included a previous aSAH, stroke, or brain injury, and patients with an existing pacemaker, as HRV registrations would not be accurate.

## 3.3 STUDY DESIGN

The study designs for studies I-IV are presented in **Tables 6** and **7.**

*Table 6. Study Design- Acute phase*

| Day | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| GCS[1] | X | | | | | | | | | | |
| WFNS[2] | X | | | | | | | | | | |
| Fisher[3] | X | | | | | | | | | | |
| H&H[4] | X | | | | | | | | | | |
| NE[5] | X | X | X | X | X | X | X | X | X | X | X |
| TCD[6] | X | X | X | X | X | (X) | (X) | X | X | X | X |
| CT[7] | X | (X) | (X) | (X) | (X) | (X) | (X) | (X) | (X) | (X) | (X) |
| MRI[8] | (X) | (X) | (X) | (X) | (X) | (X) | (X) | (X) | (X) | (X) | (X) |
| HRV[9] | X | X | X | X | X | X | X | X | X | X | X |
| CRP[10] | X | X | X | X | X | X | X | X | X | X | X |
| IL-6[11] | (X) | (X) | (X) | (X) | (X) | (X) | (X) | (X) | (X) | (X) | (X) |
| TNF-α[12] | (X) | (X) | (X) | (X) | (X) | (X) | (X) | (X) | (X) | (X) | (X) |
| IL-1Ra[13] | (X) | (X) | (X) | (X) | (X) | (X) | (X) | (X) | (X) | (X) | (X) |
| ICAM-1[14] | (X) | (X) | (X) | (X) | (X) | (X) | (X) | (X) | (X) | (X) | (X) |

*X = performed, (X) = not always performed on the day indicated*
*[1]GCS; Glasgow coma scale, [2] WFNS; World Federation of Neurosurgical societies scale, [3] Fisher; Modified Fisher scale, [4] H&H, Hunt and Hess scale, [5] NE, Neurological examination performed at least three times daily by NICU nurses, [6] TCD; Transcranial Doppler; performed regularly only on weekdays (missing values depending of day of admission), [7] CT; Computerized tomography; performed on admission and on other days at the discretion of the attending physician, [8] MRI; Magnetic Resonance Imaging; performed at the discretion of the attending physician, [9] HRV; Heart rate variability, [10] CRP; C-reactive protein, [11] IL-6, Interleukin-6; Sample 1 as soon as possible after study inclusion and Sample 2 later in the acute phase, [12] TNF-α; Tumor Necrosis Factor-α; Sample 1 as soon as possible after study inclusion and Sample 2 later in the acute phase, [13] IL-1Ra; Interleukin-1Ra; Sample 1 as soon as possible after study inclusion and Sample 2 later in the acute phase [14] ICAM-1; Intracellular Adhesion Molecule-1; Sample 1 as soon as possible after study inclusion and Sample 2 later in the acute phase*

*Table 7. Study Design at 1, 3, and 5 years*

| Year | 1 | 3 | 5 |
|---|---|---|---|
| GOSE[1] | X | X | X |
| Li-SAT-11[2] | X | X | |
| MPAI-4[3] | X | X | |
| MFS[4] | X | X | X |

*[1] Glasgow outcome scale extended, [2] Life Satisfaction Questionnaire-11, [3] The Mayo-Portland Adaptability Inventory-4, [4] Mental Fatigue Scale*

## 3.4 GENERAL TREATMENT STUDIES I-IV

Patients received treatment according to local protocol following international guidelines from the American Heart Association/American Stroke Association and European Stroke Organization [30,32]. Aneurysms were secured as soon as possible, usually within 24 hours after admission, using either an endovascular or neurosurgical approach. Intravenous nimodipine (Nimotop®, Bayer) 0.2 mg/mL was administered prophylactically. Blood pressure was monitored with an arterial catheter, and hypotension was treated with norepinephrine titrated to adequate mean arterial blood pressure. Intravenous fluids, primarily Ringer-Acetate or Albumin 20%, were administered to target normovolemia. If a deteriorating respiratory or neurological status was observed, patients were intubated and sedated primarily with propofol and fentanyl. Mechanical ventilation was provided at $pCO_2$ 4.5-6 kPa and $pO_2$ > 12 kPa to target normoventilation. Patients developing hydrocephalus were treated with an EVD. A positive culture from blood, tracheal secretion or CSF, and clinical signs of infection were treated with antibiotics. Patients developing clinical indications of DCI were managed using induced hypertension and, in some cases, an increased nimodipine dosage. If symptoms did not resolve, further angiographic investigation was performed, and intra-arterial nimodipine administration or balloon angioplasty were potentially considered.

## 3.5 DATA COLLECTION STUDIES I-IV

All clinical and radiological admission data, complications, or specific interventions were documented. The day of admission was defined as day 0. Patients' clinical status at admission was scored according to the GCS, WFNS, and H&H [23]. The first GCS registered by a physician, regardless of which hospital was the first to admit the patient, was used. The WFNS and H&H were recorded by the admitting neurosurgeon at the Sahlgrenska University Hospital. The GOSE was used for outcome assessment, and it was stratified into favorable (GOSE 5-8) and unfavorable (GOSE 1-4) outcomes according to recommendations [166].

*Table 8. The Glasgow Outcome Scale Extended*

| Level | | Level clarification |
|---|---|---|
| 1 | Dead | |
| 2 | Vegetative state | Total absence of awareness |
| 3 | Severe Disability/Lower | Need help with all ADL[1] |
| 4 | Severe Disability/Upper | Need some help with ADL |
| 5 | Moderate Disability/Lower | Independent; but not able to return to work, school, or previous social activities |
| 6 | Moderate Disability/Upper | Independent; may partially return to work, school, or social activities |
| 7 | Good recovery/Lower | Independent; minor insufficiencies in daily life |
| 8 | Good recovery/Upper | Full recovery |

[1] *ADL; Activities of daily living, GOSE 1-4; unfavorable outcome, GOSE 5-8; favorable outcome*

## 3.6 DEFINITION OF DELAYED CEREBRAL ISCHEMIA

The definition of DCI, initially proposed by Vergouwen et al. [4] was used in all studies. According to this definition, the clinical deterioration caused by DCI is characterized by the occurrence of focal neurological impairment, including hemiparesis, aphasia, apraxia, hemianopia, or neglect, or a decrease of at least two points on the GCS. Notably, these symptoms must persist for at least 1 h and should not be immediately apparent after aneurysm occlusion. Furthermore, to attribute the observed deterioration to DCI, other possible causes must be ruled out through clinical assessment, brain CT or MRI, or other relevant laboratory studies, including electrolyte imbalance or infection. In addition, cerebral infarction resulting from DCI should be apparent on CT or MRI within 6 weeks post-aSAH or on the most recent CT or MRI scan conducted prior to death within the same timeframe or confirmed during autopsy. It should not be present on the CT or MRI scan taken between 24 and 48 hours after early aneurysm occlusion or attributed to other causes such as surgical clipping or endovascular treatment.

## 3.7 STUDY I. HEART RATE VARIABILITY

HRV data were continuously sampled at 1000 Hz by an external HRV monitoring device (eMotion LAB Mega Electronics Ltd., Kuopio, Finland). The data were subsequently extracted and analyzed offline in the time -and frequency domains according to recommendations of the European Society of Cardiology Task Force and the North American Society of Pacing and Electrophysiology [88]. The three 5-minute (300 s) intervals were selected from predefined periods spread evenly over the day with minimal artifacts and ectopic beats, preferably with the patient at rest. The parameters used for the study are presented in **Table 5** and in further detail in the introduction, page 33. The mean values for each HRV variable registered during the first 48 hours after admission were used as baseline values in the analysis of DCI development and the 1-year outcome.

## 3.8 STUDY II. SERUM INFLAMMATORY BIOMARKERS

Two blood samples were drawn for the analysis of inflammatory markers: the first sample, early after admission, and the second, later during the acute phase. The intention was for the early sample to be obtained within 72 hours after admission and the second after approximately 7 days. The samples were drawn via either an arterial catheter or a central venous line and were immediately centrifuged, frozen, and stored at -80º C. CRP and LPK were analyzed at the accredited Sahlgrenska University Hospital laboratory, and TNF-α, IL-6, IL-1Ra, and ICAM-1 were analyzed at the Department of Physiology, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden. Three types of Bio-plex Pro Assays were used; the Bio-Plex Pro Human Cytokine 27-Plex Group I (Bio-Rad, Hercules, CA, USA; catalog # M500KCAFOY), MIG (Bio-Rad; catalog # 171B6015 M), Bio-Plex Pro Human TGF-β 3-Plex (Bio-Rad; catalog # 171W4001 M) and Bio-Plex Pro Human ICAM-1/VCAM 2-Plex sets (Bio-Rad; catalog # 171B6009 M/171B6022 M). The samples were thawed and prepared according to the manufacturer's instructions. To each assay with patient samples, a solution of fluorophores colored beads and specific coupled antibodies was added. The biomarker solution was subsequently further analyzed with the Luminex 200 system (Bio-Rad) using a laser to read the color code of each bead and its bound analytes thereby obtaining quantitative data on the biomarkers. This data was automatically plotted against standard solutions with pre-known diluted concentrations of each biomarker thus providing the concentration of the examined biomarkers. If the concentration of a biomarker was below the detection limit, the value was set as 1/8 of the detection limit of the most diluted standard solution.

# 3.9 STUDIES III AND IV. EVALUATION OF LONG-TERM OUTCOMES

## 3.9.1 ASSESSMENT OF OUTCOME

The outcome was assessed by a telephone interview at 1, 3, and 5 years post-aSAH using the GOSE. In addition, three self-assessment questionnaires, the Life Satisfaction Questionnaire-11 (LiSat-11), the Mental Fatigue Scale (MFS), and the Mayo-Portland Adaptability Inventory-4 (MPAI-4), were sent by post to the patients.

*Table 9. Self-assessment questionnaires*

| Questionnaire and question content | Answer options |
|---|---|
| Life Satisfaction Questionnaire 11 (*LiSat-11)*<br>▪ Life as a Whole<br>▪ Vocation<br>▪ Economy<br>▪ Leisure<br>▪ Contacts<br>▪ Sexual Life<br>▪ ADL‡<br>▪ Family life<br>▪ Partner Relationship<br>▪ Somatic Health<br>▪ Psychological Health | 1 -Very Dissatisfied<br>2 - Dissatisfied<br>3 - Rather Dissatisfied<br>4 - Rather Satisfied<br>5 - Satisfied<br>6 - Very Satisfied |
| The Mayo-Portland Adaptability Inventory (*MPAI-4)*§<br><u>Part A- Abilities (Question 1 to 12)</u><br>1.Mobility, 2. Use of hands, 3. Vision 4. Audition, 5. Dizziness, 6. Motor speech, 7A. Verbal communication, 7B. Nonverbal communication, 8. Attention/concentration, 9. Memory, 10. Fund of information, 11. Novel problem-solving, 12. Visuospatial abilities<br><br><u>Part B- Adjustment (Questions 13 to 21)</u><br>13. Anxiety, 14. Depression, 15. Irritability, anger, aggression 16. Pain/headache, 17. Fatigue, 18. Sensitivity to mild symptoms, 19. Inappropriate social interaction, 20. Impaired self-awareness, 21. Family/significant relationships<br><br><u>Part C- Participation (Question 22 to 29)</u><br>22. Initiation, 23. Social contacts (not family), 24. Leisure and recreational activities, 25. Self-care, 26. Residence, 27. Transportation, 28A. Paid employment, 28B. Other employment, 29. Managing money and finances | <u>For questions 1 to 22, 25-27, 29:</u><br>0- no problems, 1- mild problems no interference with activities, 2- mild problems with interference 5-24% of the time, 3- moderate problems with interference 25-75% of the time , 4- severe problems with interference >75% of the time<br><br><u>For questions 23 and 24-</u><br>0-normal involvement/participation, 1- mild difficulty with involvement/participation, 2- mildly limited 75-95% normal involvement/participation, 3- moderately limited, 25-75% normal involvement/participation. 4- no or rare involvement/participation<br><br><u>For question 28A, 28B</u><br>0- Full time, 1- Part time (3-30 hours/wk) without support, 2- Full-time or part-time with support, 3- sheltered work/supervised environment, 4- unemployment/inactive |
| Mental Fatigue Scale (*MFS*)<br>▪ Mental fatigue<br>▪ Fatigue in general<br>▪ Lack of initiative<br>▪ Mental recovery<br>▪ Concentration difficulties<br>▪ Memory problems<br>▪ Slowness of thinking<br>▪ Sensitivity to stress<br>▪ Increased tendency to become emotional<br>▪ Irritability<br>▪ Sensitivity to light/noise<br>▪ Decreased/increased duration of sleep<br>▪ Diurnal variations | 0- No problems/discomfort<br>0.5- No to some mild problems/discomfort<br>1.0- Mild problems/discomfort<br>1.5- Mild to moderate problems/discomfort<br>2.0- Moderate problems/discomfort<br>2.5- Moderate-severe problems/discomfort<br>3.0- Severe problems/discomfort<br><br>A total score of ≥ 10.5 indicates mental fatigue |

*The three self-assessment questionnaires used; the Life Satisfaction Questionnaire-11 (LiSat-11), the Mental Fatigue Scale (MFS), and the Mayo-Portland Adaptability Inventory-4 (MPAI-4) ‡ADL; Activities of daily living. § Only parts A–C were used. Adaptation from source: Wenneberg, S.B. et al. Acta Neurologica Scandinavica, 2022. Creative Commons BY 4.0 License*

### 3.9.2 LIFE SATISFACTION QUESTIONNAIRE-11

The LiSat-11 comprises 11 items, For the analysis, the answer options were stratified into "satisfied" (ranging from "rather satisfied" to "very satisfied) and "dissatisfied" ("rather dissatisfied "to "very dissatisfied").

### 3.9.3 THE MAYO-PORTLAND ADAPTABILITY INVENTORY-4

The MPAI-4 is divided into four parts as follows: A; Abilities, B; Adjustment, C; participations, and D; pre-existing and associated conditions. The answers were dichotomized as "no problems" (no to mild problems with no interference with activities) and "problems" (mild problems with interference with activities to moderate and severe problems). In parts A and part B, all items were analyzed. In part C, questions regarding employment were excluded from the statistical analysis due to an insufficient number of responses and the entire part of D was excluded for the same reason.

### 3.9.4 THE MENTAL FATIGUE SCALE

The maximum score for the MFS is 42, with a score ≥10.5 indicating mental fatigue. Therefore, it was dichotomized as < 10.5 (no mental fatigue) and ≥10.5 (mental fatigue). The MFS can by the total score be divided into levels of severity [190,193 192].

*Table 10. Mental Fatigue Scale divided by total score*

| Severity of mental fatigue | Total MFS[1] Score |
|---|---|
| No mental fatigue | < 10.5 |
| Mild mental fatigue | 10.5-14.5 |
| Moderate mental fatigue | 15-20 |
| Severe mental fatigue | 20.5 |

[1] *MFS, Mental Fatigue Scale*

# 3.10 COMPARISON BETWEEN DIFFERENT GROUPS OF PATIENTS

Comparisons were made between different groups of patients with regard to events during the acute phase. Variables used for comparisons were LOCi, DCI, and hydrocephalus. Patients were also divided by sex and age (age < 60 or ≥60 years at ictus).

# 3.11 STATISTICAL ANALYSIS STUDIES I-IV

Data are presented as mean, standard deviation (SD), sum and percentage, or median with either interquartile range (IQR) or range when appropriate. For continuous data, the Student T-test and the Mann-Whitney test were used to compare the means and the mean ranks, respectively. Categorical and dichotomized data was analyzed by Pearson's Chi-square or Fisher exact test. Spearman's correlation coefficient was calculated to evaluate the association between two ordered or continuous variables. For all studies, $p \leq 0.05$ was considered statistically significant. For study, I, IBM SPSS 24.0 was used for statistical calculations, and SAS for Windows version 9.4 for studies II and III. For study IV, statistical analysis was performed with IBM SPSS Statistics Version 29.0. For studies II and III, external statistical consultation was used.

## 3.11.1 STUDY I

The mean values for each HRV variable registered during the first 48 hours after admission were used as baseline values in the analysis of DCI development and the 1-year outcome. For the temporal analysis of HRV variables between patients who developed DCI and those who did not, a linear mixed model with an autoregressive covariance matrix and random intercept was used.

## 3.11.2 STUDY II

A multivariable analysis with multiple logistic regression was performed. Owning to the small study cohort, each model included only two independent variables. A strong correlation between IL-1Ra and IL-6 was found; therefore, no model including both biomarkers was calculated. For the unadjusted association between biomarkers and unfavorable outcomes, a comparison of

the areas under the receiver operating characteristic curve with the non-parametric approach of DeLong was performed.

### 3.11.3 STUDIES III AND IV

For the temporal analysis between the follow-up time points, the Wilcoxon signed-rank test was used. The development over time, at 1, 3, and 5 years was analyzed using the Friedman test. A mixed model univariable logistic regression analysis with a covariance matrix was used to analyze the effect of patients' demographics and events during the acute phase on mental fatigue.

