Tampere University

Salla Jokilehto

NEUROPSYCHOLOGICAL DEFICITS AND DELAYED CEREBRAL ISCHEMIA AFTER SUBARACHNOID HEMORRHAGE

Faculty of Medicine and Health Technology
Advanced studies, thesis
December 2022

TIIVISTELMÄ

Salla Jokilehto: Neuropsykologiset puutosoireet ja viivästynyt aivoiskemia subaraknoidaalivuodon jälkeen
Syventävien opintojen kirjallinen työ
Tampereen yliopisto
Lääketieteen lisensiaatin tutkinto-ohjelma
Joulukuu 2022

Lukinkalvonalaiset verenvuodot (subaraknoidaalivuoto, SAV) aiheuttavat noin 5 % kaikista aivohalvauksista. Suurin osa niistä on aivoverisuonten pullistumien eli aneurysmien repeämisen aiheuttamia (aneurysmaattinen SAV, aSAV). Noin kolmannes aSAV-potilaista kuolee vuodon seurauksena. Henkiin jääneistä suurelle osalle jää vuodosta eritasoisia neurokognitiivisia ja -psykologisia haittoja. Noin kolmannekselle akuutista tilanteesta selvinneistä kehittyy viivästyneen aivojen hapenpuutteen eli aivoiskemian (delayed cerebral ischemia, DCI) oirekuva. DCI:n oireet ovat tyypillisesti neurologisia puutosoireita. Tutkimuksissa DCI-oireisilla on havaittu olevan viisinkertainen riski pysyviin neuropsykologisiin puutosoireisiin muihin aSAV-potilaisiin verrattuna.

Tämä havainnoiva seurantatutkimus toteutettiin osana isompaa tutkimuskokonaisuutta, johon rekrytoitiin 60 Tampereen yliopistollisessa sairaalassa hoidettua aikuista aSAV-potilasta. Poissulkukriteereinä tutkimukseen olivat veren hyytymiseen vaikuttava lääkitys, raskaus tai aktiivinen syöpä. Tähän tutkimusosioon liittyen tutkimusprotokollaan kuului tavanomaisen hoidon lisäksi toipumisvaiheessa tehdyt neuropsykologiset tutkimukset (verbaaliset toiminnot, visuaaliset toiminnot, muisti ja oppiminen sekä tarkkaavuus ja toiminnanohjaus). Karkea neurologinen toipuminen arvioitiin extended Glasgow Outcome (eGOSE) -luokituksella.

Koska yksi potilaista kieltäytyi neuropsykologisista tutkimuksista, tähän tutkimukseen potilaita kertyi lähtökohtaisesti 59. Heistä 20 % (12/59) kuoli vuodon seurauksena. Henkiin jääneistä potilaista 43 %:lla (20/47) diagnosoitiin DCI. Viiden potilaan neuropsykologinen tila jäi hoidon jälkeen liian huonoksi neuropsykologisten tutkimusten suorittamiseen. Lopuista 42 potilaasta neuropsykologisten tutkimusten tulokset saatiin 29:ltä. Heistä kymmenellä (35 %) diagnosoitiin DCI.

Koko tutkimuspopulaatiosta neurologinen toipuminen kolmen kuukauden kuluttua vuodosta katsottiin hyväksi (eGOSE tulos 5–8) 53 %:lla (32/60) potilaista. Neuropsykologisissa testeissä tulokset olivat yleisesti keskimäärin hieman ikätasoista huonompia. Selkeimmin alle ikätason jäätiin tarkkaavuuden ja toiminnanohjauksen osalta. Selkeää eroa neuropsykologisten testien tuloksissa DCI-potilaiden ja muiden potilaiden välillä ei todettu. Osassa testeistä DCI-potilaiden suoriutumispisteet olivat jopa paremmat. Pienen potilasaineiston vuoksi tilastollisia merkitsevyyksiä ei neuropsykologisten testien osalta testattu.

Tässä tutkimuksessa DCI-oirekuvan kehittyminen ei ollut yhteydessä heikompaan neurologiseen toipumiseen. Neuropsykologisissa tutkimuksissa potilaat, joilla diagnosoitiin DCI, eivät pärjänneet selkeästi muita huonommin toisin kuin aiemmissa tutkimuksissa. Jatkossa olisi toivottavaa, että tutkimukset käyttäisivät yhteneviä, kohdennettuja ja juuri tälle potilasryhmälle soveltuvia testejä, mikä lisäisi tutkimusten luotettavuutta ja vertailukelpoisuutta.

Avainsanat: subaraknoidaalivuoto, aneurysma, viivästynyt aivoiskemia, neuropsykologia

ABSTRACT

Salla Jokilehto: Neuropsychological deficits and delayed cerebral ischemia after subarachnoid hemorrhage
Advanced studies, thesis
Tampere University
Licentiate Degree Programme in Medicine
December 2022

Subarachnoid hemorrhages (SAH) cause approximately 5 % of all strokes. Most of those hemorrhages are caused by aneurysm ruptures (aneurysmal SAH, aSAH). Mortality rate after aSAH is approximately 30 %. Many of surviving patients are left with neurocognitive and neuropsychological deficits. About one third of patients who survive the acute hemorrhage are shown to develop symptoms of delayed cerebral ischemia (DCI) within two to three weeks after aSAH. DCI symptoms are typically neurological deficits such as aphasia or hemiparesis. Earlier studies have shown that patients with DCI have fivefold risk to permanent neuropsychological deficits when compared with other aSAH patients.

This prospective observational study was performed as a part of a larger study in patients with aSAH. Sixty adult aSAH patients treated in intensive care unit of Tampere University Hospital were recruited to the larger study. Exclusion criteria were anticoagulant or antithrombotic medication, known pregnancy and known active cancer. Besides standard clinical care, this study protocol included neuropsychological studies performed during recovery. Neurological outcome was estimated using extended Glasgow Outcome Score (eGOSE) 90 days after the hemorrhage.

Because one of the patients declined from neuropsychological studies, 59 patients were included to this study. From those 20 % (12/59) died after hemorrhage. 43 % (20/47) patients surviving the acute phase were diagnosed with DCI. Five patients' neuropsychological state remained too poor to perform neuropsychological studies. Finally, the results of neuropsychological testing were recorded and analyzed from 29/42 patients. From these, ten (35 %) were diagnosed with DCI.

Within the whole study population neurological outcome was good (eGOSE result 5–8) in 53 % (32/60) patients. Neuropsychological functions were divided to four categories (verbal, visual, memory and learning and attentiveness and executive functions). In all patients the mean scores were close to the age standards, mainly a bit under. In attentiveness and executive functions patients of this study were below the age standards. In this study, there was no clear difference between DCI and non-DCI patients in neuropsychological tests. In some tests DCI patients had even better scores. Because of small sample size statistical significances of neuropsychological studies were not tested.