# 4 RESULTS

## 4.1 PATIENT POPULATIONS STUDIES I-IV

Totally, 64 patients were included in the study cohort. An overview of the inclusion for each study is illustrated in the flowchart, **Figure 4.** The median (range) age was 58 (25-75) years, and 75% were female. Patient demographics and comorbidities are detailed in **Table 11.**

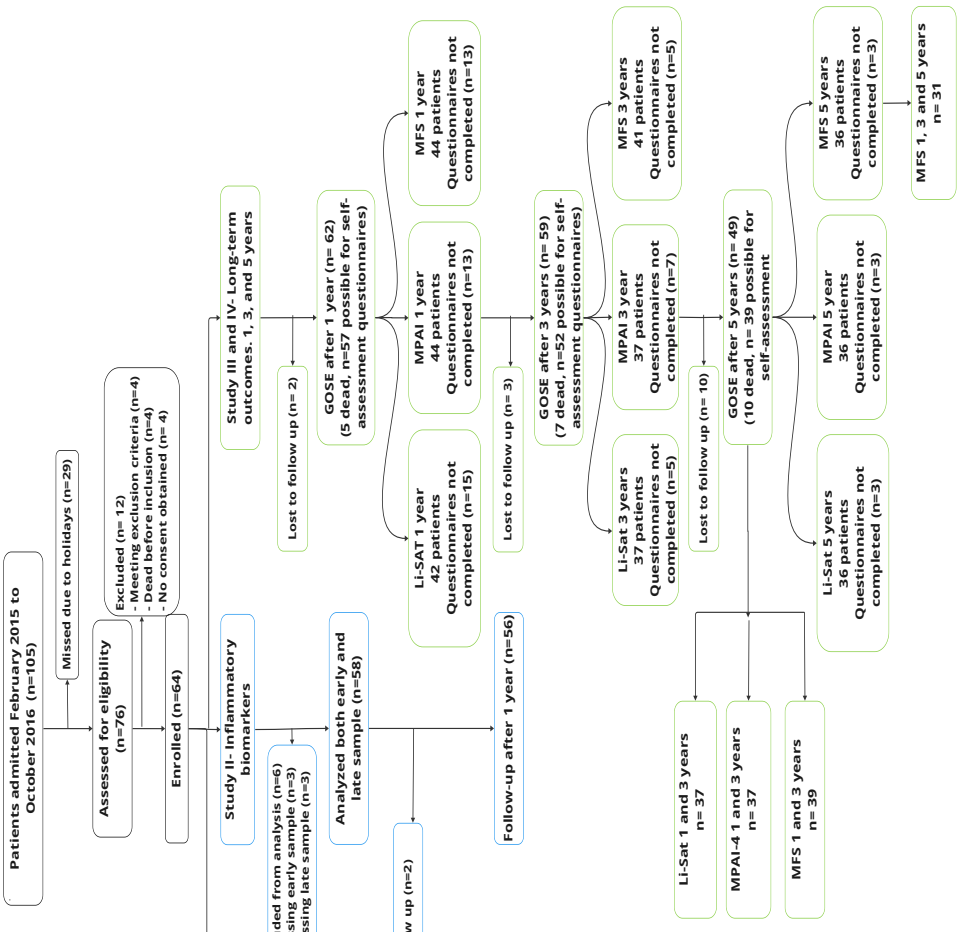



*Figure 4. Flow chart for inclusion studies I-IV*

*HRV; Heart Rate Variability, GOSE; Glasgow Outcome Scale Extended, LiSat-11; Life Satisfaction, MPAI-4; Mayo-Portland Adaptability Inventory-4, MFS; Mental Fatigue Scale*

*Table 11. Patient characteristics and outcome data*

| | |
|---|---|
| **Age**, years, median (range) | 58 (27-78) |
| **Female** n (%) | 48 (75) |
| **Mortality 1 year** n (%) | 5 (8) |
| **GCS** median(range) | 13 (4-15) |
| GCS 3-8 n (%) | 11 (17) |
| GCS 9-12 n (%) | 8 (13) |
| GCS 13-15 n (%) | 45 (70) |
| **H&H scale** median (range) | 3 (1-5) |
| H&H 1-2 n (%) | 28 (44) |
| H&H 3-5 n (%) | 36 (56) |
| **WFNS median** (range) | 2 (1-5) |
| WFNS 1-3 n (%) | 45 (70) |
| WFNS 4-5 n (%) | 19 (30) |
| **Modified Fisher scale median** (range) | 4 (0-4) |
| Fisher 0-2 n (%) | 6 (9) |
| Fisher 3-4 n (%) | 58 (91) |
| **Aneurysm location** | |
| Anterior n (%) | 47 (73) |
| Posterior n (%) | 17 (27) |
| **Aneurysm treatment** | |
| Surgical n (%) | 17 (27) |
| Endovascular n (%) | 47 (73) |
| **EBI** n (%) | 24 (40) |
| **DCI** n (%) | 16 (25) |
| **EVD** n (%) | 32 (50) |
| **GOSE**[1], **1 year** median (range) | 5 (1-8) |
| 1 n (%) | 5/62 (8) |
| 2-4 n (%) | 13/62 (21) |
| 5-8 n (%) | 44/62 (71) |

*[1] Two patients lost to follow-up, GCS; Glasgow Coma Scale, H&H; Hunt and Hess scale, WFNS; World Federation of Neurosurgical Societies, EBI; Early Brain Injury, DCI; Delayed Cerebral Ischemia, EVD; External Ventricular Drainage, GOSE; Glasgow Outcome Scale Extended*

# 4.2 DELAYED CEREBRAL ISCHEMIA

During the acute phase, 16 out of 64 patients (25%) developed DCI. Among them the time of symptom onset was conclusively diagnosed in 9 patients, with the median debut day being on day 7 (range, 2-12) post-aSAH.

A significant difference was observed in TCD velocities (cm/s) between patients who developed DCI and those who did not (median [range], 265 [183-392] vs. 180 [64-310] ($p < 0.001$), F**igure 5.**

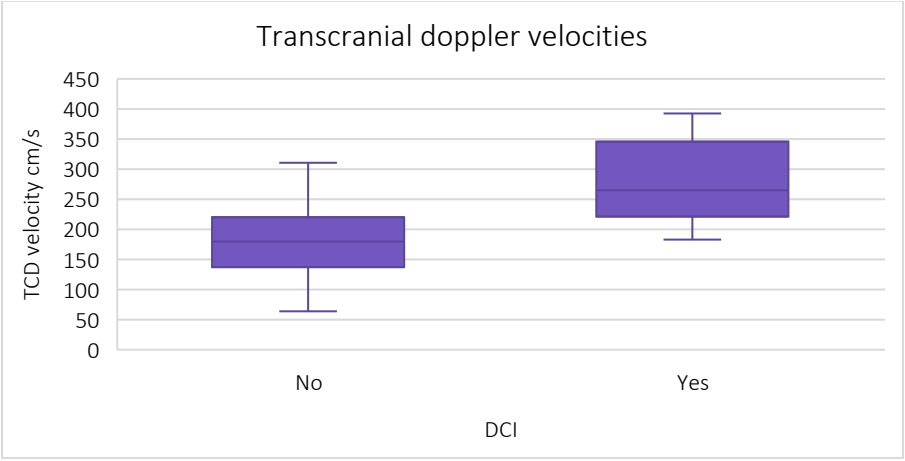



*Figure 5. Maximum Transcranial Doppler (TCD) velocities significantly differed between patients developing DCI or not during the acute phase ($p < 0.001$).*

## 4.3 STUDY I - HEART RATE VARIABILITY

In study I, we aimed to explore the potential of intermittently analyzed HRV as a predictor and detection method for DCI during the acute phase and evaluate the association between HRV at admission and the 1-year outcome.

For the cohort with possible HRV registrations, the length of total registration per patient ranged from 2 to 10 days, corresponding to three to thirty-one periods of 5-minute registrations. Thus, between 15 and 155 minutes of total registration time per patient were recorded. For all 55 included patients, the temporal pattern of several HRV parameters significantly changed during the study period. The SDRR, RMSSD, and nHF significantly decreased (p=0.044, 0.001, and 0.001, respectively), and nLF and the LF/HF ratio significantly increased (p=0.001 and < 0.001, respectively).

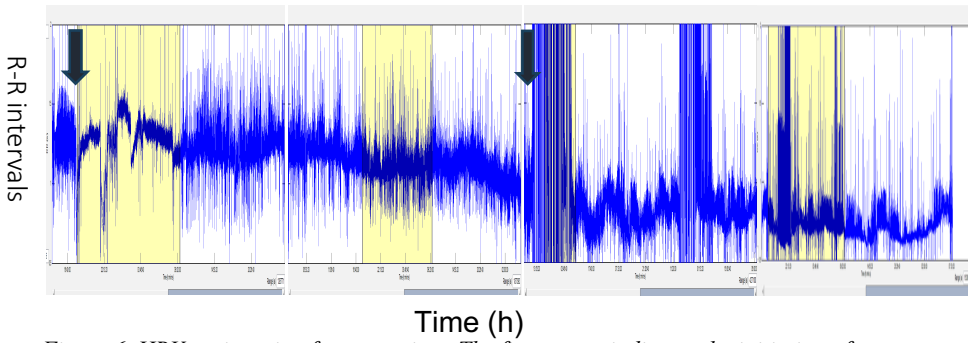



*Figure 6. HRV registration from a patient. The first arrow indicates the initiation of anesthesia for endovascular treatment of the aneurysm and placement of an EVD. The second arrow indicates the time point when the patients began having neurological symptoms indicative of DCI development.*

### 4.3.1 HEART RATE VARIABILITY AND DELAYED CEREBRAL ISCHEMIA

The mean values of all assessed HRV variables from the first 48 h after admission could not predict DCI development, nor could HRV registrations analyzed 24 h before symptom onset detect DCI. However, for the patients who developed DCI, a significantly higher LF/HF ratio over time was observed than in patients without DCI (p=0.012), **Figure 7**.

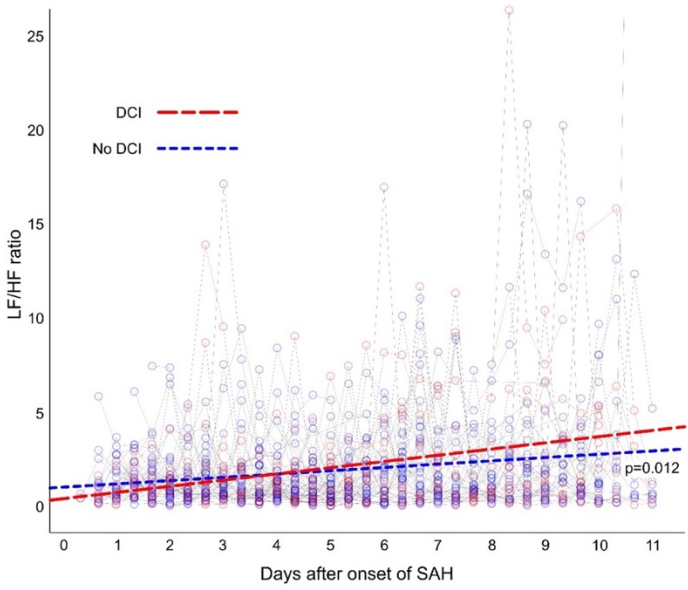



*Figure 7. LF/HF ratio for patients developing DCI compared to non-DCI patients. The dashed lines indicate the mean ratio for patients developing DCI (red) and patients without DCI (blue). The LF/HF increased over time for both populations; however, patients developing DCI had a significantly higher increase (p=0.012). Source: Bjerkne Wenneberg, S et al., Acta Anaesthesiol Scand. 2020, Creative Commons BY 4.0 License*

### 4.3.2 HEART RATE VARIABILITY AND 1-YEAR MORTALITY

The mean values of the parameters, STDRR, RMSSD, and total power during the first 48 h after admission were significantly lower for patients who died within the first year than those of survivors (p=0.03, p=0.007, and p=0.004, respectively), **Table 12**.

*Table 12. Mean HRV values for the first 48 h after admission in patients who are alive vs. those who are dead during the first year after aSAH*

| HRV parameter | Alive after 1 year | Dead within 1 year | p value |
|---|---|---|---|
| STDRR | 27.6 (20.7-41.6) | 8.17 (8.11-9.13) | 0.003 |
| RMSSD | 23.5(13.5-40.3) | 7.98 (6.61-11.5) | 0.007 |
| Total power | 867(387-1560) | 68.3 (57.7-118.5) | 0.004 |

*RMSSD; root mean square of the successive differences; STDRR, standard deviation of all RR intervals.*

## 4.4 STUDY II - SYSTEMIC INFLAMMATORY BIOMARKERS

In study II, we investigated whether increased levels of systemic inflammatory biomarkers (TNF-α, IL-6, IL-1Ra, ICAM-1, and CRP) can predict DCI development and if the levels of biomarkers were associated with the 1-year outcome. Out of 64 patients, blood samples (one early, sample 1, and one late, sample 2) from 58 patients were analyzed.

### 4.4.1 INFLAMMATORY BIOMARKERS AND DELAYED CEREBRAL ISCHEMIA

No differences were observed in the serum inflammatory biomarker levels in either sample 1 or sample 2 between patients with DCI or those without DCI. A significantly higher percentage of the patients with DCI were diagnosed and treated for infection by sample 2 than those without DCI (69 vs. 31%, p=0.02). Moreover, patients with DCI had significantly higher median temperatures, 38.6 (IQR 38.4-38.8), than patients without DCI, 37.9 (IQR 37.4-38.1), p= 0.004.

## 4.4.2 INFLAMMATORY BIOMARKERS AND 1-YEAR OUTCOME

### 4.4.2.1 SAMPLE 1

Patients with an unfavorable outcome (GOSE 1-4) had significantly elevated TNF-α, IL-6, IL-1Ra, ICAM-1, and CRP compared to patients with a favorable outcome (GOSE 5-8), **Figure 8.** A significant difference was observed in GCS scores at admission between patients with unfavorable and favorable outcomes (median [range] 11 [7-13] vs. 14 [13-15], p= 0.01). Therefore, the biomarkers were adjusted for GCS, with only IL-1Ra remaining significant (p=0.012). Patients with an unfavorable outcome had a Modified Fisher score of 3-4 at admission. Among the patients with favorable outcomes, 90% had a Modified Fisher score of 3-4 and 10% a score of 0-2. When adjusted for Modified Fisher scores, TNF-α, IL-6, IL-1Ra, and CRP remained significant (p= 0.03, 0.01, 0.007, and 0.02, respectively).

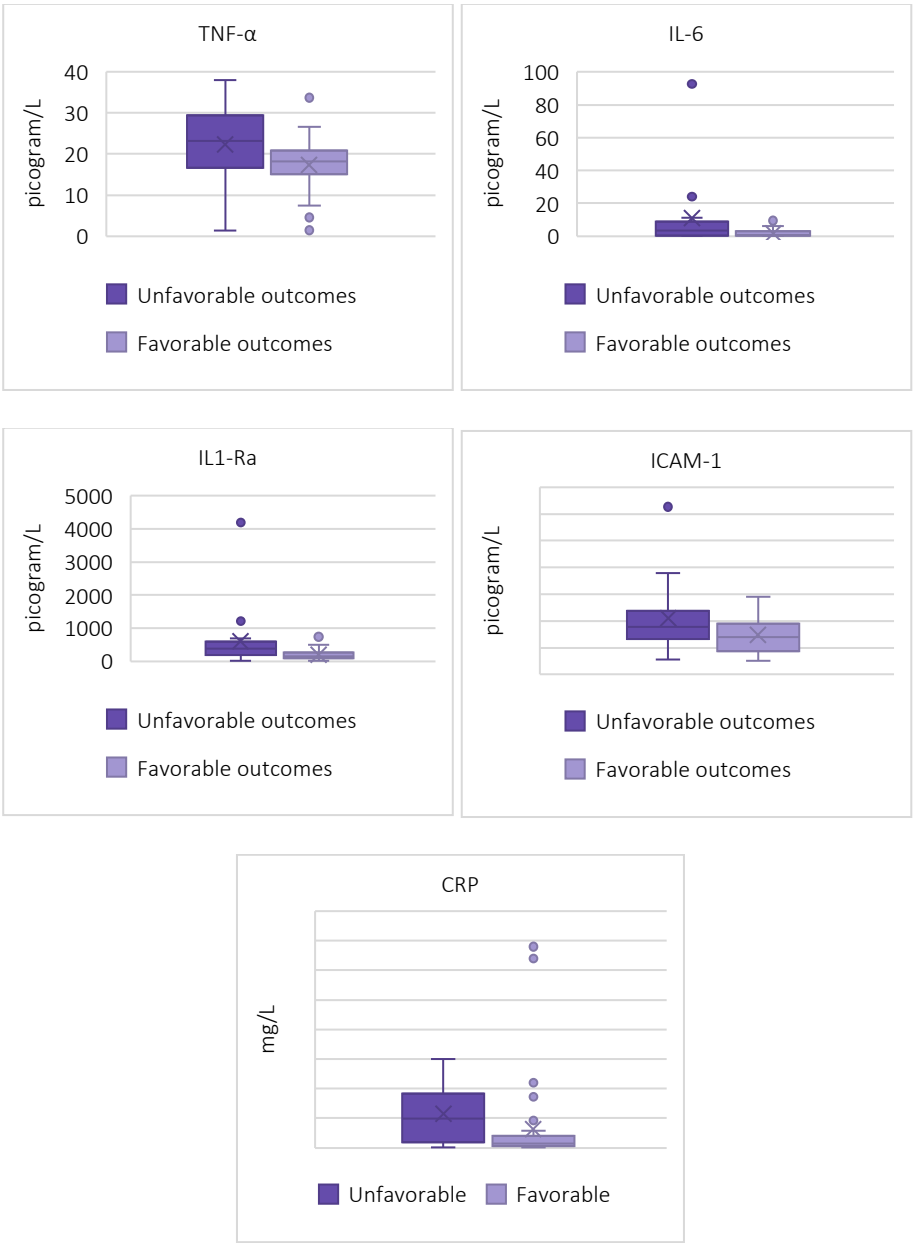



*Figure 8. A significant difference is observed in the concentrations of examined biomarkers from the early sample, sample 1, between patients with unfavorable and favorable outcomes. TNF- α (p=0.02), IL-6 (p= 0.01), IL-1Ra (p=0.007), ICAM-1 (p=0.05), and CRP (p= 0.01).*
*TNF-α; Tumor necrosis factor alpha; IL-6, Interleukin 6; IL-1Ra, Interleukin-1 receptor antagonist, ICAM; Intracellular Adhesion Molecule, CRP; C-reactive protein*

#### 4.4.2.2 SAMPLE 2

In sample 2, only CRP significantly differed between patients with unfavorable and favorable outcomes (36 [20-71] vs. 10 [6-39], p= 0.02). A significantly higher percentage of patients with unfavorable outcomes developed hydrocephalus and infections than patients with favorable outcomes (82 vs. 41%, p= 0.008, and 76 vs. 28%, p= 0.001, respectively).