In this study the development of DCI symptoms was not associated with poor neurological outcome. In neuropsychological studies patients with DCI did not perform worse than non-DCI patients unlike in previous studies. In the future it would be more informative to use the same suitable test pattern to evaluate patients' neuropsychological outcome in the studies. This would make the studies more reliable and comparable.

Keywords: subarachnoid hemorrhage, aneurysm, delayed cerebral ischemia, neuropsychology

TABLE OF CONTENTS

1 BACKGROUND

1.1 Introduction

Subarachnoid hemorrhage (SAH) causes 5% of all strokes and has high morbidity and mortality. The cause for 85% of SAH cases is a rupture of an intracranial aneurysm. (1) The prevalence of aneurysmal subarachnoid hemorrhage (aSAH) is 6–11 per 100 000 people per year. The prevalence of ruptured aneurysms has been higher within Finnish and Japanese population. (1, 2, 3) Although less than 5% of strokes are caused by aSAH, it is the reason for one third of all stroke-related potential life lost years before the age of 65 (1, 3). The total mortality rate of the aSAH patients is 25–40%. About 20% of the patients remain dependent which means up to 55% regain independent function. Among those, some are, however, partly left with neurocognitive impairment. (1, 4, 5, 6)

Ruptured aneurysm usually bleeds into the subarachnoid space. Bleeding into the ventricles and brain tissue are also common. Toxic effects of the blood in the subarachnoid space cause primary brain injury together with transient global ischemia. One of the main causes for the secondary brain injury is delayed cerebral ischemia (DCI). (1) In addition to intracranial injuries, aSAH can cause multiple extracranial symptoms and disorders, including hemodynamic and respiratory failure, fluid and electrolyte imbalance and systemic inflammatory response syndrome (1, 4).

The main symptom of aSAH is generally described as “the most severe headache ever”. The beginning of the headache is sudden, in half of the cases the pain reaches its maximum within a minute. Other symptoms can be vomiting, loss of consciousness or focal neurological deficits. The most efficient way to diagnose or rule out aSAH is computed tomography (CT). (1)

Risk factors for aneurysms include chronic alcohol use, family history of intracranial aneurysms in first-degree relatives and some inherited diseases. Smoking, female sex and hypertension are risk factors for both formation and rupture of intracranial aneurysms. Cocaine abuse, older age, giant size of an aneurysm and aneurysm location in posterior circulation are risk factors for the rupture. (1, 2) Early intervention is a challenging surgical task, but it is associated with improved outcome irrespective of the treatment method (2). Endovascular coiling (poor outcome for 20%) seems to be a preferable aneurysm occlusion method in aSAH compared with neurosurgical clipping (poor outcome for 30%), but it is not suitable for all patients (2, 5). Therefore, both methods should be available for the treatment of aSAH patients.

Delayed cerebral ischemia (DCI) is one of the most common and serious complications after aSAH (2, 7). Earlier it was thought that the etiology of DCI was vasospasm (7). Nowadays it has been shown that DCI can occur

without it, although vasospasms most likely have some role in the pathogenesis of the DCI (3, 4 ,7). The mechanism behind DCI is not known with certainty and there are multiple hypotheses on which factors could indicate developing of the DCI (3, 4). At least the volume of bleeding, the location of the aneurysm, loss of cerebral autoregulation, smoking and metabolic stress are shown to be risk factors for DCI development (2, 7). Suggested mechanisms of DCI include loss of blood-brain integrity from early brain injury, initial cerebral edema, cortical spreading depression, and microthrombosis (2). Vasospasms and DCI are also associated with a single nucleotide polymorphism in the gene encoding nitric oxide synthase and polymorphisms in a plasminogen activator inhibitor 1 gene (4). High levels of C-reactive protein and IL-6 are associated with poor outcome and might have some role with the development of the DCI (2).

Even though DCI is a common complication, its early detection has been a difficult, especially with poor grade patients (4, 7, 8). Mild symptoms of DCI are hard to detect from sedated and ventilated patients (4, 9). Typical DCI symptoms are neurological deficits, such as hemiparesis, aphasia, apraxia, and neglect, and/or decreased consciousness (9). Intracranial Doppler (TCD) and cerebral angiography are both feasible techniques for detecting vasospasms but not DCI (2, 4). The early detection of DCI, even without vasospasm, might be possible with, in addition to clinical neurology status, continuous EEG (cEEG) monitoring but both hardware and software need artefact reduction and MRI-compatible electrodes. Since it takes considerable number of resources to interpret all the data, automated software ischemia detection software would make it possible to use cEEG monitoring with all aSAH patients. (8) Alpha/delta ratio (ADR) or alpha variability reductions are sensitive and specific for detecting DCI (7, 8). For now, the proposed diagnose criteria is below (figure 1). Criteria is based on neurological status and exclusion of other causes for neurological impairment. For differential diagnosis radiological imaging and laboratory investigations are mandatory. (9)

Approximated 30–40% of patients survived from aSAH suffer DCI between 3 and 14 days after initial aSAH (1, 3, 8). Up to half of aSAH patients with DCI have a poor outcome (3, 5). Only 6% of aSAH related deaths are caused by DCI but patients with DCI are more likely to be left with cognitive impairment based on MMSE scores (4, 6). DCI patients may have up to 5-fold risk for neuropsychological deficits compared with non-DCI aSAH patients (11). The deficits include mood disorders, fatigue and sleep disturbances (12).

Figure 1. Diagnose criteria of DCI by Mervyn D.I. Vergouwen, Marinus Vermeulen et al. (9)

The proposed definition of clinical deterioration caused by DCI is:

"The occurrence of focal neurological impairment (such as hemiparesis, aphasia, apraxia, hemianopia, or neglect), or a decrease of at least 2 points on the Glasgow Coma Scale (either on the total score or on one of its individual components [eye, motor on either side, verbal]). This should last for at least 1 hour, is not apparent immediately after aneurysm occlusion, and cannot be attributed to other causes by means of clinical assessment, CT or MRI scanning of the brain, and appropriate laboratory studies."

The proposed definition of cerebral infarction is:

"The presence of cerebral infarction on CT or MR scan of the brain within 6 weeks after SAH, or on the latest CT or MR scan made before death within 6 weeks, or proven at autopsy, not present on the CT or MR scan between 24 and 48 hours after early aneurysm occlusion, and not attributable to other causes such as surgical clipping or endovascular treatment. Hypodensities on CT imaging resulting from ventricular catheter or intraparenchymal hematoma should not be regarded as cerebral infarctions from DCI."