## 4.5 STUDIES III AND IV, LONG-TERM OUTCOMES AND MENTAL FATIGUE

In study III, we focused on patient's functional outcomes after 1 and 3 years in a broad range of cognitive domains using the GOSE and three self-assessment questionnaires (LiSat-11, MPAI-4, and MFS). We further explored the development and potential changes in functional and self-assessed outcomes between 1 and 3 years. Finally, we investigated whether the long-term outcomes were associated with patients' demographics or events during the acute phase. After 5 years, follow-up was assessed with the same instruments; however, the main focus for study IV was mental fatigue and its components.

In study III, 37 patients were assessed with the LiSat-11 and the MPAI-4 at 1 and 3 years and 39 with the MFS. In study IV, 31 patients could be assessed with the MFS at 1, 3, and 5 years. The overall patient cohort mortality was 8, 11, and 16% at 1, 3, and 5 years, respectively.

*"I feel cheated out of the last few years of my professional life. I was unable to continue working because of paralyzing fatigue. However, I have developed a closer relationship with my family, and we cherish each other more. But I have to limit my social life because I tire more quickly."*

*Citation from a patient during a follow-up interview*

### 4.5.1 GLASGOW OUTCOME SCALE EXTENDED

For the 49 patients who were scored according to the GOSE, the median (range) GOSE was 5 (1-8), 6 (1-8), and 6 (1-8) after 1, 3, and 5 years, respectively. None had a GOSE score of 2, **Figure 9.**

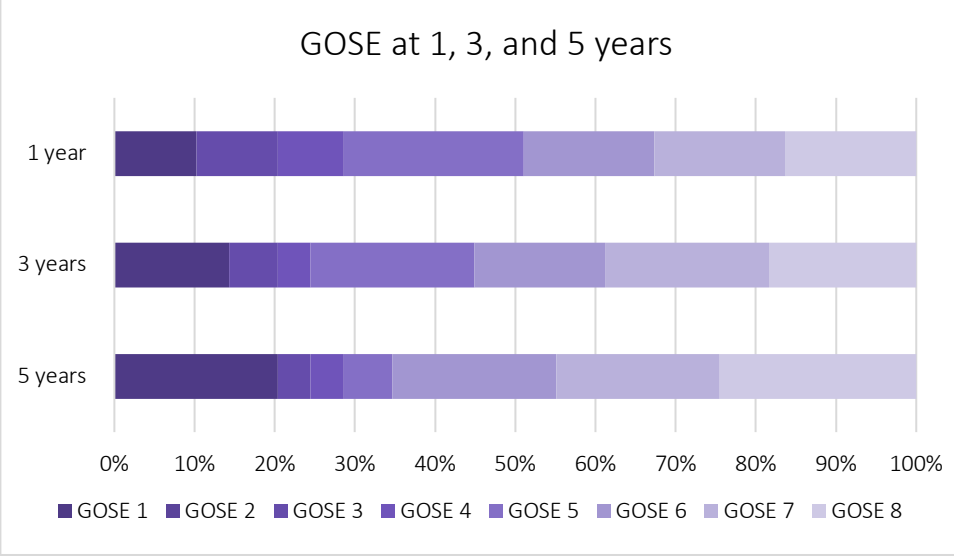



*Figure 9. Glasgow Outcome Scale Extended at 1, 3, and 5 years. Percentage of patients within each category. GOSE, Glasgow Outcome Scale Extended.*

*" I have resumed my studies, and I am able to manage independently now. However, it is disheartening that I am no longer as socially active as I used to be. I can only cope with small, peaceful social gatherings, as larger parties trigger headaches and excessive fatigue".*

*Citation from a patient during a follow-up interview*

## 4.5.2 LIFE SATISFACTION QUESTIONNAIRE-11

### 4.5.2.1 1 YEAR

At the 1-year follow-up, 79% of the patients rated "life as a whole" as satisfying. "Family life" (95%) and "ADL" (90%) had the highest proportion of satisfied patients, whereas "sexual life" (42%) and "vocation" (36%) had the highest proportion of dissatisfied patients.

### 4.5.2.2 1 TO 3 YEARS

A large variation was observed between the items in the proportions of patients improving or deteriorating. The items "Leisure" (46%) and "somatic health" (43%) had the greatest improvement, whereas "life as a whole" (34%) and "economy" (30%) had the greatest deterioration, **Table 13**

*Table 13. Life Satisfaction Questionnaire (LiSat-11), proportions of patients with the same, worse, or better scores at 3 years than those at 1 year.*

| Area | Answers at both 1 and 3 years (n) | Equal (%) | Deterioration (%) | Improvement (%) |
|---|---|---|---|---|
| Life as a whole | 35 | 46 | 34 | 20 |
| Vocation | 32 | 41 | 22 | 38 |
| Economy | 37 | 38 | 30 | 32 |
| Leisure | 35 | 26 | 29 | 46 |
| Contacts | 36 | 56 | 14 | 31 |
| Sexual Life | 33 | 52 | 18 | 30 |
| ADL[1] | 37 | 65 | 13 | 22 |
| Family life | 36 | 56 | 28 | 17 |
| Partner relationship | 28 | 50 | 25 | 25 |
| Somatic health | 37 | 32 | 24 | 43 |
| Psychological Health | 36 | 44 | 19 | 36 |

[1]*ADL; activities of daily life. Source: Appendix Bjerkne Wenneberg, S et al., Acta Neurolog Scand. 2022, Creative Commons BY 4.0 License*

### 4.5.2.3 IMPACT OF AGE

At the 1-year follow-up, a significant difference was found between patients aged > 60 and ≥ 60 years at ictus. Patients aged < 60 years were significantly more dissatisfied with all items except "sexual life", "ADL", and "partner

relationships", **Table 14.** At the 3-year follow-up, no significance was found in any item between the age groups.

*Table 14. Life Satisfaction Questionnaire-11 divided by age < 60 and ≥ 60 years*

| | < 60 years n (%) | ≥ 60 years n (%) | p-value |
|---|---|---|---|
| **Life as a whole** | | | |
| Dissatisfied | 8/27 (30) | 1/15 (7) | |
| Satisfied | 19/27 (70) | 14/15 (93) | 0.0038 |
| **Vocation** | | | |
| Dissatisfied | 12/25 (48) | 2/14 (14) | |
| Satisfied | 13/25 (52) | 12/14 (86) | 0.014 |
| **Economy** | | | |
| Dissatisfied | 11/27 (41) | 2/15 (13) | |
| Satisfied | 16/27 (59) | 13/15 (87) | 0.0051 |
| **Leisure** | | | |
| Dissatisfied | 12/27 (44) | 1/14 (7) | |
| Satisfied | 15/27 (56) | 13/14 (93) | 0.0034 |
| **Contacts** | | | |
| Dissatisfied | 9/27 (33) | 1/15 (7) | |
| Satisfied | 18/27 (67) | 14/15 (93) | 0.0007 |
| **Sexual life** | | | |
| Dissatisfied | 14/24 (58) | 2/14 (14) | |
| Satisfied | 10/24 (42) | 12/14 (86) | ns |
| **ADL**[1] | | | |
| Dissatisfied | 4/27 (15) | 0/15 (0) | |
| Satisfied | 23/27 (85) | 15/15 (100) | ns |
| **Family Life** | | | |
| Dissatisfied | 2/27 (7) | 0/15 (0) | |
| Satisfied | 25/27 (93) | 15/15 (100) | 0.012 |
| **Partner relationship** | | | |
| Dissatisfied | 4/22 (18) | 1/14 (7) | |
| Satisfied | 18/22 (82) | 13/14 (93) | ns |
| **Somatic Health** | | | |
| Dissatisfied | 9/27 (33) | 0/15 (0) | |
| Satisfied | 18/27 (67) | 15/15 (100) | 0.014 |
| **Psychological Health** | | | |
| Dissatisfied | 8/26 (31) | 1/15 (7) | |
| Satisfied | 18/26 (69) | 14/15 (93) | 0.0024 |

[1]*ADL; activities of daily life. Source: Appendix Bjerkne Wenneberg, S et al., Acta Neurolog Scand. 2022, Creative Commons BY 4.0 License*

#### 4.5.2.4 IMPACT OF DELAYED CEREBRAL ISCHEMIA

No difference was observed after 1 year between patients with DCI and those without DCI. However, at the 3-year follow-up, patients with DCI reported significantly more dissatisfaction with their ADL (p= 0.02).

*"I have experienced increased dizziness and poor balance following the injury. I am trying to maintain my social life by going to concerts and movies with friends, but I become so tired… I believe it is worth the fatigue to continue enjoying social activities, but I know I must rest for a long time afterward. I am trying to stay active by Nordic walking and working in the garden."*

*Citation from a patient during a follow-up interview*

### 4.5.3 MAYO-PORTLAND ADAPTABILITY INVENTORY-4

#### 4.5.3.1 1 YEAR

Fatigue was the item where the highest proportion of patients experienced problems, with 55 % of the patient's reporting problems after one year.

#### 4.5.3.2 1 TO 3 YEARS

The proportions of patients improving or deteriorating between the items displayed a large variation. The highest proportion of patients deteriorated in "memory" (37%) and improved in "depression" (29%), **Table 15.**

*Table 15. Mayo-Portland Adaptability Inventory-4, proportions of patients with the same, worse, or better scores at 3 years compared with 1 year*

| **Area** | **Answers at both 1 and 3 years (n)** | **Equal** *(%)* | **Deterioration** *(%)* | **Improvemen** *(%)* |
|---|---|---|---|---|
| Part A- Ability index | | | | |
| Mobility | 37 | 81 | 11 | 8 |
| Use of hand | 36 | 83 | 6 | 11 |
| Vision | 37 | 76 | 8 | 16 |
| Audition | 37 | 76 | 16 | 8 |
| Dizziness | 37 | 75 | 8 | 17 |
| Motor speech | 35 | 69 | 20 | 11 |
| Verbal communication | 36 | 64 | 19 | 17 |
| Non-verbal communication | 33 | 76 | 9 | 15 |
| Attention/concentration | 34 | 68 | 15 | 18 |
| Memory | 36 | 50 | 36 | 14 |
| Fund of information | 35 | 54 | 37 | 9 |
| Problem solving | 35 | 60 | 20 | 20 |
| Visuospatial abilities | 35 | 77 | 9 | 14 |
| Part B- Adjustment index | | | | |
| Anxiety | 36 | 58 | 25 | 17 |
| Depression | 35 | 46 | 26 | 29 |
| Irritability/anger | 35 | 69 | 20 | 11 |
| Pain/headache | 35 | 63 | 20 | 17 |
| Fatigue | 36 | 53 | 22 | 25 |
| Sensitivity to mild symptoms | 33 | 58 | 24 | 18 |
| Inappropriate social interaction | 32 | 94 | 3 | 3 |
| Impaired self-awareness | 34 | 85 | 9 | 6 |
| Family/significant relationships | 29 | 55 | 21 | 24 |
| Part C- Participation index | | | | |
| Initiation | 36 | 61 | 14 | 25 |
| Social contacts | 37 | 62 | 19 | 19 |
| Leisure/recreational activities | 37 | 68 | 14 | 19 |
| Self-care | 37 | 86 | 5 | 8 |
| Residence | 37 | 76 | 11 | 14 |
| Transportation | 36 | 81 | 6 | 14 |
| Money management | 35 | 89 | 6 | 6 |

*Source: Appendix Bjerkne Wenneberg, S et al., Acta Neurolog Scand. 2022, Creative Commons BY 4.0 License.*

#### 4.5.3.3 IMPACT OF AGE

At the 1-year follow-up, patients aged < 60 years were significantly more dissatisfied than patients aged ≥ 60 years at ictus in the items of vision (p=0.016), anxiety (p= 0.009), pain/headache (p= 0.0004), family relationships (p= 0.020) and social contact (p=0.032). At 3 years, a significant difference remained for only pain/headache (p=0.010); however, a difference could also be seen for leisure (p=0.016).

#### 4.5.3.4 IMPACT OF DELAYED CEREBRAL ISCHEMIA

At the 1-year follow-up, no difference was observed in self-assessed problems between patients who developed DCI during the acute phase and those who did not. Patients with DCI reported significantly more problems in several items after 3 years, including mobility (p=0.005), use of hands (p=0.014), vision (p=0.002), dizziness (p=0.020), non-verbal communication (p=0.024), attention/concentration (p=0.030), visuospatial abilities (p=0.04), anxiety (p=0.015), sensitivity to mild symptoms (p=0.070), inappropriate social behavior (p=0.040), impaired self-awareness (p=0.018), initiation (p=0.040), and transportation (p=0.037).

#### 4.5.3.5 FATIGUE IN GENERAL AT 1, 3, AND 5 YEARS

At the 1-, 3-, and 5-year follow-ups, 29 patients were assessed regarding the item “fatigue in general” from the MPAI-4 questionnaire. Among these patients, 59, 45, and 38 % were graded as having mild to severe problems for each year, respectively. **Figure 10** illustrates the distribution at 1, 3, and 5 years. A statistically significant improvement was observed between 1 to 5 years (p=0.006) though not between 1 to 3 and 3 to 5 years.

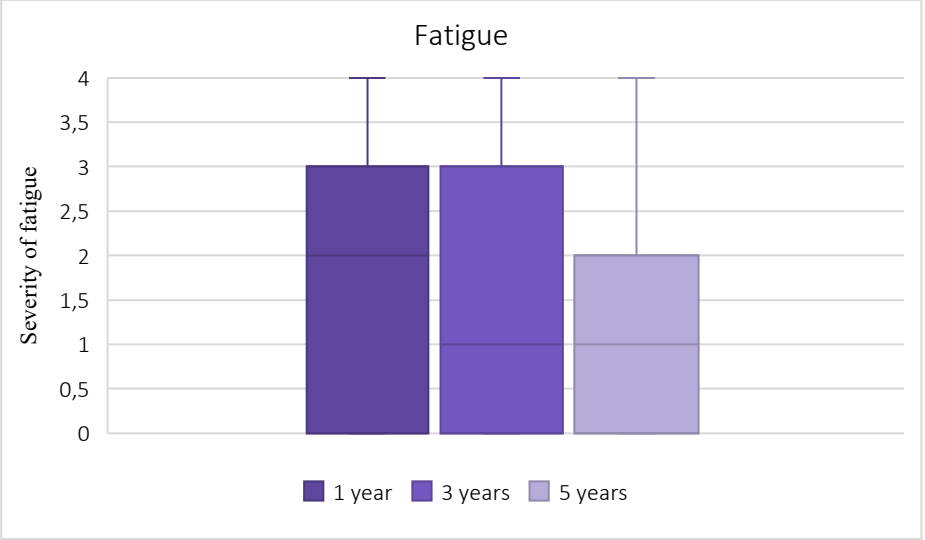



*Figure 10. Answer distribution for item "fatigue in general" from the MPAI-4 questionnaire at the 1-, 3-, and 5-year follow-ups. Answer options: 0 (no problems), 1 (mild problems with no interference with activities), 2 (mild problems with interference 5-24% of the time), 3 (moderate problems with interference 25-75% of the time) or 4 (severe problems with interference > 75% of the time).*

*"I try to keep up with my activities like before the injury, but I am getting older too. The biggest impact is the brain fatigue or fog that I experience. I have to rest and rest, and still, I feel tired most days."*

*Citation from a patient during a follow-up interview*

### 4.5.4 MENTAL FATIGUE SCALE AT 1, 3, AND 5 YEARS

In study IV, we evaluated the prevalence and severity of mental fatigue up to 5 years after an aSAH. Additionally, we explored the components within the MFS regarding which area patients reported the most problems. Finally, we examined any associations between patient demographics and events during the acute phase and the development of mental fatigue.

In study III, we concluded that mental fatigue (total sum ≥10.5 on the MFS score) was observed in more than half of the patients after 1 year and 3 years

(57% and 54%, respectively). Neither age nor DCI development impacted the incidence of mental fatigue at 1- or 3-years post aSAH.


*Figure 11. Distribution of total MFS scores at 1, 3, and 5 years. A total score of ≥ 10.5 indicates the presence of mental fatigue. MFS; Mental Fatigue Scale*

#### 4.5.4.1 MENTAL FATIGUE

Thirty-one patients completed the MFS questionnaire at all three time points, and mental fatigue (total score ≥ 10.5) was observed in 58%, 48%, and 52% at 1, 3, and 5 years, respectively. The MFS scores at 1, 3, and 5 years are presented in **Figure 11.** A significant decrease in total MFS scores could be observed over 1, 3, and 5 years (p=0.014).

#### 4.5.4.2 COMPONENTS OF THE MENTAL FATIGUE SCALE

One year post-aSAH, patients experienced more problems with items mental fatigue, sensitivity to stress, irritability, and decreased sleep. When analyzing the items over 1, 3, and 5 years, a significant decrease was found in fatigue scores (p=0.03) and sensitivity to stress (p=0.014).

#### 4.5.4.3 PATIENT DEMOGRAPHICS AND EVENTS DURING THE ACUTE PHASE

No difference was found in MFS scores at 1 year, or over time from 1 to 3, and 5 years when analyzing the cohort divided by age at ictus; < 60 vs. ≥ 60 years,

WFNS (scores 1-3 vs. 4-5), H&H (scores 1-2 vs. 3-5), aneurysm location (anterior vs. posterior), aneurysm treatment (coil vs. clip), EVD yes/no, or DCI yes/no.

However, a significant difference was found in median MFS scores between the genders after 1 year. Women had a higher median (range) of 14.5 (0-29.5) than men, who had a median (range) of 3 (0-17.5) ($p=0.043$). No difference was found in median MFS scores at 1 year between patients with EBI and those without EBI. Nevertheless, a significant difference in MFS scores was found over 1, 3, and 5 years ($p=0.003$), where patients without EBI improved, whereas patients with EBI did not.

*"I'm doing better now; I've increased my work hours to 75%. However, I still get drained after social activities. I can handle about an hour before the fatigue sets in, and then I need to rest. But after resting, I'm usually able to go back to the party and enjoy myself. I need to be mindful of my energy levels and plan accordingly".*

*Citation from a patient during a follow-up interview*

*"My body is okay; it's just my brain that gets exhausted, and it's frustrating! I must be careful and plan social events because I know I can't handle activities two days in a row."*

*Citation from a patient during a follow-up interview*

*Textboxes with quotations from patients during interviews grading functional outcomes according to the GOSE. The quotes have been freely translated from Swedish and rephrased where needed to ensure anonymity.*

# 5 METHODOLOGICAL CONSIDERATIONS

In this prospective longitudinal cohort study, patients after an aSAH admitted to the NICU at Sahlgrenska University Hospital were consecutively included to avoid systemic bias. During the study period of 18 months, 105 patients with an aSAH were admitted. However, for several reasons, mainly a lack of research nurses during holiday seasons, only 64/105 (61%) were finally included in the study, **Figure 4.** The cohort is representative of a general aSAH population according to demographics and incidence of DCI [19]. At the time of the final 5-year follow-up, data from 31/64 (48%) patients were available for complete analysis, including data from the acute phase and assessment at all three follow-up points. A strength of this thesis is the prospective data collection from the acute phase to 1-, 3-, and 5 years post-aSAH, thus making it possible to assess the dynamics in recovery for the same patients and relate it to the acute phase. However, we did not consider if the patient's recovery was affected by additional morbidities during the follow-up period. This was a single-center study with a relatively small cohort that did not include a control group. Thus, the generalizability of our findings may be limited. Despite these limitations, our results are noteworthy and provide novel and meaningful insights into post-aSAH recovery dynamics.

## 5.1 STUDY 1. HEART RATE VARIABILITY

The HRV data were continuously recorded using an external device (emotion LAB Mega Electronics Ltd., Kuopio, Finland) placed on the patient's chest. This device was chosen to facilitate continued registration even if patients were transferred to intermediate care. However, this was not feasible due to logistical problems and the need for the device for the next patient. Furthermore, the devices sometimes required new batteries, lost contact with the patient's skin, and were sensitive to movements, thus losing HRV registrations for varying periods. Analyzing HRV data directly from more robust ECG signals from existing patient monitors would potentially have reduced these errors. Three periods of 5-minute registration with minimal artifacts were manually identified for every 24 h [88]. This resulted in the analysis of approximately 1% of all collected HRV data. However, our results might

have differed if we had analyzed all collected HRV data, as unrecognized signals related to DCI development could have been present in the unanalyzed data. Furthermore, not all patients could participate in regular clinical examinations. Of the 15 patients in our HRV study who developed DCI, only 8 could be clinically assessed during the acute phase to determine the time of onset of DCI symptoms accurately.

## 5.2 STUDY II. SYSTEMIC INFLAMMATORY BIOMARKERS

Systemic inflammation was assessed using two blood samples obtained during the acute phase: one shortly after admission, 1-3 days, and another after approximately 7-10 days. In this pilot study, we explored whether elevated inflammatory markers, early or later, during the acute phase were associated with poor 1-year outcomes and DCI development. In an optimal study setting, obtaining blood samples at the same time point for each patient in relation to the initial hemorrhage would be ideal. However, this is difficult in a clinical setting where patients are admitted 24/7 for acute diagnoses. Other factors affecting the timing of samples were whether the aSAH was rapidly and accurately identified when the patients sought medical care and whether they were initially admitted to a different hospital and subsequently transferred for aneurysm securement. Our study's limited number of samples increased the risk of overlooking important changes in biomarkers, given their varying peak concentrations over time. Hence, a higher sampling frequency should be considered if designing a new study. The samples underwent delayed analysis; they were first frozen and subsequently analyzed at a later stage. However, if the biomarkers are to be used in clinical practice, they must be directly analyzable. Another limitation is that the samples were obtained exclusively from blood and not simultaneously from the CSF, which might have yielded a more apparent association. However, not all patients have a ventricular drain, and regular CSF sampling is otherwise clinically unfeasible.

## 5.3 STUDY III AND IV. LONG-TERM OUTCOMES

The Sahlgrenska University Hospital is the regional center for the acute treatment of patients with an aSAH; therefore, our cohort is from a relatively large geographical area. Following the initial treatment period, the patients were transferred to their regional hospitals or primary care units for further care. This patient dispersion posed challenges in reaching them for follow-up assessments, particularly for those who experienced more severe deficits and complications, which may have limited their capacity to participate in telephone interviews and questionnaire assessments. Moreover, the burden on their immediate family members is sometimes substantial, potentially leading to a lower prioritization of study participation. Consequently, the patient cohort who responded to the questionnaires exhibited a higher score on the GOSE than those who did not respond, thus skewing towards patients with a more favorable outcome. The three questionnaires varied in scope and length, each with advantages and disadvantages. We used a combination of instruments to encompass several domains. Nevertheless, a trade-off was necessary between the desire to get as much detailed information as possible and to ensure it was not too difficult for patients with less favorable outcomes to complete the questionnaires.

The LiSat-11 is a short and relatively simple questionnaire providing information on self-assessed life satisfaction. In contrast, although the MPAI-4 covers all components of the International Classification of Function (ICF), it might have been overly comprehensive in this context, with frequently inaccurately completed questions resulting in data loss. Finally, the MFS is a scale explicitly focusing on the mental aspect of fatigue. The timing and frequency of administering the MFS should be considered. Given the fluctuating nature of mental fatigue, administering the scale at multiple time points and assessing its responsiveness to changes over time may enhance its validity and reliability. The MFS is available online or as a mobile application, allowing patients to regularly answer the questionnaire and gain insight into their well-being and symptomatologic progression. In the future, providing simultaneous online questionnaires may help reduce the number of patients lost to follow-up.

# 6 DISCUSSION

Aneurysmal SAH is a sudden and acute condition with catastrophic short- and long-term consequences. Survivors of the acute phase often experience long-lasting functional and cognitive impairments that significantly impact their quality of life, their families, the healthcare systems, and society as a whole [194,195]. The development of DCI further exacerbates the detrimental effects on mortality and morbidity. Prompt and accurate detection of impending DCI, even in sedated or unconscious patients, can improve the long-term consequences experienced by many patients. With advancements in the treatment of ruptured aneurysms and subsequent care, leading to improved survival rates, even for individuals with severe aSAH, the importance of considering the long-term implications of aSAH has increased [196,197]. The level of care and rehabilitation provided to patients varies significantly between hospitals, regions, and countries [198]. Thus, it is important to develop a comprehensive understanding of the clinical trajectory following an aSAH, identifying areas where patients require additional support to improve the rehabilitation process and ensure effective monitoring of their recovery progress.

## 6.1 MONITORING DURING THE ACUTE PHASE AFTER ANEURYSMAL SUBARACHNOID HEMORRHAGE

DCI is a major complication after aSAH. It is a complex diagnosis with many unanswered questions regarding its pathophysiology [51,199]. To better aid in understanding and treating DCI and improve patient outcomes, effective monitoring methods for the early detection of cerebral ischemia are needed. Given the challenges in monitoring the brain, particularly in patients with impaired consciousness or those sedated, research for surrogate markers capable of indicating the presence of impending ischemia is ongoing. An ideal monitoring method should be easily accessible, interpretable, non-invasive, and applicable across various healthcare settings, regardless of the time of day or year. Furthermore, it should provide real-time alerts to help prevent permanent brain injury. A comparison can be made to the cardiology field; ECG monitoring is combined with the assessment of serum Troponin I (TnI) or Troponin T (TnT) levels to diagnose suspected myocardial ischemia further. Despite extensive research efforts, identifying predictive biomarkers, a "brain-

ECG, and TnI" that can be widely used in the clinical management of aSAH remains elusive [76,106,109,200,201].

HRV possesses several of the desired features for a physiological biomarker, and it does not impose additional risk or discomfort on the patient. Associations between secondary complications after an aSAH and changes in HRV during the post-hemorrhagic phase have been found [41,87]. However, the results and evidence regarding methodology, including choice of HRV parameters, length, and timing of registration, are conflicting [68,106,202]. In Study I, we found that intermittently analysis of HRV was insufficient for detecting or predicting DCI development in our cohort. However, we did observe changes in the LF/HF ratio, suggesting increased sympathetic activity. This was even more evident in patients who developed DCI. Changes in the LF/HF ratio preceding secondary complications were reported by Su et al. as well [87]. HRV is susceptible to multiple confounding variables such as medication, age, sex, and posture, complicating its interpretation [81,203]. Consequently, accurately determining the specific impact of DCI on HRV is challenging. Moreover, HRV registration yields substantial data, necessitating techniques capable of identifying patterns and changes in HRV that correlate with impending ischemia. Artificial intelligence and big data management have emerged as potential tools to aid in this context. Thus, the promising features of HRV, in combination with these modern tools, may open new possibilities for HRV monitoring in patients with an aSAH [204]. Two recently published systematic reviews, including our HRV study, suggest that HRV reveals promise in detecting neurological and cardiovascular complications. However, more extensive prospective studies are needed where HRV should be monitored from admission and an online analysis performed, preferably [205,206].

The ideal serum biomarker for detecting brain ischemia should have its synthesis and degradation closely time-correlated to the injury and the severity of the injury. Furthermore, it should also have the possibility of an easy and accurate online analysis from peripheral blood samples. Numerous inflammatory biomarkers have been investigated in relation to aSAH, with continuous research to find new biomarkers and analyzing methods [162,207]. We selected five biomarkers (TNF-α, IL-6, IL-1Ra ICAM-1, and CRP) previously associated with DCI development and unfavorable long-term outcomes [208-211]. In Study II, we could not find a clear association between the biomarker levels in either the early or the late sample and DCI development. Several patients who developed DCI were diagnosed with an infection, which complicated the distinction of the effect of DCI by specific inflammatory biomarkers.

Similarly, in a study by Rasmussen et al., the DCI development was not associated with IL-6, ICAM-1, and TNF-α in peripheral blood at 3 and 8 days post-aSAH [212]. Ridwan et al. found a correlation between IL-6 levels in CSF and DCI, particularly with infarction development [208]. However, IL-6 levels in CSF and serum were simultaneously compared, with higher IL-6 levels found in CSF. Although analyzing biomarkers in CSF might yield more precise results, obtaining CSF in all patients is unfeasible compared with peripheral blood. Considerable effort is required to establish the temporal dynamics and cut-off levels of biomarkers in relation to the progression of ischemic brain injury and to ascertain their diagnostic accuracy and potential to guide management decisions during the acute phase [128,213-217]. Rather than relying solely on a single biomarker, a pattern of multiple markers may aid in identifying patients at a heightened risk for secondary injuries [211,218,219]. Nonetheless, prematurely dismissing these monitoring techniques might overlook their potential benefits as biomarkers for predicting and detecting DCI.

## 6.2 OUTCOME PREDICTION

During the acute phase, questions often arise about the patient's future and potential outcomes for clinicians, patients, and their families. Therefore, it is vital to identify factors or events during the acute phase that may increase the risk of worse outcomes. With advancements in aneurysm treatment and post-hemorrhage care, traditional prediction models based on admission scales, including the H&H and Modified Fisher scales, are insufficient [220]. Using biomarkers to identify patients at higher risk for unfavorable outcomes would aid in allocating resources and interventions, potentially improving the patients' outcomes.

Previous studies have reported that HRV monitoring can aid in predicting mortality and complications after cardiac events and ischemic stroke [95,221]. Similarly, changes in HRV have also been associated with unfavorable outcomes after aSAH [84]. Study I found a significant association between HRV parameters and 1-year mortality. Patients who died within the first year had values indicating lower HRV. Similar results were obtained in a retrospective study by Uryga et al., which examined in-hospital non-survivors with an aSAH [222]. These findings suggest that monitoring HRV during the initial phase after an aSAH may predict mortality in this patient population.

Furthermore, we found a correlation between elevated concentrations of the examined serum biomarkers and an unfavorable 1-year outcome (GOSE 1-4) in study II. However, the associations were unambiguous when adjusting the analysis for clinical presentation at admission. Similar to our findings, a recent meta-analysis investigating peripheral inflammatory biomarkers in patients with an SAH revealed that those with a favorable outcome exhibited significantly reduced CRP and IL-6 levels [213]. Patients with a more extensive hemorrhage are at a higher risk of developing more complications, such as respiratory failure, and the need for surgical interventions. These factors contribute to an increased inflammatory burden and a heightened susceptibility to infections affecting the inflammatory biomarkers levels.

In a study by Suwatcharangkoo et al., LOCi was found to be an independent predictor of unfavorable outcomes measured by the mRS at 1 year [3]. In our cohort, LOCi contributed to the divergence seen in long-term recovery. Patients without LOCi demonstrated significant improvement in mental fatigue symptoms between 1 and 5 years, whereas patients with LOCi did not demonstrate similar improvements.

In Study III, we did not observe significant differences between patients who developed DCI and those who did not at the 1-year follow-up. DCI is a major prognostic factor regarding mortality, morbidity, and long-term quality of life [65,194]. However, at the 3-year follow-up, patients with DCI reported greater dissatisfaction or difficulties across various items in all the administered questionnaires. We can only speculate on the possible explanation for this finding. During the first year, many patients, regardless of the presence of DCI, may continue to be actively involved in rehabilitation programs, attempting to reintegrate into the workforce or dealing with residual symptoms; however, the situation has generally stabilized by the 3-year mark. Many patients begin to acknowledge, adapt to, and accept the persistent symptoms associated with life after the hemorrhage. During this period, the additional impact of DCI may become more discernible, leading to noticeable disparities between patient groups.

Older age has previously been identified as a predicting factor of worse outcomes [223]. However, in Study III, we found that patients aged $< 60$ exhibited a higher level of dissatisfaction across the self-assessment questionnaires than those aged $\geq 60$. One possible explanation for this finding may be that younger patients face additional challenges and demands from their environment regarding the resumption of work, childcare, and engagement in numerous

activities. Consequently, the difference between their pre-injury abilities and post-injury limitations can become more pronounced. Belonging to the female sex has also been identified as relating to developing more secondary complications and worse outcomes [224]. In study IV, women reported significantly more mental fatigue after 1 year than men. However, over time, between 1 to 5 years, the MFS score decreased for both women and men.

## 6.3 ASSESSMENT OF LONG-TERM OUTCOMES AFTER ANEURYSMAL SUBARACHNOID HEMORRHAGE

It is impossible to cover all domains of dysfunction and impairments that patients after an aSAH may experience. Suggested follow-ups vary considerably, ranging from non-existent to thorough in-hospital evaluations; however, they most often represent a trade-off between the most relevant and desired information and what is feasible. When comparing studies, diverse outcome measures with different endpoints and a wide range of follow-up periods complicate the interpretation and comparison of findings and results. To mitigate this, the Neurocritical Care Society released a set of recommendations in 2019 [166]. None of the outcome scales or questionnaires reached the highest priority level ("core"). The mRS and the MoCA were classified as "Highly Recommended," and the GOSE as "Supplemental." Other instruments were regarded as exploratory. However, the recommendations were published after the studies included in this thesis commenced, thereby rendering it logistically impossible to include them. In recent years, progress has been made in developing novel outcome measures specifically designed for patients who have experienced an aSAH. However, they need continuous validation and translation to multiple languages, including Swedish [225,226].

When using only functional outcome measures such as the GOSE and mRS, the results may be too blunt, and the full extent of the patient's experiences and disabilities might be lost [225]. In study III, we could demonstrate that relying solely on the GOSE as an outcome measure would have classified our patient cohort as having a favorable outcome with a median GOSE of > 5 at all years. However, patients in all GOSE groups expressed dissatisfaction and perceived problems across all the included questionnaires. Specifically, patients indicated higher levels of dissatisfaction and identified more issues related to cognitive impairments than ADL. A similar pattern was observed by Persson et al. and Sonesson et al., where patients exhibited a high level of physical

function and independence in ADL; however, cognitive impairments were observed up to 20 years post-aSAH [158,227]. Furthermore, we found that patients experienced more improvement in functional areas, including somatic health and leisure, while cognitive functions, including memory and attention, declined. This indicates the need for a broader follow-up method supplementing the often-used functional outcome measures.