Table 1. Glasgow Coma Scale (10)

	EYES (opening)	**VERBAL**	**MOTOR**
SCORING	4 - Spontaneous 3 - To sound 2 - To pressure 1 - None	5 - Orientated 4 - Confused 3 - Words 2 - Sounds 1 - None	6 - Obey commands 5 - Localizing pain 4 - Normal flexion 3 - Abnormal flexion 2 - Extension 1 - None

There are multiple studies how to prevent DCI and which treatments could improve outcome. Still the only therapy with proven efficacy on both preventing and treating DCI is oral administration of an L-type calcium channel antagonist, nimodipine. (2, 3, 7, 9) New treatment methods studied without success include magnesium, statins and anti-inflammatory drugs (may improve one-year outcome). Drugs under evaluation are albumin, erythropoietin and dantrolene. In addition, drugs that may reduce risk for vasospasms and/or DCI include fasudil (may be even better for treating DCI than nimodipine, approved in Japan and China), thrombolysis (also reduced hydrocephalus and poor outcome) and nicardipine (also reduced mortality) but none of these is approved for use in Europe or USA. (2, 4)

As a part of larger study this evaluation will focus on DCI and neuropsychological deficits (NPDs). The aim of this prospective study is to evaluate the prevalence and the profile of NPDs after aSAH and the association between DCI and NPDs.

1.2 Aims of the study

The aim of this study was to find out the incidence and the type of the NPDs after aSAH and the association between DCI and NPDs. The results could affect how to assess cognitive impairments and carry out the rehabilitation of aSAH patients.

2 METHODS

2.1 Study protocol

This study was executed side by side with larger study *Delayed cerebral ischaemia after aneurysmal subarachnoid haemorrhage: a clinical observational trial* (Essi Raatikainen, Annukka Vahtera et al.). Only the methods concerning this study are described in the methods section. Besides these, e.g. continuous electroencephalography, daily blood samples and radiological examinations were recorded according to the larger study protocol.

2.1.1 Design

A prospective, observational clinical study.

2.1.2 Patients

60 consecutive critically ill patients with acute aSAH were recruited and studied in the Tampere University Hospital intensive care unit (ICU). All patients received a standard clinical care in the ICU and in the neurosurgical ward. The data during the acute phase and follow up until 16.11.2022 were included into this study analysis.

2.1.3 Inclusion criteria

- Age ≥ 18 years
- Admitted to the Tampere University Hospital ICU due to aSAH
- Acute subarachnoid hemorrhage (confirmed by computed tomography, CT, AND confirmed origin either with computed angiography [CTA] or digital subtraction angiography [DSA])
- Definite or approximated time for the onset of symptoms and delay to ICU admission no more than 24 hours
- Expected length of stay at least 120 hours in the Tampere University Hospital

2.1.4 Exclusion criteria

- Known pregnancy
- Any long-term anticoagulant or antithrombotic medication, except for low-dose aspirin
- Known active cancer or cirrhotic liver disease or end-stage renal disease requiring renal replacement therapy

2.1.5 Measured parameters and registered events

- Early brain injury (EBI) assessed
    - using Hunt and Hess grade at admission (table 2)
    - Subarachnoid hemorrhage early brain score (SEBES) from the primary head CT scan on a scale of 0 to 4 (table 3)
- Fisher grade is determined from the first head CT scan (table 4)
- The general clinical characteristics of the patients
- Presence of DCI assessed daily from 48 hours up to 14 days after the onset of aSAH, defined as
    - Decline of Glasgow Coma Scale (GCS) (table 1) of 2 or more points for at least one hour and cannot be explained by other features (e.g. seizure, metabolic disturbance, infection, hydrocephalus or disruption of cerebrospinal fluid [CSF] circulation)
    - New neurological symptom lasting for at least one hour and cannot be explained by other features (e.g. seizure or metabolic disturbance, infection, hydrocephalus, or disruption of cerebrospinal fluid [CSF] circulation)

- New ischemia on neuroimaging (within 6 weeks after SAH, which is not present on the CT or MR scan between 24 and 48 hours after early aneurysm occlusion) and not related to primary aSAH or neurosurgery (surgical clipping or endovascular occlusion)

- Patients' neurological outcome up to day 90 by extended Glasgow Outcome Score (eGOSE) (table 5) and by neuropsychological evaluation in patients who gain functional independence
    - Patients met neuropsychologist who estimated their neuropsychological outcome using Boston naming test (BNT), Rey-Osterrieth Complex Figure Test (ROCFT), Wechsler memory scale, 3rd edition (WMS-III), Wechsler Adult Intelligence Scale, 4th edition (WAIS-IV), Trail Making Test A and B (TMA and TMB), STROOP 45 s, Beck Depression Inventory, 2nd edition (BDI-II), clock-face, fluency and pattern copying (table 6)

Table 2. Hunt and Hess grade (13)

CATEGORY	CRITERIA
GRADE I	Asymptomatic, or minimal headache and slight nuchal rigidity.
GRADE II	Moderate to severe headache, nuchal rigidity, no neurological deficit other than cranial nerve palsy.
GRADE III	Drowsiness, confusion, or mild focal deficit.
GRADE IV	Stupor, moderate to severe hemiparesis, possibly early decerebrate rigidity and vegetative disturbances.
GRADE V	Deep coma, decerebrate rigidity, moribund appearance.

Table 3. Subarachnoid hemorrhage early brain score (SEBES) (14)

DESCRIPTION	POINTS
ABSENCE OF VISIBLE SULCI CAUSED BY EFFACEMENT OF SULCI	0–1 per slice per side
ABSENCE OF VISIBLE SULCI WITH DISRUPTION OF THE GRAY–WHITE MATTER	0–1 per slice per side
TWO PREDETERMINED LEVELS IN EACH HEMISPHERE: **1. At the level of the insular cortex showing the thalamus and basal ganglion above the basal cistern** **2. At the level of the centrum semiovale above the level of the lateral ventricle**	**TOTAL:** Minimum score: 0 Maximum score: 4

Table 4. Fisher grade (15)

SCORE	DESCRIPTION
1	No blood detected
2	Diffuse deposition or thin layer with all vertical layers of blood < 1mm thick
3	Localized clots and/or vertical layers of blood ≥ 1mm thick
4	Diffuse or no subarachnoid blood, but with intracerebral or intraventricular clots

Table 5. Extended Glasgow Outcome Scale (eGOSE) (16)

SCORE	DESCRIPTION
1. DEAD	Dead.
2. VEGETATIVE STATE	Alive but unconscious.
3. LOWER SEVERE DISABILITY	Conscious but dependent, needs frequent help.
4. UPPER SEVERE DISABILITY	No need for frequent help but needs some help.
5. LOWER MODERATE DISABILITY	Independent but unable to participate one or more life roles.
6. UPPER MODERATE DISABILITY	Able to participate but limited in one or more roles.
7. LOWER GOOD RECOVERY	Returned to normal life with some symptoms.
8. UPPER GOOD RECOVERY	Fully returned to normal life.

2.2 Ethical aspects

All patients received a routine care in the ICU and in the neurosurgical ward. This study provides new information from neuropsychological deficits after aSAH, especially in case of DCI. This follows the guideline for the management of aSAH patients by American Heart Association/American Stroke Association, which recommends that after discharge aSAH survivors are referred for a comprehensive evaluation, including cognitive, behavioral, and psychosocial assessments (17). All included patients agreed to take part to the larger study and to neurological studies. Since this study does not add any measured parameters or registered events and all information is processed with care and confidence, I do not see any ethical issues in this study protocol.

2.3 Analysis

The aim of this study was to find out the prevalence and profile of NPDs and the association between NPDs and DCI. Hunt and Hess score and Fisher grade at admission and extended Glasgow Outcome Score at 90 days after aSAH were used to estimate patients' neurological status. The existence of DCI was diagnosed as described earlier. NPDs were estimated with neuropsychological reviews (table 6).

The research material, demographics and the numeral data of neuropsychological reviews are shown quantitatively. There is also qualitative description of neuropsychological reviews.

Almost all the results could be converted to Z-scores which takes account of patients' age and often also gender. Therefore, it's been used to compare results. Z-score means how many standard deviations from the mean score the result is. (Table 7) Only clock-face and pattern copying couldn't be converted. In clock-face both setting the time and telling the time are scored from 0 to 5: both have 5 parts which are scored either

right or false. Copying a cube is scored from 0 to 4 based on how correct the copied picture is using Consortium to Establish a Registry for Alzheimer´s Disease (CERAD)-scoring (table 8).

Table 6. Measured variables.

	NAME OF THE TEST	VARIABLE
VERBAL FUNCTIONS	Boston Naming Test (BNT)	Raw score and Z-score
	WAIS-IV / similarities	Raw score, standardized score and Z-score
VISUAL FUNCTIONS	ROCFT / copying	Time, raw score and Z-score
	WAIS-IV / block design	Raw score, standardized score and Z-score
	Clock-face	Setting the time, X/5 Telling the time, X/5
	Pattern copying / cube	CERAD-scoring, X/4 (table 8)
MEMORY AND LEARNING	WMS-III / logical memory I	Raw score, standardized score and Z-score
	WMS-III / logical memory II	Raw score, standardized score and Z-score
	WMS-III / word list I	Raw score, standardized score and Z-score
	WMS-III / word list II	Raw score, standardized score and Z-score
	WMS-III / word list, recognition	Raw score, standardized score and Z-score
	WMS-III / visual memory I	Raw score, standardized score and Z-score
	WMS-III / visual memory II	Raw score, standardized score and Z-score
	ROCFT / immediate recall	Raw score and Z-score
ATTENTIVENESS AND EXECUTIVE FUNCTIONS	WMS-III / digit span	Raw score, standardized score and Z-score
	WMS-III / digit span forward	Raw score and Z-score
	WMS-III / digit span backward	Raw score and Z-score
	Verbal fluency / animal- and s-words	Raw score and Z-score
	Trail-Making A (TMA)	Time and Z-score
	Trail-Making B (TMB)	Time and Z-score
	WAIS-IV / coding	Raw score, standardized score and Z-score
	Stroop / 45s	Raw score and Z-score