Fatigue, especially mental fatigue, is a prevalent residual symptom that can be more subtle and challenging to comprehend or address [181,188,228]. During the follow-up interviews conducted at 1, 3, and 5 years, mental fatigue was an often-mentioned factor hindering the patient's reintegration into life as before the hemorrhage. Approximately half of the patients in our cohort experienced mental fatigue at all follow-up time points. Samuelsson et al. reported similar findings in their study, where up to 38% of patients who were graded as having a good outcome experienced mental fatigue > 15 years post-aSAH [229]. In a study by Buunk et al., mental fatigue was significantly more prevalent than physical fatigue after aSAH, and only mental fatigue was associated with long-term unfavorable functional outcomes [186]. Although patients may appear well outwardly and perform adequately in short periods, they often experience subsequent energy depletion and the need for prolonged rest. This detrimentally affects their ability to maintain concentration and productivity, compromising their engagement in work and social interactions [230]. Despite their considerable impact on patients' lives, the underlying causes of fatigue and mental fatigue remain unclear, and therefore, an effective treatment remains elusive [231]. A recent study by Ghafaji regarding fatigue after aSAH revealed that acceptance as a coping strategy was the only coping mechanism with a significant inverse relationship with fatigue levels [183]. Therefore, fatigue and mental fatigue are important post-aSAH sequelae that must be addressed, even in patients with favorable outcomes. In a study by Dulhanty et al., patients considered post-aSAH fatigue a main area where they felt their needs were unmet regarding follow-up and rehabilitation [232]. Therefore, extensive research on cognitive impairments, especially fatigue and mental fatigue, is needed to discover effective treatment options and optimal rehabilitation plans.

Our studies further found that the post-aSAH recovery process is a multifaceted and continuous phenomenon extending beyond the initial months, often several years. Therefore, drawing premature conclusions shortly after an aSAH should be avoided due to the potential for improvement years after the initial hemorrhage. From the recommendations proposed by Stienen et al., follow-ups were suggested at 3 and 12 months for long-term outcomes. Our

results indicate that the follow-up should extend beyond this period. As with many aspects of healthcare, the most optimal approach may involve individualizing follow-up assessments and combining functional and self-assessment questionnaires. It is important to not only categorize patients into outcome groups but also to integrate their perspectives. Merely calculating survival rates or hospital discharges is insufficient; understanding the quality of survival and life after an aSAH is imperative for providing comprehensive patient care and optimizing long-term outcomes.

## 6.4 ETHICAL COMMENTARY

Ethical considerations are crucial in all medical studies, particularly when including critically ill patients. In our studies, patients and their families were informed that the inclusion process was entirely independent of the medical attention provided and that declining study participation would not affect their treatment. Written consent was obtained from all patients or their families before study participation. All patient data were de-identified, and each patient was assigned a study number. The original data were stored in a file accessible only by the lead researcher, and the results were presented as anonymous data. All included studies in this research were observational and did not involve any interventions regarding care, procedures, or medication. The HRV registration was conducted using a small external device. The registration process did not interfere with the care provided, as no part of the registration was visible during the study period. The blood drawn for each sample was negligible compared with the daily laboratory workup. The storage and analysis of samples followed standard practices and protocols. As mentioned, analysis was limited to preapproved markers and was not utilized in other studies. Patient outcomes were assessed through telephone interviews, where the patient or their families were initially asked about their willingness to participate. If willing, patients were evaluated using the GOSE and informed about the three questionnaires sent by mail. Conducting outcome studies through telephone interviews can raise concerns among patients who may perceive the researcher as someone who can influence their rehabilitation and ongoing care. This presents moral dilemmas for the interviewer, who can only provide recommendations to reach out to their regular caregivers. Therefore, for future studies on outcomes and follow-up, formulating a structured plan including designated caregivers who can address any upcoming concerns and new symptoms would be ideal.

# 7 CONCLUSION

The development of DCI post-aSAH can have devastating effects on a patient's survival and long-term disabilities. Therefore, it would be of great value to have the possibility to detect DCI development before an ischemic injury is manifested. However, despite extensive research, a method for the accurate and timely detection of DCI remains elusive. Our methods of assessing HRV and inflammatory biomarkers could not sufficiently predict or detect DCI development. However, changes in HRV parameters early after admission were associated with 1-year mortality, and elevated inflammatory biomarker levels during the acute phase were associated with unfavorable outcomes. Therefore, further research might clarify HRV and inflammatory biomarkers analysis as potential secondary complication and outcome prediction monitoring methods.

The long-term prognosis becomes increasingly important, with more patients surviving several years after the initial hemorrhage. We could conclude that cognitive impairments are common in patients after an aSAH, with fatigue and mental fatigue being especially prominent sequala. To improve rehabilitation and care, follow-up assessments should preferably extend several years after the acute phase. It should also include broad assessment instruments focusing on functional and cognitive outcomes, particularly regarding mental fatigue.

# 8 FUTURE PERSPECTIVES

In recent decades, significant advancements in aneurysm repair techniques and post-repair care have led to increased post-aSAH survival rates. This progress has allowed patients with a severe bleed or advanced age to regain a good quality of life. However, despite these improvements, mortality and morbidity rates remain high, and uncertainty surrounding the complex pathophysiological developments following the initial hemorrhage persists. The cascade of reactions triggered by the bleed leads to the development of EBI and DCI, which profoundly affect patient outcomes. Therefore, considerable efforts are needed to uncover the underlying causes of these injuries and identify appropriate treatments. Notably, the timely detection of DCI is vital in preventing permanent ischemic injuries and significantly influencing patient outcomes. However, no method has reached sufficient clinical viability to replace existing methods.

As survival rates continue to rise, the long-term perspectives for aSAH survivors become increasingly important. Aneurysmal SAH is more than an acute event; it is an event that often subjects patients to a lengthy recovery journey, transitioning from an acute bleeding phase to a chronic, often life-altering phase. While considerable attention has been directed toward understanding the long-lasting cognitive impairments associated with aSAH, further research is needed to precisely identify the affected areas and explore differing temporal dynamic patterns of recovery in an aSAH stroke compared with other stroke types. There is ongoing research regarding an outcome measure specific to aSAH to better grasp the specifics of outcome pathophysiology for these patients [225]. Exploring the clinical trajectory may improve rehabilitation and post-hemorrhage support, potentially enhancing patients' quality of life and facilitating their return to work and pre-hemorrhage normalcy.

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# 9 APPENDIX

9.1 Study I

HRV temporal pattern in relation to DCI development

9.2 Study II

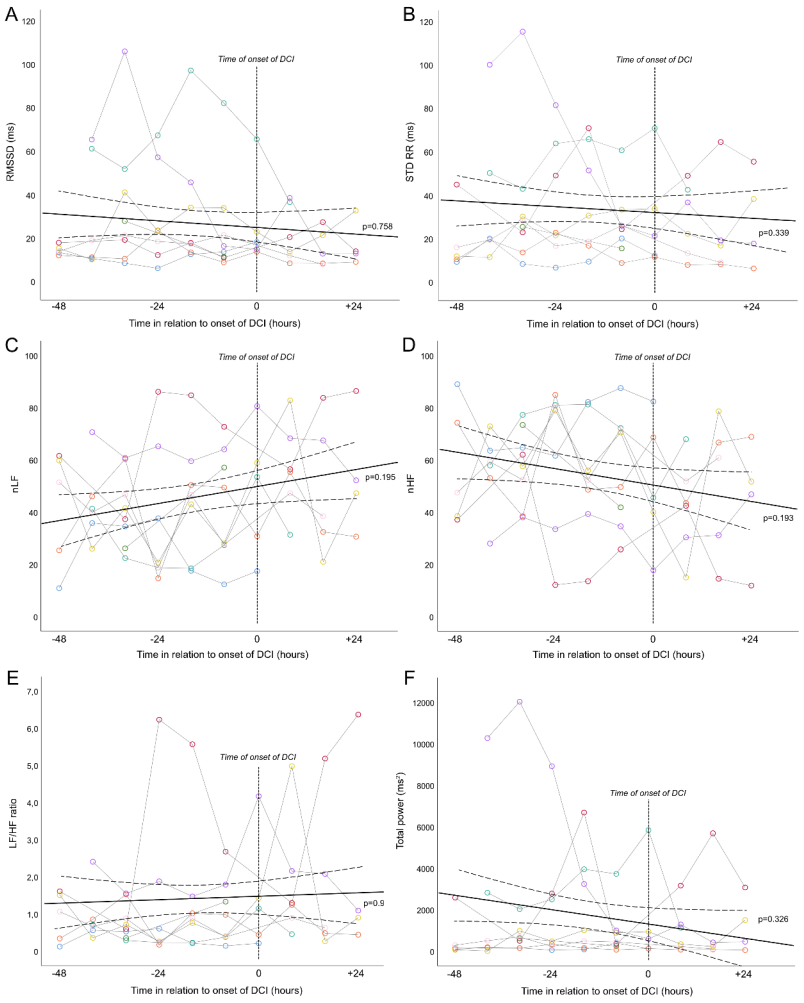
Table 1A. Patient data and results from sample 1 - GOSE
Table 1B. Patient data and results from sample 2 -GOSE
Table 2A. Patient data and results from sample 1 -DCI
Table 2B. Patient data and results from sample 2 -DCI

9.3 Study III

Table 1C. Mental Fatigue at 1 and 3 years after aSAH
Table 2:1 LiSat-11. Self-questionnaire assessment at 1 year and 3 years. after aneurysmal subarachnoid hemorrhage divided in patients < 60 years and ≥ 60 years
Table 2:2. MPAI-4. Self-questionnaire assessment at 1 year and 3 years. after aneurysmal subarachnoid hemorrhage divided in patients < 60 years and ≥ 60 years, all significant changes at 1 or 3 years are given and compared at 1 and 3 years
Table 2:3. MFS. Self-questionnaire assessment at 1 year and 3 years. after aneurysmal subarachnoid hemorrhage divided in patients < 60 years and ≥ 60 years, all significant changes at 1 or 3 years are given and compared at 1 and 3 years
Table 3:1 LiSat-11. Self-questionnaire assessment at 1 year and 3 years. after aneurysmal subarachnoid hemorrhage divided in patients DCI yes/no. LiSat-11
Table 3:2 MPAI-4. Self-questionnaire assessment at 1 year and 3 years. after aneurysmal subarachnoid hemorrhage divided in patients DCI yes/no. MPAI-4
Table 3:3 MFS. Self-questionnaire assessment at 1 year and 3 years. after aneurysmal subarachnoid hemorrhage divided in patients DCI yes/no. MFS

# 9.1 STUDY I

**HRV temporal pattern in relation to DCI development**




None of the HRV variables had a visually recognizable specific temporal pattern before DCI onset. DCI, delayed cerebral ischemia; HF, high-frequency power in normalized units; LF, low-frequency power in normalized units; LF/HF, ratio of low-frequency power/high-frequency power; RMSSD, root mean square of the successive differences between adjacent RR intervals; STDRR, standard deviation of all RR intervals

## 9.2 STUDY II

Table 1A. Patient data and results from sample 1 - GOSE

| | Unfavourable GOSE 1-4 (n=17) | Favourable GOSE 5-8 (n=39) | p |
|---|---|---|---|
| Sex (female) | 14 (82) | 28 (72) | 0.51 |
| Age (years) | 58 (54-64) | 56 (48-64) | 0.28 |
| GCS | 11 (7-13) | 14 (13-15) | 0.01 |
| Modified Fischer Grade 0-2 | 0 | 4 (10) | 0.02 |
| Modified Fischer Grade 3-4 | 17 (100) | 35 (90) | 0.02 |
| IL-1b | 0.16 (0.08-0.41) | 0.08 (0.08-0.36) | 0.33 |
| IL-1ra | 369 (187-524) | 155 (87-253) | 0.007 |
| IL-2 | 3.59 (2.07-4.19) | 2.98 (0.52-4.04) | 0.49 |
| IL-4 | 0.71 (0.52-1.92) | 0.89 (0.31-1.92) | 0.77 |
| IL-5 | 0.66 (0.48-5.05) | 0.48 (0.48-5.05) | 0.75 |
| IL-6 | 3.30 (0.45-6.93) | 0.45 (0.06-2.92) | 0.01 |
| IL-7 | 0.28 (0.28-0.28) | 0.28 (0.28-0.28) | 0.42 |
| IL-8 | 21.3 (9.6-32.1) | 9.6 (7.0-16.8) | 0.02 |
| IL-9 | 72.8 (60.3-83.2) | 72.2 (52.0-90.6) | 0.87 |
| IL-10 | 0.21 (0.21-1.45) | 0.21 (0.21-1.45) | 0.99 |
| IL-12 | 0.15 (0.15-1.69) | 0.15 (0.15-0.50) | 0.34 |
| IL-13 | 0.04 (0.04-0.67 | 0.04 (0.04-4.86) | 0.51 |
| IL-15 | 0.72 (0.72-0.72) | 0.72 (0.72-146.32) | 0.36 |
| IL-17 | 3.98 (2.91-4.53) | 3.72 (1.43-6.15) | 0.54 |
| Eotaxin | 41.6 (37.1-66.1) | 47.2 (30.2-67.9) | 0.91 |
| FGF basic | 29.1 (24.7-38.5) | 33.2 (20.2-45.6) | 0.86 |
| G-CSF | 8.76 (0.86-40.16) | 0.86 (0.86-1.85) | 0.003 |
| GM-CFS | 0.05 (0.05-3.83) | 0.05 (0.05-7.26) | 0.30 |
| IFN-g | 6.92 (2.23-12.05) | 5.44 (2.51-9.22) | 0.40 |
| IP-10 | 372 (260-665) | 245 (185-379) | 0.13 |
| MCP-1 (MCAF) | 47.0 (25.5-137.2) | 38.8 (22.4-73.8) | 0.30 |
| MIP-1a | 1.86 (0.90-2.30) | 1.32 (0.90-1.67) | 0.26 |
| PDGF-bb | 3795 (2212-5630) | 3580 (2494-4375) | 0.56 |
| MIP-1b | 84.4 (75.0-103.1) | 79.4 (69.4-93.0) | 0.53 |
| RANTES | 8488 (4572-9825) | 8016 (5034-10162) | 0.84 |
| TNF-α | 23.2 (18.2-29.5) | 18.2 (15.1-20.9) | 0.02 |
| VEGF (0/4)* | 144.2 (1.5-284.2) | 93.6 (1.5-218.8) | 0.49 |
| MIG | 321 (136-448) | 224 (114-371) | 0.32 |
| TBG-B1 | 52479 (41714-61002) | 48185 (40668-55148) | 0.56 |
| TGF-B2 | 543 (499-596) | 568 (519-662) | 0.24 |
| TGF-B3 | 72.4 (67.5-77.1) | 71.4 (67.5-79.3) | 0.80 |
| VCAM-1 | 300463 (208071-491423) | 242903 (147868-323320) | 0.11 |
| ICAM-1 | 178082 (144650-235454) | 138668 (87755-190669) | 0.05 |
| WCC (1/0)* | 12.7 (10.4-16.0) | 11.2 (8.9-14.1) | 0.23 |
| CRP | 49 (15-73) | 7 (3-20) | 0.01 |
| Platelets (1/0)* | 220 (180-252) | 251 (199-297) | 0.09 |
| Temperature (1/0)* | 38.2 (37.6-38.7) | 37.9 (37.4-38.2) | 0.14 |

Number (percent) or median with interquartile ranges. IL-1Ra, IL-6, TNF-α, ICAM-1 concentrations in picogram/litre, CRP in mg/l, WCC and platelets count $10^9$/L, temperature in degrees Celsius IL; interleukin, IL-1Ra; Interleukin-1 receptor antagonist, FGF; fibroblast growth factor, G-CSF; Granulocyte-colony stimulating factor, IFN-gamma; Interferon Gamma, IP; Interferon gamma induced Protein, MCP-1 (MCAF); Monocyte chemoattractant protein (monocyte chemotactic and activating factor), MIP; Macrophage Inflammatory Proteins, PDGF; Platelet-derived growth factor, TNF-α; Tumour necrosis factor alpha, VGEF; Vascular endothelial growth factor, MIG; Monokine induced by gamma, TBG; thyroxine binding globulin, TGF; Transforming growth factor, VCAM; vascular cell adhesion molecule, ICAM; Intracellular Adhesion Molecule, WCC; White cell count, CRP; C reactive protein. 2 patients were lost to follow-up-making the total patients with scored GOSE n=56. *Number of missing in the two groups respectively.

Table 1B. Patient data and results from sample 2 -GOSE

| | Unfavourable GOSE 1-4 (n=17) | Favourable GOSE 5-8 (n=39) | p |
|---|---|---|---|
| Hydrocephalus | 14 (82) | 61 (41) | 0.008 |
| Infection | 13 (76) | 11 (28) | 0.001 |
| IL-1b | 0.08 (0.08-0.24) | 0.19 (0.08-0.36) | 0.33 |
| IL-1ra | 157 (124-295) | 157 (106-275) | 0.68 |
| IL-2 | 2.37 (1.76-2.98) | 2.98 (1.14-4.04) | 0.57 |
| IL-4 | 0.31 (0.07-0.71) | 0.65 (0.01-1.92) | 0.22 |
| IL-5 | 0.48 (0.48-0.66) | 0.48 (0.48-5.05) | 0.62 |
| IL-6 | 0.78 (0.06-1.42) | 0.10 (0.06-2.04) | 0.35 |
| IL-7 | 0.28 (0.28-0.28) | 0.28 (0.28-0.28) | 0.28 |
| IL-8 | 11.2 10.0-19.2) | 10.6 (5.6-20.2) | 0.44 |
| IL-9 | 66.6 (61.0-81.8) | 72.9 (53.9-97.5) | 0.24 |
| IL-10 | 0.21 (0.21-0.21) | 0.21 (0.21-0.71) | 0.12 |
| IL-12 | 0.15 (0.15-0.50) | 0.15 (0.15-0.50) | 0.86 |
| IL-13 | 0.04 (0.04-4.86) | 0.04 (0.04-4.86) | 0.51 |
| IL-15 | 0.72 (0.72-0.72) | 0.72 (0.72-46.65) | 0.12 |
| IL-17 | 2.91 (1.30-4.53) | 3.72 (1.43-3.98) | 0.91 |
| Eotaxin | 44.4 (33.2-63.6) | 49.7 (35.6-72.8) | 0.50 |
| FGF basic (1/0)* | 26.9 (19.9-37.8) | 30.4 (24.7-45.6) | 0.19 |
| G-CSF | 0.86 (0.86-0.86) | 0.86 (0.86-0.86) | 0.39 |
| GM-CFS | 0.05 (0.05-0.87) | 0.05 (0.05-5.76) | 0.16 |
| IFN-g | 2.51 (1.00-6.40) | 4.60 (2.23-6.88) | 0.18 |
| IP-10 | 449 (318-550) | 318 (231-459) | 0.10 |
| MCP-1 (MCAF) | 28.3 (22.4-40.2) | 34.6 (22.4-54.0) | 0.31 |
| MIP-1a | 1.36 (1.06-1.74) | 1.67 (0.90-2.23) | 0.58 |
| PDGF-bb | 3891 (3229-4932) | 4596 (3293-5791) | 0.32 |
| MIP-1b | 79.0 (72.8-88.0) | 85.7 (67.4-103.5) | 0.18 |
| RANTES | 8675 (6030-9190) | 8288 (5093-9762) | 0.94 |
| TNF-α | 20.9 (16.6-25.2) | 18.2 (13.7-20.9) | 0.23 |
| VEGF (0/1)* | 1.5 (1.5–104.4) | 100.8 (1.5–209.8) | 0.06 |
| MIG | 373 (282–458) | 305 (152–484) | 0.33 |
| TBG-B1 | 55 594 (49925–58378) | 60 655 (46952–67013) | 0.56 |
| TGF-B2 | 530 (470–582) | 550 (523–607) | 0.12 |
| TGF-B3 | 69.5 (65.6-79.3) | 77.1 (71.4-83.6) | 0.09 |
| VCAM-1 | 299409 (195334-323367) | 232199 (186753-334593) | 0.64 |
| ICAM-1 | 166606 (140480-216188) | 164875 (126551-193014) | 0.57 |
| WCC (0/8)* | 10.8 (10.3-12.5) | 10.4 (8.6-12.6) | 0.24 |
| CRP (0/1)* | 36 (20-71) | 10 (6-39) | 0.02 |
| Platelets (2/7)* | 266 (215-343) | 300 (267-390) | 0.39 |
| Temperature (2/8)* | 38.1 (38.0-38.6) | 37.9 (37.5-38.7) | 0.36 |

Number (percent) or median with interquartile ranges.IL-1Ra, IL-6, TNF-α, ICAM-1 concentrations in picogram/litre, CRP in mg/l, WCC and platelets count $10^9$/L, temperature in degrees Celsius. IL; interleukin, IL-1Ra; Interleukin-1 receptor antagonist, FGF; fibroblast growth factor, G-CSF; Granulocyte-colony stimulating factor, IFN-gamma; Interferon Gamma, IP; Interferon gamma induced Protein, MCP-1 (MCAF); Monocyte chemoattractant protein (monocyte chemotactic and activating factor), MIP; Macrophage Inflammatory Proteins, PDGF; Platelet-derived growth factor, TNF-α; Tumour necrosis factor alpha, VGEF; Vascular endothelial growth factor, MIG; Monokine induced by gamma, TBG; thyroxine binding globulin, TGF; Transforming growth factor, VCAM; vascular cell adhesion molecule, ICAM; Intracellular Adhesion Molecule, WCC; White cell count, CRP; C reactive protein. 2 patients were lost to follow-up- making the total patients with scored GOSE n= 56. *Number of missing in the two groups respectively.

Table 2A. Patient data and results from sample 1 -DCI

| | DCI (n=16) | Non-DCI (n=42) | p |
|---|---|---|---|
| Sex (female) | 10 (62) | 34 (81) | 0.18 |
| Age (years) | 56 (48-60) | 58 (48-65) | 0.69 |
| GCS | 13 (10-14) | 14 (12-15) | 0.08 |
| Modified Fischer Grade 0-2 | (0) | 4 (9) | 1.00 |
| Modified Fischer Grade 3-4 | 16 (100) | 38 (90) | 1.00 |
| IL-1b | 0.13 (0.08-0.36) | 0.08 (0.08-0.36) | 0.95 |
| IL-1ra | 197 (87-366) | 177 (124-275) | 0.82 |
| IL-2 | 3.96 (2.06-4.04) | 2.37 (1.76-4.04) | 0.32 |
| IL-4 | 1.82 (0.31-2.74) | 0.71 (0.52-1.55) | 0.08 |
| IL-5 | 4.08 (0.48-14.38) | 0.48 (0.48-5.05) | 0.25 |
| IL-6 | 2.92 (0.08-3.67) | 1.08 (0.06-3.30) | 0.42 |
| IL-7 | 0.28 (0.28-0.46) | 0.28 (0.28-0.28) | 0.70 |
| IL-8 | 14.0 (7.0-24.5) | 10.4 (7.0-19.1) | 0.41 |
| IL-9 | 76.4 (56.1-86.2) | 69.5 (57.3-85.9) | 0.68 |
| IL-10 | 0.89 (0.21-1.83) | 0.21 (0.21-1.45) | 0.19 |
| IL-12 | 0.15 (0.15-1.10) | 0.15 (0.15-0.50) | 0.97 |
| IL-13 | 0.36 (0.04-4.86) | 0.04 (0.04-0.67) | 0.29 |
| IL-15 | 0.72 (0.72-201.15) | 0.72 (0.72-71.19) | 0.66 |
| IL-17 | 3.98 (1.43-6.22) | 3.32 (2.10-4.53) | 0.45 |
| Eotaxin | 64.9 (31.4-106.8) | 42.7 (30.5-61.8) | 0.10 |
| FGF basic | 35.1 (24.7-42.1) | 29.1 (24.7-38.5) | 0.31 |
| G-CSF | 0.86 (0.86-22.20) | 0.86 (0.86-8.76) | 0.65 |
| GM-CFS | 0.05 (0.05-6.51) | 0.05 (0.05-6.54) | 0.81 |
| IFN-g | 8.28 (2.67-12.05) | 5.32 (1.92-7.35) | 0.14 |
| IP-10 | 287 (201-638) | 250 (172-379) | 0.51 |
| MCP-1 (MCAF) | 74.5 (20.5-146.4) | 37.2 (24.0-52.8) | 0.29 |
| MIP-1a | 1.32 (0.90-2.88) | 1.32 (0.90-1.67) | 0.46 |
| PDGF-bb | 3829 (2617-5427) | 3585 (2388-5308) | 0.41 |
| MIP-1b | 89.1 (75.6-106.1) | 79.8 (68.9-89.2) | 0.10 |
| RANTES | 8068 (5393-10994) | 8018 (4950-9921) | 0.68 |
| TNF-α | 20.7 (15.4-23.8) | 18.2 (15.6-22.4) | 0.90 |
| VEGF (2/2)* | 127.2 (1.5-299.2) | 74.6 (1.5-199.3) | 0.44 |
| MIG | 250 (162-467) | 219 (114-335) | 0.36 |
| TBG-B1 | 54502 (47478-63258) | 46577 (39623-56241) | 0.03 |
| TGF-B2 | 565 (535-666) | 546 (509-650) | 0.30 |
| TGF-B3 | 73.1 (68.5-80.4) | 71.9 (66.2-77.3) | 0.25 |
| VCAM-1 | 239433 (143914-331932) | 257575 (176074-381857) | 0.73 |
| ICAM-1 | 132951 (100732-179923) | 163054 (110488-206250) | 0.28 |
| WCC (0/1)* | 10.2 (8.8-12.2) | 12.7 (9.9-16.4) | 0.05 |
| CRP | 14 (5-48) | 8 (3-29) | 0.38 |
| Platelets (0/1)* | 236 (207-293) | 248 (197-292) | 0.78 |
| Temperature (0/1)* | 38.2 (37.6-38.4) | 37.7 (37.4-38.2) | 0.14 |

Number (percent) or median with interquartile ranges. IL-1Ra, IL-6, TNF-α, ICAM-1 concentrations in picogram/litre, CRP in mg/l, WCC and platelets count $10^9$/L, temperature in degrees Celsius. IL; interleukin, IL-1Ra; Interleukin-1 receptor antagonist, FGF; fibroblast growth factor, G-CSF; Granulocyte-colony stimulating factor, IFN-gamma; Interferon Gamma, IP; Interferon gamma induced Protein, MCP-1 (MCAF); Monocyte chemoattractant protein (monocyte chemotactic and activating factor), MIP; Macrophage Inflammatory Proteins, PDGF; Platelet-derived growth factor, TNF-α; Tumour necrosis factor alpha, VGEF; Vascular endothelial growth factor, MIG; Monokine induced by gamma, TBG; thyroxine binding globulin, TGF; Transforming growth factor, VCAM; vascular cell adhesion molecule, ICAM; Intracellular Adhesion Molecule, WCC; White cell count, CRP; C reactive protein. *Number of missing in the two groups respectively.

Table 2B. Patient data and results from sample 2 -DCI

| | DCI (n=16) | Non-DCI (n=42) | p |
|---|---|---|---|
| Hydrocephalus | 9 (56) | 21 (50) | 0.77 |
| Infection | 11 (69) | 13 (31) | 0.02 |
| IL-1b | 0.13 (0.08-0.44) | 0.08 (0.08-0.36) | 0.62 |
| IL-1ra | 165 (115-316) | 155 (106-275) | 0.43 |
| IL-2 | 2.98 (1.45-5.07) | 2.37 (1.76-4.04) | 0.48 |
| IL-4 | 0.65 (0.19-1.92) | 0.58 (0.01-1.23) | 0.48 |
| IL-5 | 1.44 (0.48-5.80) | 0.48 (0.48-0.66) | 0.09 |
| IL-6 | 0.28 (0.06-1.08) | 0.28 (0.06-1.74) | 0.76 |
| IL-7 | 0.28 (0.28-0.28) | 0.28 (0.28-0.28) | 0.85 |
| IL-8 | 19.4 12.1-25.9) | 10.1 (5.6-14.2) | 0.02 |
| IL-9 | 72.3 (61.0-99.8) | 67.4 (53.9-89.4) | 0.24 |
| IL-10 | 0.21 (0.21-0.89) | 0.21 (0.21-0.21) | 0.07 |
| IL-12 | 0.15 (0.15-0.32) | 0.15 (0.15-0.50) | 0.69 |
| IL-13 | 0.04 (0.04-4.08) | 0.04 (0.04-4.86) | 0.81 |
| IL-15 | 0.72 (0.72-0.72) | 0.72 (0.72-0.72) | 0.99 |
| IL-17 | 3.85 (1.43-5.74) | 2.91 (1.30-3.98) | 0.30 |
| Eotaxin | 52.6 (31.0-69.4) | 45.4 (35.6-69.2) | 0.87 |
| FGF basic (0/1)* | 33.8 (20.1-45.6) | 29.1 (24.7-38.5) | 0.56 |
| G-CSF | 0.86 (0.86-1.36) | 0.86 (0.86-0.86) | 0.06 |
| GM-CFS | 0.05 (0.05-4.80) | 0.05 (0.05-3.83) | 0.62 |
| IFN-g | 5.02 (1.87-7.35) | 3.61 (1.62-6.40) | 0.41 |
| IP-10 | 419 (272-717) | 329 (250-459) | 0.25 |
| MCP-1 (MCAF) | 41.2 (19.8-84.7) | 31.0 (17.4-49.5) | 0.33 |
| MIP-1a | 1.52 (1.11-2.56) | 1.42 (0.90-2.09) | 0.40 |
| PDGF-bb | 5177 (2975-6090) | 4012 (3421-5254) | 0.51 |
| MIP-1b | 88.3 (77.4-97.8) | 78.5 (66.9-91.4) | 0.21 |
| RANTES | 9983 (4719-11279) | 8069 (5132-9343) | 0.10 |
| TNF-α | 18.1 (15.4-23.8) | 18.2 (15.1-23.2) | 0.86 |
| VEGF (0/1)* | 85.1 (1.5-195.6) | 85.1 (1.5-171.2) | 0.91 |
| MIG | 325 (151-764) | 337 (194-457) | 0.73 |
| TBG-B1 | 57041 (48352-66665) | 59372 (49925-65853) | 0.64 |
| TGF-B2 | 569 (489-609) | 545 (518-599) | 0.66 |
| TGF-B3 | 76.0 (68.5-85.2) | 75.1 (69.5-83.6) | 0.74 |
| VCAM-1 | 233086 (187837-324617) | 243478 (187719-334593) | 0.70 |
| ICAM-1 | 150789 (137488-174421) | 174005 (126687-210409) | 0.26 |
| WCC (2/6)* | 10.9 (8.2-12.6) | 10.5 (9.0-11.9) | 0.95 |
| CRP (0/1) | 24 (8-89) | 20 (7-44) | 0.41 |
| Platelets (1/8)* | 323 (236-412) | 293 (243-340) | 0.51 |
| Temperature (0/10)* | 38.6 (38.4-38.8) | 37.9 (37.4-38.1) | 0.0004 |

Number (percent) or median with interquartile ranges. IL-1Ra, IL-6, TNF-α, ICAM-1 concentrations in picogram/litre, CRP in mg/l, WCC and platelets count $10^9$/L, temperature in degrees Celsius. IL; interleukin, IL-1Ra; Interleukin-1 receptor antagonist, FGF; fibroblast growth factor, G-CSF; Granulocyte-colony stimulating factor, IFN-gamma; Interferon Gamma, IP; Interferon gamma induced Protein, MCP-1 (MCAF); Monocyte chemoattractant protein (monocyte chemotactic and activating factor), MIP; Macrophage Inflammatory Proteins, PDGF; Platelet-derived growth factor, TNF-α; Tumour necrosis factor alpha, VGEF; Vascular endothelial growth factor, MIG; Monokine induced by gamma, TBG; thyroxine binding globulin, TGF; Transforming growth factor, VCAM; vascular cell adhesion molecule, ICAM; Intracellular Adhesion Molecule, WCC; White cell count, CRP; C reactive protein. *Number of missing in the two groups respectively.

# 9.3 STUDY III

Table 1C. Mental Fatigue at 1 and 3 years after aSAH

Table 2:1 LiSat-11. Self-questionnaire assessment at 1 year and 3 years. after aneurysmal subarachnoid hemorrhage divided in patients < 60 years and ≥ 60 years

Table 2:2. MPAI-4. Self-questionnaire assessment at 1 year and 3 years. after aneurysmal subarachnoid hemorrhage divided in patients < 60 years and ≥ 60 years, all significant changes at 1 or 3 years are given and compared at 1 and 3 years

Table 2:3. MFS. Self-questionnaire assessment at 1 year and 3 years. after aneurysmal subarachnoid hemorrhage divided in patients < 60 years and ≥ 60 years, all significant changes at 1 or 3 years are given and compared at 1 and 3 years

Table 3:1 LiSat-11. Self-questionnaire assessment at 1 year and 3 years. after aneurysmal subarachnoid hemorrhage divided in patients DCI yes/no. LiSat-11

Table 3:2 MPAI-4. Self-questionnaire assessment at 1 year and 3 years. after aneurysmal subarachnoid hemorrhage divided in patients DCI yes/no. MPAI-4

Table 3:3 MFS. Self-questionnaire assessment at 1 year and 3 years. after aneurysmal subarachnoid hemorrhage divided in patients DCI yes/no. MFS

**Table 1C Mental fatigue at 1 and 3 years after SAH.**

| Area | **Number with answers at both 1 and 3 years** | **Equal** *(%)* | **Deterioration** *(%)* | **Improvement** *(%)* |
|---|---|---|---|---|
| Fatigue | 39 | 44 | 33 | 23 |
| Lack of initiative | 39 | 51 | 15 | 33 |
| Mental fatigue | 39 | 33 | 21 | 46 |
| Mental recovery | 39 | 49 | 21 | 31 |
| Concentration Difficulties | 39 | 44 | 26 | 31 |
| Memory problems | 39 | 59 | 21 | 21 |
| Slowness of thinking | 37 | 49 | 22 | 30 |
| Sensitivity to stress | 39 | 49 | 10 | 41 |
| Increased tendency to become emotional | 38 | 53 | 24 | 24 |
| Irritability | 39 | 49 | 21 | 31 |
| Sensitivity to light | 39 | 59 | 10 | 31 |
| Sensitivity to noise | 39 | 54 | 13 | 33 |
| Decreased sleep at night | 38 | 53 | 16 | 27 |
| Increased sleep | 37 | 57 | 16 | 27 |

Percentage of patients scoring the same, equal between 1 and 3 years, and patients improving or deteriorating.