Flowchart 1. Patient selection for the study

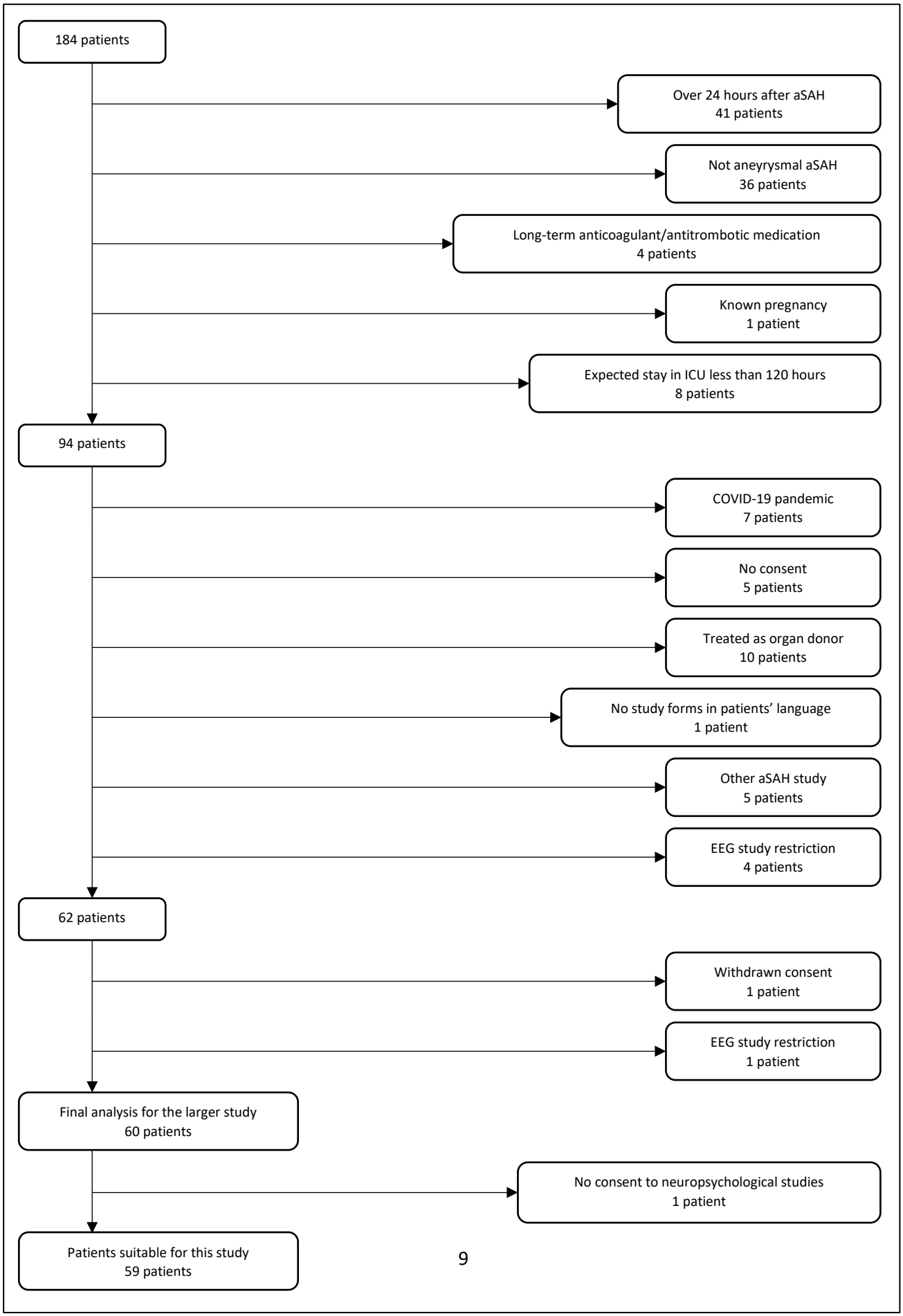


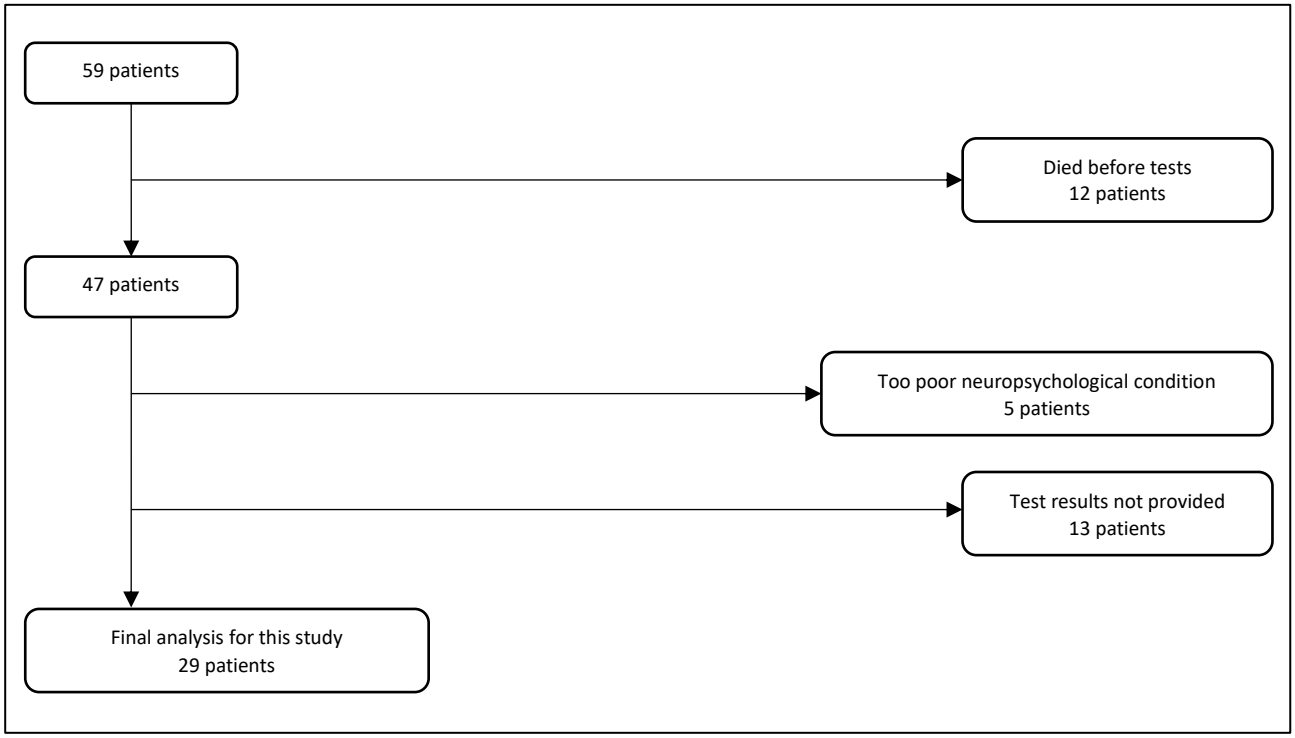
Table 7. Z-scores.

Z-SCORE	MEANING
-3	Result extremely poor
-2	Result significantly lower than age standards
-1	Result mildly lower than age standards
0	Age-standard result
1	Result mildly better than age standards
2	Result significantly better than age standards
3	Result extremely good

Table 8. Consortium to Establish a Registry for Alzheimer´s Disease CERAD-scoring for copying a cube.

POINTS	DESCRIPTION
0 OR 1	Three-dimensional shape
0 OR 1	Front side in the right position
0 OR 1	Inner lines correctly drawn
0 OR 1	Opposite sides correctly drawn (within 10 degrees accuracy)
0–4	Total

Flowchart 2. Results of the neuropsychological studies obtained



3 RESULTS

This study included 60 patients but one of them did not give consent to neuropsychological studies (Flowchart 1). Patients' mean age was 59 ± 14 years. 45/60 (78 %) of patients were female. Patients were treated with either endovascular coiling (63 %), stent-assisted coiling (13 %) or surgical clipping (22 %), except one patient who did not receive treatment (thrombosed aneurysm and poor neurological status, 3 %). 25 (42 %) of the patients were diagnosed with DCI, 18 based on GCS decline, 3 based on focal deficits and 4 based on both. All 60 patients had severe bleedings based on the Fisher grade (grades 3–4). After three months the neurological outcome was good (eGOSE result 5–8) in 32 (53 %) of patients. (Table 9)

Consent to neuropsychological testing was received from 59 patients. Twelve (20 %) patients died in acute phase, all caused by aSAH. In five patients, neuropsychological outcome was too poor for neuropsychological testing, one of them had Alzheimer before aSAH and other four were left with poor neuropsychological outcome after aSAH. In 13 patients, results from neuropsychological tests were not provided or the studies were not performed. At least one test was performed to 29 patients, all of whom were included to this study. (Flowchart 2) Performed pattern of test varied widely, and most of these are not able to utilize in this study. All tests were performed to four patients (table 13). BDI was done to 5 of 59 patients and therefore was not included to the analysis.

Ten of 29 (31 %) patients finally included to this analysis were diagnosed with DCI. From 12 patients who died four patients were diagnosed with DCI. Twenty (43 %) of 47 patients who survived aSAH were diagnosed with DCI. Three of those five patients left with too poor neurological outcome were diagnosed with DCI. Patients with missing test results 7/13 (54 %) were diagnosed with DCI. Diagnosis of DCI was not associated with poor neurological outcome (poor eGOSE 1–4 52 % of DCI patients and 43 % of non-DCI patients, p = 0,66) unlike Hunt and Hess grade (p = 0,62) and Fisher grade (p = 0,04) were (table 9).