**Table 2:1 Self-questionnaire assessment at 1 year and 3 years. after aneurysmal subarachnoid hemorrhage divided in patients < 60 years and ≥ 60 years**

| | **Outcome 1 year** | | | **Outcome 3 years** | | |
|---|---|---|---|---|---|---|
| **Questionnaire** | **Age < 60 n (%)** | **Age ≥ 60 n (%)** | | **Age < 60 n (%)** | **Age ≥ 60 n (%)** | |
| ***LiSat 11*** | | | | | | |
| *Life as a whole* | | | | | | |
| Dissatisfied[2] | 8/27 (30) | 1/15 (7) | | 6/21 (29) | 2/14 (14) | |
| Satisfied[3] | 19/27 (70) | 14/15 (93) | 0.0038 | 15/21 (71) | 12/14 (86) | ns |
| *Vocation* | | | | | | |
| Dissatisfied[2] | 12/25 (48) | 2/14 (14) | | 7/23 (30) | 3/12 (25) | |
| Satisfied[3] | 13/25 (52) | 12/14 (86) | 0.014 | 16/23 (70) | 9/12 (75) | ns |
| *Economy* | | | | | | |
| Dissatisfied[2] | 11/27 (41) | 2/15 (13) | | 9/23 (39) | 3/14 (21) | |
| Satisfied[3] | 16/27 (59) | 13/15 (87) | 0.0051 | 14/23 (61) | 11/14 (79) | ns |
| *Leisure* | | | | | | |
| Dissatisfied[2] | 12/27 (44) | 1/14 (7) | | 7/22 (32) | 1/14 (7) | |
| Satisfied[3] | 15/27 (56) | 13/14 (93) | 0.0034 | 15/22 (68) | 13/14 (93) | ns |
| *Contacts* | | | | | | |
| Dissatisfied[2] | 9/27 (33) | 1/15 (7) | | 5/22 (23) | 1/14 (7) | |
| Satisfied[3] | 18/27 (67) | 14/15 (93) | 0.0007 | 17/22 (77) | 13/14 (93) | ns |
| *Sexual life* | | | | | | |
| Dissatisfied[2] | 14/24 (58) | 2/14 (14) | | 11/22 (50) | 4/13 (31) | |
| Satisfied[3] | 10/24 (42) | 12/14 (86) | ns | 11/22 (50) | 9/13 (69) | ns |
| *ADL[10]* | | | | | | |
| Dissatisfied[2] | 4/27 (15) | 0/15 (0) | | 2/23 (9) | 1/14 (7) | |
| Satisfied[3] | 23/27 (85) | 15/15 (100) | ns | 21/23 (91) | 13/14 (93) | ns |
| *Family Life* | | | | | | |
| Dissatisfied[2] | 2/27 (7) | 0/15 (0) | | 2/23 (9) | 0/13 (0) | |
| Satisfied[3] | 25/27 (93) | 15/15 (100) | 0.012 | 21/23 (91) | 13/13 (100) | ns |
| *Partner relationship* | | | | | | |
| Dissatisfied[2] | 4/22 (18) | 1/14 (7) | ns | 2/16 (13) | 2/13 (15) | |
| Satisfied[3] | 18/22 (82) | 13/14 (93) | | 14/16 (88) | 11/13 (85) | ns |
| *Somatic Health* | | | | | | |
| Dissatisfied[2] | 9/27 (33) | 0/15 (0) | 0.014 | 7/23 (30) | 1/14 (7) | |
| Satisfied[3] | 18/27 (67) | 15/15 (100) | | 16/23 (70) | 13/14 (93) | ns |
| *Psychological Health* | | | | | | |
| Dissatisfied[2] | 8/26 (31) | 1/15 (7) | | 3/23 (13) | 2/14 (14) | |
| Satisfied[3] | 18/26 (69) | 14/15 (93) | 0.0024 | 20/23 (87) | 12/14 (86) | ns |

**Table 2:2. Self-questionnaire assessment at 1 year and 3 years. after aneurysmal subarachnoid hemorrhage divided in patients < 60 years and ≥ 60 years, all significant changes at 1 or 3 years are given and compared at 1 and 3 years**

| **Outcome 1 year** | | | | **Outcome 3 years** | | |
|---|---|---|---|---|---|---|
| **Questionnaire/ question content** | **Age < 60 n (%)** | **Age ≥ 60 n (%)** | | **Age < 60 n (%)** | **Age ≥ 60 n (%)** | |
| ***MPAI-4***[3] | | | | | | |
| *Mobility* | | | | | | |
| Problems[4] | 8/28 (29) | 4/16 (25) | | 6/23 (26) | 2/14 (14) | |
| No problems[5] | 20/28 (71) | 12/16 (75) | ns | 17/23 (74) | 12/14 (86) | ns |
| *Use of hands* | | | | | | |
| Problems[4] | 8/27 (30) | 2/14 (14) | | 3/22 (14) | 2/14 (14) | |
| No problems[5] | 19/27 (70) | 12/14 (86) | ns | 19/22 (86) | 12/14 (86) | ns |
| *Vision* | | | | | | |
| Problems[4] | 5/28 (18) | 0/16 (0) | | 4/23 (17) | 0/14 (0) | |
| No problems[5] | 23/28 (82) | 16/16 (100) | 0.016 | 19/23 (83) | 14/14 (100) | ns |
| *Audition* | | | | | | |
| No problems[5] | 5/28 (18) | 0/16 (0) | | 3/23 (13) | 3/14 (21) | |
| Problems[4] | 23/28 (82) | 16/16 (100) | ns | 20/23 (87) | 11/14 (79) | ns |
| *Dizziness* | | | | | | |
| Problems[4] | 8/27 (30) | 3/15 (20) | | 6/23 (26) | 2/14 (14) | |
| No problems[5] | 19/27 (70) | 12/15 (80) | Ns | 17/23 (74) | 12/14 (86) | ns |
| *Motor speech* | | | | | | |
| Problems[4] | 20/26 (77) | 1/16 (6) | | 3/23 (13) | 2/14 (14) | |
| No problems[5] | 6/26 (23) | 15/16 (94) | ns | 20/23 (87) | 12/14 (86) | ns |
| *Verbal communication* | | | | | | |
| Problems[4] | 8/27 (30) | 1/16 (6) | | 4/23 (17) | 1/14 (7) | |
| No problems[5] | 19/27 (70) | 15/16 (94 | ns | 19/23 (83) | 13/14 (93) | ns |
| *Nonverbal communication* | | | | | | |
| Problems[4] | 4/27 (15) | 1/15 (7) | | 1/21 (5) | 1/14 (7) | |
| No problems[5] | 23/27 (85) | 14/15 (93) | ns | 20/21 (95) | 13/14 (93) | ns |
| *Attention/concentration* | | | | | | |
| Problems[4] | 10/27 (37) | 2/15 (13) | | 10/22 (45) | 2/14 (14) | |
| No problems[5] | 17/27 (63) | 13/15 (87) | ns | 12/22 (55) | 12/14 (86) | ns |
| *Memory* | | | | | | |
| Problems[4] | 10/28 (36) | 3/15 (20) | | 10/23 (43) | 7/14 (50) | |
| No problems[5] | 18/28 (64) | 12/15 (80) | ns | 13/23 (57) | 7/14 (50) | ns |
| *Fund of information* | | | | | | |
| Problems[4] | 2/28 (7) | 3/15 (20) | | 8/22 (36) | 3/14 (21) | |
| No problems[5] | 26/28 (93) | 12/15 (80) | ns | 14/22 (64) | 11/14 (79) | ns |
| *Novel problem-solving* | | | | | | |
| Problems[4] | 6/27 (22) | 3/15 (20) | | 5/23 (22) | 0/14 (0) | |
| No problems[5] | 21/27 (73) | 12/15 (80) | ns | 18/23 (78) | 14/14 (100) | ns |

| | | | | | | |
|---|---|---|---|---|---|---|
| *Visuospatial abilities* | | | | | | |
| Problems[4] | 22/27 (81) | 2/15 (13) | | 3/22 (14) | 1/14 (7) | |
| No problems[5] | 5/27 ((19) | 13/15 (87) | ns | 19/22 (86) | 13/14 (93) | ns |
| *Anxiety* | | | | | | |
| Problems[4] | 11/28 (39) | 1/16 (94) | | 7/22 (32) | 3/14 (21) | |
| No problems[5] | 17/28 (61) | 15/16 (6) | 0.0093 | 15/22 (68) | 11/14 (79) | ns |
| *Depression* | | | | | | |
| Problems[4] | 12/28 (43) | 3/16 (19) | | 7/21 (33) | 3/14 (21) | |
| No problems[5] | 16/28 (57) | 13/16 (81) | 0.034 | 14/21 (67) | 11/14 (79) | ns |
| *Irritability/anger* | | | | | | |
| Problems[4] | 6/27 (22) | 3/16 (19) | | 8/22 (36) | 3/14 (21) | |
| No problems[5] | 21/27 (73) | 13/16 (81) | ns | 14/22 (64) | 11/14 (79) | ns |
| *Pain/headache* | | | | | | |
| Problems[4] | 9/27 (33) | 0/16 (0) | | 10/22 (45) | 1/14 (7) | |
| No problems[5] | 18/27 (67) | 16/16 (100) | 0.0004 | 12/22 (55) | 13/14 (93) | 0.01 |
| *Fatigue* | | | | | | |
| Problems[4] | 11/28 (39) | 7/16 (44) | | 13/22 (59) | 5/14 (36) | |
| No problems[5] | 17/28 (61) | 9/16 (56) | ns | 9/22 (43) | 9/14 (64) | Ns |
| *Sensativity to mild symptoms* | | | | | | |
| Problems[4] | 7/27 (26) | 3/15 (20) | | 5/20 (25) | 1/14 (7) | |
| No problems[5] | 20/27 (74) | 12/15 (80) | ns | 15/20 (75) | 13/14 (93) | Ns |
| *Inappropriate social interactions* | | | | | | |
| Problems[4] | 0/0 (0) | 1/15 (7) | | 1/21 (5) | 1/14 (7) | |
| No problems[5] | 26/26(100) | 14/15 (93) | ns | 20/21 (95) | 13/14 (93) | ns |
| *Impaired self-awareness* | | | | | | |
| Problems[4] | 3/27 (11) | 2/16 (13) | | 3/21 (14) | 1/14 (7) | |
| No problems[5] | 24/27 (89) | 14/16 (88) | ns | 18/21 (86) | 13/14 (93) | ns |
| *Family relationship* | | | | | | |
| Problems[4] | 11/24 (46) | 1/13 (8) | | 7/20 (35) | 1/12 (8) | |
| No problems[5] | 13/24 (54) | 12/13(92) | 0.02 | 13/20 (65) | 11/12 (92) | ns |
| *Initiation* | | | | | | |
| Problems[4] | 11/28 (39) | 2/14 (14) | | 5/22 (23) | 1/14 (7) | |
| No problems[5] | 17/28 (61) | 12/14 (86) | ns | 17/22 (77) | 13/14 (93) | ns |
| *Social contact* | | | | | | |
| Problems[4] | 9/28 (32) | 0/16 (0) | | 7/23 (30) | 2/14 (14) | |
| No problems[5] | 19/28 (68) | 16/16 (100) | 0.032 | 16/23 (70) | 12/14 (86) | ns |
| *Leisure* | | | | | | |
| Problems[4] | 11/28 (39) | 1/15 (7) | | 8/23 (35) | 0/14 (0) | |
| No problems[5] | 17/28 (61) | 14/15 (93) | Ns | 15/23 (65) | 14/14 (100) | 0.016 |
| *Self-care* | | | | | | |
| Problems[4] | 2/28 (7) | 1/16 (94) | | 1/23 (4) | 1/14 (7) | |

| | | | | | | |
|---|---|---|---|---|---|---|
| *Residence* | | | | | | |
| Problems[4] | 6/28 (21) | 4/16 (25) | | 3/23 (13) | 2/14 (14) | |
| No problems[5] | 22/28 (79) | 12/16 (75) | ns | 20/23 (87) | 12/14 (86) | ns |
| *Transportation* | | | | | | |
| Problems[4] | 6/27 (22) | 2/16 (13) | | 19/23 (83) | 1/14 (7) | |
| No problems[5] | 21/27 (78) | 14/16 (88) | ns | 4/23 (17) | 13/14 (93) | ns |
| *Money management* | | | | | | |
| Problems[4] | 2/27 (7) | 1/16 (6) | | 1/22 (4) | 1/13 (8) | |
| No problems[5] | 25/27 ((93) | 15/16 ((94) | ns | 22/22 (96) | 12/13 (92) | ns |

**Table 2:3. Self-questionnaire assessment at 1 year and 3 years. after aneurysmal subarachnoid hemorrhage divided in patients < 60 years and ≥ 60 years, all significant changes at 1 or 3 years are given and compared at 1 and 3 years**

| **Outcome 1 year** | | | | **Outcome 3 years** | | |
|---|---|---|---|---|---|---|
| **Questionnaire/ question content** | **Age < 60** | **Age ≥ 60** | | **Age < 60** | **Age ≥ 60** | |
| ***MFS***[7] | **n (%)** | **n (%)** | | **n (%)** | **n (%)** | |
| *Fatigue* | | | | | | |
| Problems[8] | 12/28 (43) | 2/16 (12) | | 11/24 (46) | 3/15 (20) | |
| No problems[9] | 16/28 (57) | 14/16 (88) | 0.009 | 13/24 (54) | 12/15 (80) | ns |
| *Lack of initiative* | | | | | | |
| Problems[8] | 9/28 (32) | 4/16 (25) | | 4/24 (17) | 2/15 (13) | |
| No problems[9] | 19/28 (68) | 12/16 (75) | ns | 20/24 (83) | 13/15 (87) | ns |
| *Mental fatigue* | | | | | | |
| Problems[8] | 17/28 (61) | 5/16 (31) | | 12/25 (50) | 4/15 (27) | |
| No problems[9] | 11/28 (39) | 11/16 (69) | 0.043 | 12/24 (50) | 11/15 (77) | ns |
| *Mental recovery* | | | | | | |
| Problems[8] | 13/27 (48) | 3/16 (19) | | 11/24 (46) | 4/15 (27) | |
| No problems[9] | 14/27 (52) | 13/16 (81) | ns | 13/24 (54) | 11/15 (77) | ns |
| *Concentration difficulties* | | | | | | |
| Problems[8] | 11/28 (39) | 4/16 (25) | | 9/24 (38) | 4/15 (27) | |
| No problems[9] | 17/28 (61) | 12/16 (75) | ns | 15/24 (62) | 11/15 (77) | ns |
| *Memory problems* | | | | | | |
| Problems[8] | 7/28 (25) | 2/16 (12) | | 5/24 (21) | 3/15 (20) | |
| No problems[9] | 21/28 (75) | 14/16 (88) | ns | 19/24 (79) | 12/15 (80) | ns |
| *Slowness of thinking* | | | | | | |
| Problems[8] | 9/28 (32) | 3/15 (20) | | 6/23 (26) | 4/15 (27) | |
| No problems[9] | 19/28 (68) | 12/15 (80) | ns | 17/23 (74) | 11/15 (77) | |
| *Sensitivity to stress* | | | | | | ns |
| Problems[8] | 15/28 (54) | 5/16 (31) | | 9/24 (38) | 6/15 (40) | |
| No problems[9] | 13/28 (46) | 11/16 (69) | ns | 15/24 (62) | 9/15 (60) | |
| *Increased tendency to become emotional* | | | | | | ns |
| Problems[8] | 9/28 (32) | 1/15 (7) | | 7/24 (29) | 1/15 (7) | |
| No problems[9] | 19/28 (68) | 14/15 (93) | ns | 17/24 (71) | 14/15 (93) | ns |
| *Irritabilituy* | | | | | | |
| Problems[8] | 10/28 (36) | 4/16 (25) | | 6/24 (25) | 2/15 (13) | |
| No problems[9] | 18/28 (64) | 12/16 (75) | ns | 18/24 (75) | 13/15 (87) | Ns |
| *Sensitivity to light* | | | | | | |
| Problems[8] | 7/28 (25) | 1/16 (6) | | 4/24 (17) | 0/0 (0) | |
| No problems[9] | 21/28 (75) | 15/16 (94) | 0.05 | 20/24 (83) | 15/15 (100) | Ns |
| *Sensitivity to noise* | | | | | | |
| Problems[8] | 11/28 (39) | 2/16 (12) | | 7/24 (29) | 3/15 (20) | |
| No problems[9] | 17/28 (61) | 14/16 (88) | Ns | 17/24 (71) | 12/15 (80) | Ns |
| *Decreased sleep night* | | | | | | |
| Problems[8] | 5/28 (18) | 6/16 (38) | | 8/23 (35) | 4/15 (27) | |
| No problems[9] | 23/28 (82) | 10/16 (62) | Ns | 15/23 (65) | 11/15 (77) | Ns |
| *Increased sleep* | | | | | | |
| Problems[8] | 7/28 (25) | 2/15 (13) | | 6/23 (26) | 1/15 (7) | |
| No problems[9] | 21/28 (75) | 13/15 (87) | ns | 17/23 (74) | 14/15 (93) | ns |

**Table 3:1 Self-questionnaire assessment at 1 year and 3 years. after aneurysmal subarachnoid hemorrhage divided in patients DCI (delayed cerebral ischemia) yes/no**

| **Outcome 1 year** | | | | **Outcome 3 years** | | |
|---|---|---|---|---|---|---|
| **Questionnaire/ question content** | **DCI, yes n (%)** | **DCI, no n (%)** | | **DCI, yes n (%)** | **DCI, no n (%)** | |
| ***LiSat 11*** | | | | | | |
| *Life as a whole* | | | | | | |
| Dissatisfied[2] | 3/12 (25) | 6/30 (20) | | 4/8 (50) | 4/27 (15) | |
| Satisfied[3] | 9/12 ((75) | 24/30 (80) | Ns | 4/8 (50) | 23/27 (85) | Ns |
| *Vocation* | | | | | | |
| Dissatisfied[2] | 4/12 (33) | 10/27 (37) | | 4/9 (44) | 6/26 (23) | |
| Satisfied[3] | 8/12 (67) | 17/27 (63) | Ns | 5/9 (56) | 20/26 (77) | ns |
| *Economy* | | | | | | |
| Dissatisfied[2] | 4/12 (33) | 9/30 (30) | | 4/9 (44) | 8/28 (29) | |
| Satisfied[3] | 8/12 (67) | 21/30 (70) | Ns | 5/9 (56) | 20/28 (71) | Ns |
| *Leisure* | | | | | | |
| Dissatisfied[2] | 5/12 (42) | 8/29 (29) | | 3/9 (33) | 5/27 (19) | |
| Satisfied[3] | 7/12 (58) | 21/29 (72) | Ns | 6/9 (67) | 22/27 (81) | Ns |
| *Contacts* | | | | | | |
| Dissatisfied[2] | 3/12 (25) | 7/ 30 (23) | | 3/9 (33) | 3/27 (11) | |
| Satisfied[3] | 9/12 ((75) | 23/30 (77) | Ns | 6/9 (67) | 24/27 (89) | Ns |
| *Sexual life* | | | | | | |
| Dissatisfied[2] | 5/10 (50) | 11/28 (39) | | 4/9 (44) | 10/26 (38) | |
| Satisfied[3] | 5/10 (50) | 17/28 (61) | Ns | 5/9 (56) | 16/26 (62) | Ns |
| *ADL[10]* | | | | | | |
| Dissatisfied[2] | 2/12 (17) | 2/30 (7) | | 2/9 (22) | 1/28 (4) | |
| Satisfied[3] | 10/12 (83) | 28/30 (93) | Ns | 7/9 (78) | 27/28 (96) | 0.02 |
| *Family Life* | | | | | | |
| Dissatisfied[2] | 0/0 (0) | 2/30 (7) | | 1/9 (11) | 1/27 (4) | |
| Satisfied[3] | 12/12 (100) | 28/30 (93) | Ns | 8/9 (89) | 27/28 (96) | ns |
| *Partner relationship* | | | | | | |
| Dissatisfied[2] | 2/10 (20) | 3/26 (12) | | 2/9 (22) | 2/21 (10) | |
| Satisfied[3] | 8/10 (80) | 23/26 (88) | Ns | 7/9 (78) | 19/21 (90) | ns |
| *Somatic Health* | | | | | | |
| Dissatisfied[2] | 2/12 (17) | 7/ 30 (23) | | 4/9 (44) | 4/28 (14) | |
| Satisfied[3] | 10/12 (83) | 23/30 (77) | Ns | 5/9 (56) | 24/28 (86) | ns |
| *Psychological Health* | | | | | | |
| Dissatisfied[2] | 3/12 (25) | 6/29 (21) | | 3/9 (33) | 2/28 (8) | |
| Satisfied[3] | 9/12 ((75) | 23/29 (79) | ns | 6/9 (67) | 26/28 (92) | ns |

[1]Life Satisfaction Questionnaire (LiSat-11) according to Fugl Meyer (*ref*), [2]Answer options; very. dissatisfied/dissatisfied/rather dissatisfied, [3]Answer options; rather satisfied/satisfied/very satisfied

LiSat; Dissatisfied; 3-1*Rather Dissatisfied/Dissatisfied/Very dissatisfied*Satisfied; 6-4 *Very Satisfied/Satisfied/Rather Satisfied*

| **Outcome 1 year** | | | | **Outcome 3 years** | | |
|---|---|---|---|---|---|---|
| **Questionnaire/ question content** | **DCI, yes n (%)** | **DCI, no n (%)** | | **DCI, yes n (%)** | **DCI, no n (%)** | |
| ***MPAI-4[3]*** | | | | | | |
| *Mobility* | | | | | | |
| Problems[4] | 4/12 (33) | 8/32 (25) | | 5/9 (56) | 3/28 (11) | |
| No problems[5] | 8/12 (67) | 24/32 (75) | Ns | 4/9 (44) | 25/28 (89) | 0,005 |
| *Use of hands* | | | | | | |
| Problems[4] | 4/12 (33) | 6/31 (19) | | 3/9 (33) | 2/27 (7) | |
| No problems[5] | 8/12 (67) | 25/31 (81) | Ns | 6/9(77) | 25/27 (93) | 0,014 |
| *Vision* | | | | | | |
| Problems[4] | 3/12 (25) | 2/32 (6) | | 3/9 (33) | 1/28 (4) | |
| No problems[5] | 9/12 ((75) | 30/32 (94) | Ns | 6/9(77) | 27/28 (96) | 0,002 |
| *Audition* | | | | | | |
| Problems[4] | 2/12 (17) | 3/32 (9) | | 1/9 (11) | 5/28 (18) | |
| No problems[5] | 10/12 (83) | 29/32 (91) | Ns | 8/9 (89) | 23/28 (82) | ns |
| *Dizziness* | | | | | | |
| Problems[4] | 5/11 (45) | 5/31 (16) | | 5/9 (56) | 3/28 (11) | |
| No problems[5] | 6/11 (55) | 26/31 (84) | Ns | 4/9 (44) | 25/28 (89) | 0.02 |
| *Motor speech* | | | | | | |
| Problems[4] | 2/11 (18) | 5/31 (16) | | 1/9 (11) | 4/28 (14) | |
| No problems[5] | 9/11 (82) | 26/31 (84) | Ns | 8/9 (89) | 24/28 (86) | ns |
| *Verbal communication* | | | | | | |
| Problems[4] | 3/12 (25) | 6/31 (19) | | 2/9 (22) | 3/28 (11) | |
| No problems[5] | 9/12 ((75) | 25/31 (81) | Ns | 7/9 (78) | 25/28 (89) | ns |
| *Nonverbal communication* | | | | | | |
| Problems[4] | 3/10 (23) | 2/30 (7) | | 2/8 (25) | 0/27 (0) | |
| No problems[5] | 10/13 (77) | 28/30 (93) | Ns | 6/8 (75) | 27/27 (100) | 0,024 |
| *Attention/concentration* | | | | | | |
| Problems[4] | 4/11 (36) | 8/31 (26) | | 6/9(77) | 6/27 (22) | |
| No problems[5] | 7/11 (64) | 23/31 (74) | Ns | 3/9 (33) | 21/27 (78) | 0.03 |
| *Memory* | | | | | | |
| Problems[4] | 4/12 (33) | 9/31 (29) | | 5/9 (56) | 12/28 (43) | |
| No problems[5] | 8/12 (67) | 22/31 (71) | Ns | 4/9 (44) | 16/28 (57) | ns |
| *Fund of information* | | | | | | |
| Problems[4] | 2/12 (17) | 3/31 (10) | | 4/8 (50) | 7/28 (25) | |
| No problems[5] | 10/12 (83) | 28/31 (90) | Ns | 4/8 (50) | 21/28 (75) | ns |
| *Novel problem-solving* | | | | | | |
| Problems[4] | 4/11 (36) | 5/31 (16) | | 2/9 (22) | 3/28 (11) | |
| No problems[5] | 7/11 (64) | 26/31 (84) | Ns | 7/9 (78) | 25/28 (89) | ns |
| *Visuospatial abilities* | | | | | | |
| Problems[4] | 4/11 (36) | 3/31 (10) | | 2/8 (25) | 2/28 (7) | |
| No problems[5] | 7/11 (64) | 28/31 (90) | Ns | 6/8 (75) | 26/28 (93) | 0.04 |
| *Anxiety* | | | | | | |
| Problems[4] | 5/12 (42) | 7/32 (22) | | 5/8 (62) | 5/28 (18) | |
| No problems[5] | 7/12 (58) | 25/32 (78) | Ns | 3/8 (38) | 23/28 (82) | 0,015 |

| | | | | | | |
|---|---|---|---|---|---|---|
| *Depression* | | | | | | |
| Problems[425] | 5/12 (42) | 10/32 (31) | | 4/8 (50) | 6/27 (22) | |
| No problems[5] | 7/12 (58) | 22/32 (69) | Ns | 4/8 (50) | 21/27 (78) | ns |
| *Irritability/anger* | | | | | | |
| Problems[4] | 3/11 (27) | 6/32 (19) | | 5/8 (62) | 6/28 (21) | |
| No problems[5] | 8/11 (73) | 26/32 (81) | Ns | 3/8 (38) | 2/28 (79) | ns |
| *Pain/headache* | | | | | | |
| Problems[4] | 4/12 (33) | 5/31 (16) | | 4/8 (50) | 7/28 (25) | |
| No problems[5] | 8/12 (67) | 26/31 (84) | Ns | 4/8 (50) | 21/28 (75) | ns |
| *Fatigue* | | | | | | |
| Problems[4] | 6/12 (50) | 18/32 (56) | | 5/8 (62) | 13/28 (46) | |
| No problems[5] | 6/12 (50) | 14/32 (44) | Ns | 3/8 (38) | 15/28 (54) | ns |
| *Sensitivity to mild symptoms* | | | | | | |
| Problems[4] | 4/11 (36) | 6/31 (19) | | 5/8 (62) | 1/26 (4) | |
| No problems[5] | 7/11 (64) | 25/31 (81) | Ns | 3/8 (38) | 25/26 (96) | 0.07 |
| *Inappropriate social interactions* | | | | | | |
| Problems[4] | 1/11 (9) | 3/30 (10) | | 1/8 (12) | 1/28 (4) | |
| No problems[5] | 10/11 (91) | 27/30 (90) | Ns | 7/8 (88) | 27/28 (96) | 0.04 |
| *Impaired self-awareness* | | | | | | |
| Problems[4] | 3/11 (27) | 2/32 (6) | | 1/7 (14) | 1/28 (4) | |
| No problems[5] | 8/11 (73) | 30/32 (94) | Ns | 6/7 (86) | 27/28 (96) | 0,018 |
| *Family relationship* | | | | | | |
| Problems[4] | 3/10 (30) | 9/27 (33) | | 3/7 (43) | 5/25 (20) | |
| No problems[5] | 7/10 (70) | 18/27 (67) | Ns | 4/7 (57) | 20/25 (80) | ns |
| *Initiation* | | | | | | |
| Problems[4] | 5/12 (42) | 8/32 (25) | | 3/9 (33) | 3/27 (11) | |
| No problems[5] | 7/12 (58) | 24/32 (75) | Ns | 6/9 (67) | 24/27 (89) | 0.04? |
| *Social contact* | | | | | | |
| Problems[4] | 4/12 (33) | 5/32 (16) | | 3/9 (33) | 6/28 (21) | |
| No problems[5] | 8/12 (67) | 27/32 (84) | Ns | 6/9 (67) | 22/28 (79) | ns |
| *Leisure* | | | | | | |
| Problems[4] | 3/12 (25) | 9/31 (29) | | 3/9 (33) | 5/28 (18) | |
| No problems[5] | 9/12 (75) | 22/31 (71) | Ns | 6/9 (67) | 23/28 (82) | ns |
| *Self-care* | | | | | | |
| Problems[4] | 1/12 (8) | 2/32 (6) | | 1/9 (11) | 1/28 (4) | |
| No problems[5] | 11/12 (92) | 30/32 (94) | Ns | 8/9 (89) | 27/28 (96) | ns |
| *Residence* | | | | | | |
| Problems[4] | 4/12 (33) | 6/32 (19) | | 3/9 (33) | 2/28 (7) | |
| No problems[5] | 8/12 (67) | 26/32 (81) | Ns | 6/9 (67) | 26/28 (93) | ns |
| *Transportation* | | | | | | |
| Problems[4] | 3/11 (27) | 5/32 (16) | | 3/9 (33) | 2/28 (7) | |
| No problems[5] | 8/11 (73) | 27/32 (84) | Ns | 6/9 (67) | 26/28 (93) | 0,037 |
| *Money management* | | | | | | |
| Problems[4] | 1/11 (9) | 2/32 (6) | | 2/9 (22) | 1/27 (4) | |
| No problems[5] | 10/11 (10) | 30/32 (94) | Ns | 7/9 (78) | 26/27 (96) | ns |

**Table 3:3. Self-questionnaire assessment at 1 year and 3 years. after aneurysmal subarachnoid hemorrhage divided in patients DCI (delayed cerebral ischemia) yes/no, all significant changes at 1 or 3 years are given and compared at 1 and 3 years**

| **Outcome 1 year** | | | | **Outcome 3 years** | | |
|---|---|---|---|---|---|---|
| **Questionnaire/ question content** | **DCI, yes n (%)** | **DCI, no n (%)** | | **DCI, yes n (%)** | **DCI, no n (%)** | |
| ***MFS***[7] | | | | | | |
| *Fatigue* | | | | | | |
| Problems[8] | 4/13 (31) | 5/31 (16) | | 4/10 (40) | 10//29 (34) | |
| No problems[9] | 9/13 (69) | 26/31 (84) | ns | 6/10 (60) | 19/29 (66) | ns |
| *Lack of initiative* | | | | | | |
| Problems[8] | 5/13 38) | 8/31 (26) | | 3/10 (30) | 3/29 (10) | |
| No problems[9] | 8/13 (62) | 23/31 (74) | ns | 7/10 (70) | 26/29 (90) | ns |
| *Mental fatigue* | | | | | | |
| Problems[8] | 5/13 (38) | 11/31 (35) | | 5/10 (50) | 11/29 (38) | |
| No problems[9] | 8/13 (62) | 20/31 (65) | ns | 5/10 (50) | 18/29 (62) | ns |
| *Mental recovery* | | | | | | |
| Problems[8] | 5/12 (42) | 11/31 (35) | | 3/10 (30) | 12/29 (41) | |
| No problems[9] | 7/12 (58) | 20/31 (65) | ns | 7/10 (70) | 17/29 (59) | ns |
| *Concentration difficulties* | | | | | | |
| Problems[8] | | | | | | |
| No problems[9] | 5/13 (38) | 10/31 (32) | | 4/10 (40) | 9/29 (31) | |
| *Memory problems* | 8/13 (62) | 21/31 (68) | ns | 6/10 (60) | 20/29 (69) | ns |
| Problems[8] | | | | | | |
| No problems[9] | 4/13 (31) | 5/31 (16) | | 3/10 (30) | 5/29 (17) | |
| *Slowness of thinking* | 9/13 (69) | 26/31 (84) | ns | 7/10 (70) | 24/29 (83) | ns |
| Problems[8] | | | | | | |
| No problems[9] | 4/13 (31) | 8/30 (27) | | 3/10 (30) | 7/28 (25) | |
| *Sensitivity to stress* | 9/13 (69) | 22/30 (73) | ns | 7/10 (70) | 21/28 (75) | ns |
| Problems[8] | | | | | | |
| No problems[9] | 7/13 (54) | 11/31 (35) | | 5/10 (50) | 10/29 (34) | |
| *Increased tendency to become emotional* | 6/13 (46) | 20/31 (65) | ns | 5/10 (50) | 19/29 (66) | ns |
| Problems[8] | | | | | | |
| No problems[9] | 4/13 (31) | 6/30 (20) | | 3/10 (30) | 5/29 (17) | |
| *Irritabilituy* | 9/13 (84) | 24/30 (80) | ns | 7/10 (70) | 24/29 (83) | ns |
| Problems[8] | | | | | | |
| No problems[9] | 3/13 (23) | 11/31 (35) | | 4/10 (40) | 4/29 (14) | |
| *Sensitivity to light* | 10/13 (77) | 20/31 (65) | ns | 6/10 (60) | 25/29 (86) | ns |
| Problems[8] | | | | | | |
| No problems[9] | 4/13 (31) | 4/31 (13) | | 1/10 (10) | 3/29 (10) | |
| *Sensitivity to noise* | 9/13 (69) | 27/31 (87) | ns | 9/10 (90) | 26/29 (90) | ns |
| Problems[8] | | | | | | |
| No problems[9] | 3/13 (23) | 10/31 (32) | | 2/10 (20) | 8/29 (28) | |
| *Decreased sleep night* | 10/13 (77) | 21/31 (68) | ns | 8/10 (80) | 21/29 (72) | ns |
| Problems[8] | | | | | | |
| No problems[9] | 4/13 (31) | 6/31 (19) | | 4/9 (44) | 8/29 (28) | |
| *Increased sleep* | 9/13 (84) | 25/31 (81) | ns | 5/9 (66) | 21/29 (72) | ns |
| Problems[8] | | | | | | |
| No problems[9] | 1/12 (8) | 8/31 (27) | | 2/9 (22) | 5/29 (17) | |
| | 11/12 (92) | 23/31 (73) | ns | 7/9 (78) | 24/29 (83) | ns |