In neuropsychological testing the mean Z-scores were mostly close to the age standards: most were between -1 and 0 and some were a bit above 0. There was no difference (at least 1 point difference in mean scores) between patients with or without DCI diagnose in verbal or visual functions. In tests concerning memory and learning there was no difference except the mean Z-score of DCI patients in WMS-III's part visual memory I was better than those without DCI. In tests concerning attentiveness and executive functions all patients' mean Z-scores were mostly below the age standards, especially in both Trail-Making tests. DCI patients' mean Z-score was higher than those without DCI in verbal fluency's part s-words, TMA and Stroop 45s. In WMS-III's part digit span patients without DCI had higher mean Z-score than patients diagnosed with DCI. (Table 14.1–14.24)

Table 9. Baseline characteristics of the study population

CHARACTERISTIC	TOTAL N = 60	DCI N = 25 (42 %)	NO DCI N = 35 (58 %)	P-VALUE	NEUROLOGICAL OUTCOME		P-VALUE
					eGOSE 1–4 n = 28 (47 %)	eGOSE 5–8 n = 32 (53 %)	
AGE, Y	59±14	58±16	60±13		64±13	55±14	
RANGE	(31–82)	(31–78)	(32–82)		(32–81)	(31–82)	
FEMALE	47 (78 %)	18 (72 %)	29 (83 %)		24 (86 %)	23 (72 %)	
HYPERTENSION	21 (35 %)	9 (36 %)	12 (34 %)		9 (32 %)	12 (38 %)	
DIABETES	5 (8 %)	1 (4 %)	4 (11 %)		3 (11 %)	2 (6 %)	
LOW-DOSE ASPIRIN	4 (7 %)	2 (8 %)	2 (6 %)		2 (7 %)	2 (6 %)	
SMOKING							
YES	20 (33 %)	8 (32 %)	12 (34 %)		9 (32 %)	11 (34 %)	
NO	22 (37 %)	9 (36 %)	13 (37 %)		8 (29 %)	14 (44 %)	
UNKNOWN	18 (30 %)	8 (32 %)	10 (29 %)		11 (39 %)	7 (22 %)	
FISHER SCALE							
3	31 (52 %)	11 (44 %)	20 (57 %)	0,46	10 (36 %)	21 (66 %)	0,04
4	29 (48 %)	14 (56 %)	15 (43 %)		18 (64 %)	11 (34 %)	
ANEURYSM LOCATION							
ANTERIOR	44 (73 %)	21 (84 %)	23 (66 %)	0,20	23 (82 %)	21 (66 %)	
POSTERIOR	16 (27 %)	4 (16 %)	12 (34 %)		5 (18 %)	11 (34 %)	
TREATMENT MODALITY							
ENDOVASCULAR	38 (63 %)	20 (80 %)	18 (51 %)		16 (57 %)	22 (69 %)	0,25
STENT-ASSISTED COILING	8 (13 %)	2 (8 %)	6 (17 %)		3 (11 %)	5 (16 %)	
SURGICAL	13 (22 %)	3 (12 %)	10 (29 %)		8 (29 %)	5 (16 %)	
NO TREATMENT	1 (2 %)	0 (0 %)	1 (3 %)		1 (4 %)	0 (0 %)	

Table 10. Hunt and Hess grade

GRADE		PATIENTS	TOTAL
MILD TO FAIR	1	7 (12 %)	37 (62 %)
	2	13 (22 %)	
	3	17 (28 %)	
SEVERE	4	12 (20 %)	23 (38 %)
	5	11 (18 %)	

Table 11. SEBES score

SCORE	PATIENTS
0	17 (28 %)
1	5 (8 %)
2	19 (32 %)
3	8 (13 %)
4	11 (18 %)

Table 12. eGOSE scale

SCALE		PATIENTS	TOTAL
POOR OUTCOME	1	12 (20 %)	28 (47 %)
	2	1 (2 %)	
	3	10 (17 %)	
	4	5 (8 %)	
GOOD OUTCOME	5	4 (7 %)	32 (53 %)
	6	6 (10 %)	
	7	8 (13 %)	
	8	14 (23 %)	

Table 13. Neuropsychological studies performed

Pt	DCI	d	Verbal		Visual					Memory and learning								Attentiveness and executive functions								
			1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.	16.	17.	18.	19.	20.	21.	22.	23.	24.
3	-	22	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
6	-	21	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
7	-	2	X	X	-	X	X	-	X	X	-	-	-	-	-	-	-	X	X	X	X	X	X	X	X	X
8	-	1	-	X	X	X	-	-	-	X	X	X	X	X	-	-	-	X	X	X	X	X	X	X	X	-
11	X	19	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
13	-	1	-	-	-	X	-	-	-	-	X	X	-	-	-	X	X	-	-	-	-	-	-	-	X	-
14	-	6	-	X	X	X	X	X	X	-	X	X	X	X	X	-	-	X	X	X	X	X	X	X	X	X
15	-	1	-	X	X	X	-	-	-	X	X	X	-	-	-	-	-	X	X	X	X	X	X	X	X	X
16	X	1	-	X	X	X	X	X	X	X	X	X	-	-	-	-	-	X	X	X	X	X	X	X	X	X
18	X	2	-	-	-	-	-	-	X	-	X	X	-	-	-	-	-	X	X	X	X	X	X	X	X	X
21	X	14	X	X	X	X	X	X	X	X	X	X	X	X	-	X	X	X	X	X	X	X	X	X	X	X
24	X	1	-	X	X	X	X	X	X	X	X	X	X	X	X	-	-	X	X	X	X	X	-	X	X	X
25	-	1	-	-	-	-	X	X	X	-	X	X	-	-	-	-	-	-	-	-	-	-	X	X	-	-
26	X	15	-	X	-	X	-	-	-	-	X	X	X	X	X	X	X	X	X	X	X	X	-	-	-	-
33	-	14	-	X	X	X	X	X	X	-	X	X	X	X	X	-	-	X	X	X	X	X	X	X	X	X
34	-	1	-	X	-	X	-	-	X	-	X	X	-	-	-	-	-	X	-	-	-	-	X	X	X	-
38	-	2	X	X	X	X	-	-	-	X	X	X	X	X	X	-	-	X	X	X	X	X	X	X	X	X
39	-	1	X	X	X	X	-	-	X	X	X	X	X	X	-	-	-	X	-	-	-	-	X	X	X	-
40	X	2	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	X	X	X	X	-	X	-	X	-
42	X	1	-	X	X	X	X	X	X	X	X	X	-	-	-	-	-	X	X	X	X	X	-	X	X	X
44	X	1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
46	-	1	-	X	-	X	X	-	X	-	X	X	-	-	-	-	-	X	-	-	-	-	X	X	X	-
47	-	1	-	X	X	X	-	-	X	-	X	X	-	-	-	-	-	X	X	X	X	-	X	X	-	-
48	-	2	-	X	X	X	-	-	X	-	X	X	-	-	-	-	-	X	-	-	-	-	X	X	X	-
50	X	4	-	X	-	-	-	-	X	-	X	X	-	-	-	-	-	X	X	X	X	-	-	-	-	-
51	-	3	-	-	-	-	-	-	X	-	-	-	-	-	-	-	-	-	-	-	X	X	-	-	-	-
54	-	2	-	X	X	X	-	-	-	X	X	-	-	-	-	-	-	X	X	X	X	X	X	X	X	X
55	-	1	-	-	-	-	X	X	X	-	-	-	-	-	-	-	-	-	-	-	-	-	X	-	-	-

- Pt: Patient number
- d: Time between the hemorrhage and neuropsychological studies (months)
- Verbal functions:
    - 1. Boston Naming Test (BNT)
    - 2. WAIS-IV / similarities
- Visual functions:
    - 3. ROCFT / copying
    - 4. WAIS-IV / block design
    - 5. Clock-face / setting
    - 6. Clock-face / telling
    - 7. Pattern copying / cube
- Memory and learning:
    - 8. ROCFT / immediate recall
    - 9. WMS-III / logical memory I
    - 10. WMS-III / logical memory II
    - 11. WMS-III / word list I
    - 12. WMS-III / word list II
    - 13. WMS-III / word list, recognition
    - 14. WMS-III / visual memory I
    - 15. WMS-III / visual memory II
- Attentiveness and executive functions
    - 16. WMS-III / digit span
    - 17. WMS-III / digit span forward
    - 18. WMS-III / digit span backward
    - 19. Verbal fluency / animal-words
    - 20. Verbal fluency / s-words
    - 21. Trail-Making A (TMA)
    - 22. Trail-Making B (TMB)
    - 23. WAIS-IV / coding
    - 24. Stroop / 45s

Table 14.1. Boston Naming Test (BNT), in all patients, mean 0,91 (SD 0,78), n = 8

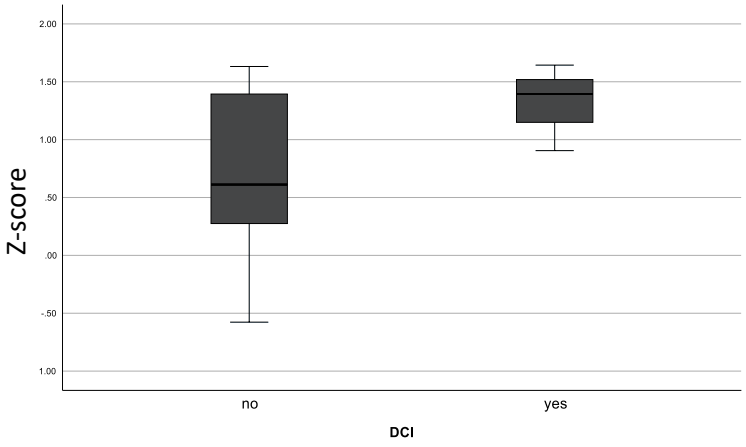


Table 14.2. WAIS-IV / similarities, in all patients, mean -0,87 (SD 1,12), n = 23

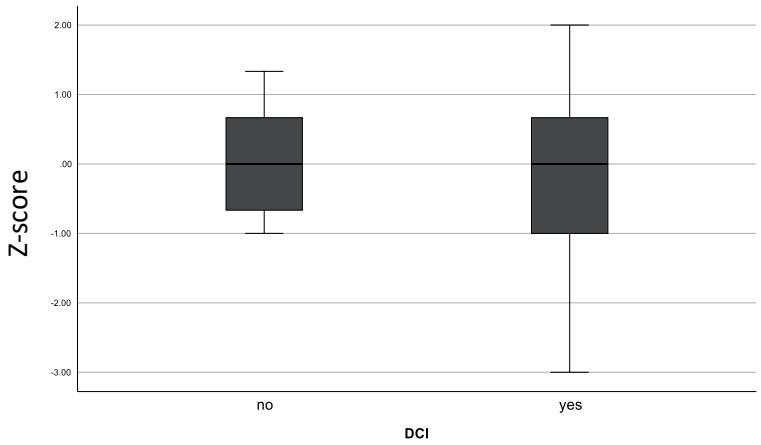


Table 14.3. ROCFT / copying, in all patients, mean 0,64 (SD 0,41), n = 17

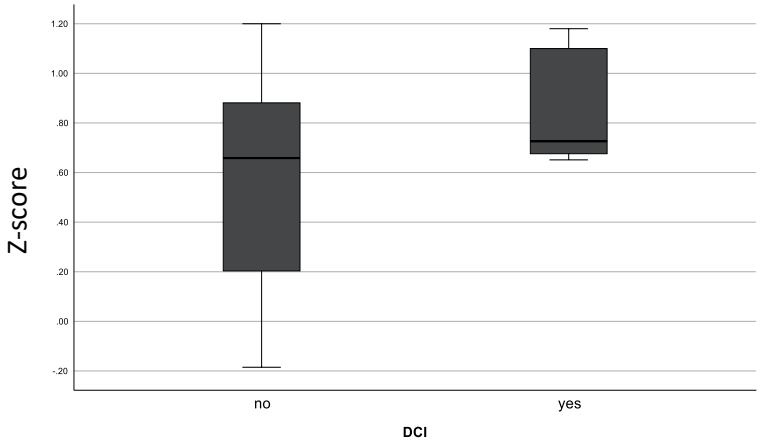


Table 14.4. WAIS-IV / block design, in all patients, mean -0,20 (SD 1,32), n = 22

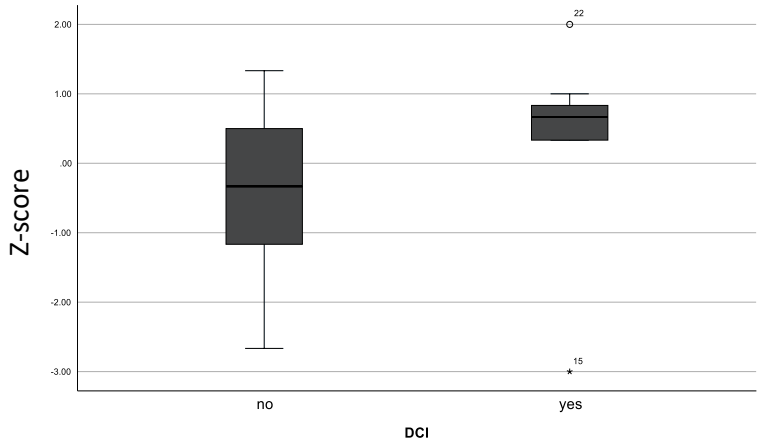


Table 14.5. Clock-face / setting, in all patients, mean 4,64 (SD 0,93), n = 14

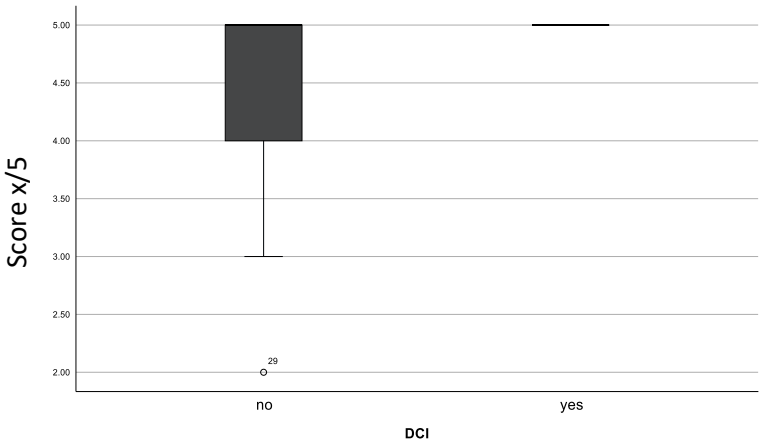


Table 14.6. Clock-face / telling, in all patients, mean 4,92 (SD 0,29), n = 12

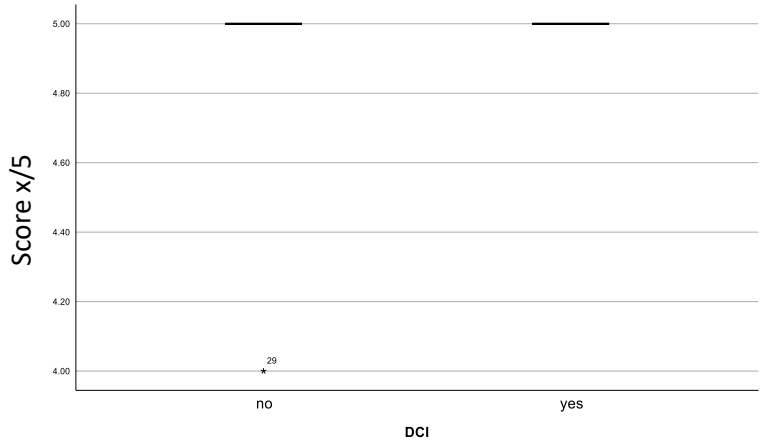


Table 14.7. Pattern copying / cube, in all patients, mean 3,23 (SD 1,34), n = 22

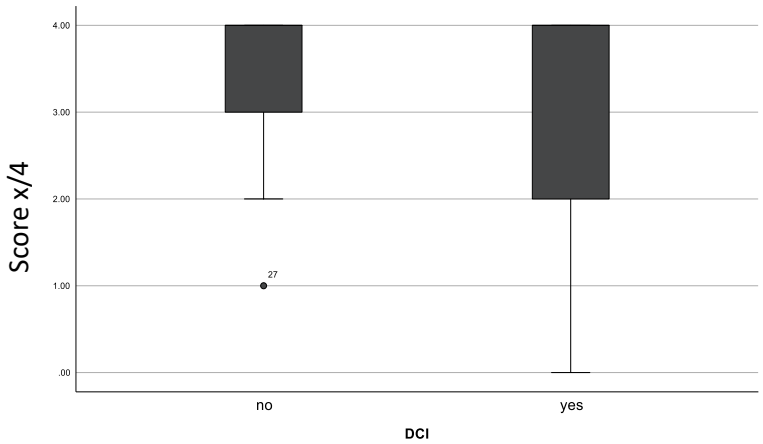


Table 14.8. ROCFT / immediate recall, in all patients, mean -0,46 (SD 1,12), n = 14

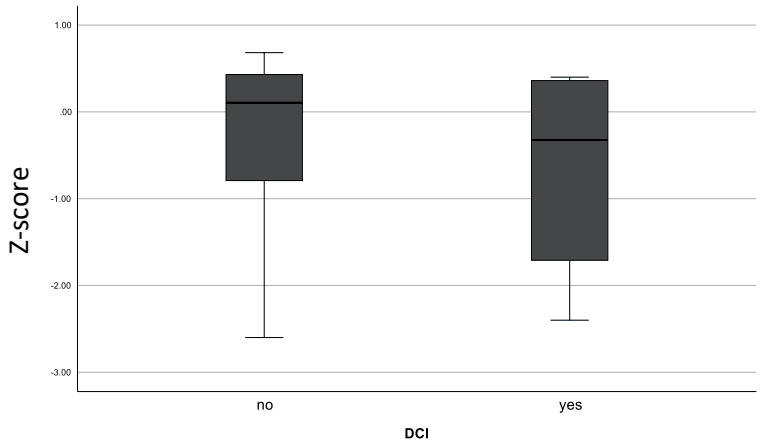


Table 14.9. WMS-III / logical memory I, in all patients, mean -0,51 (SD 1,08), n = 25

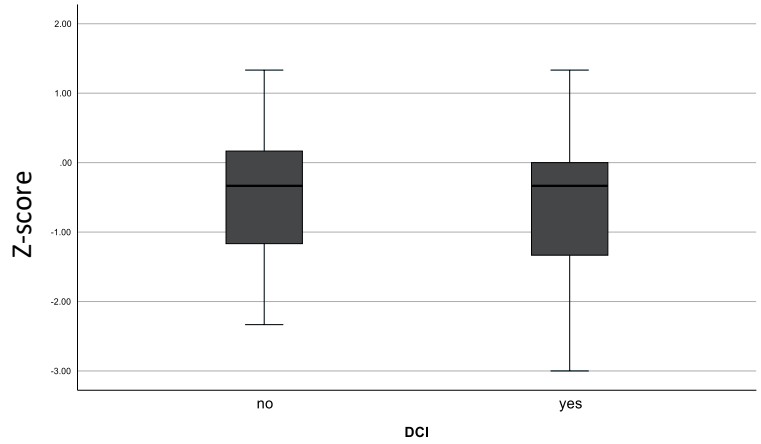


Table 14.10. WMS-III / logical memory II, in all patients, mean -0,47 (SD 1,28), n = 24

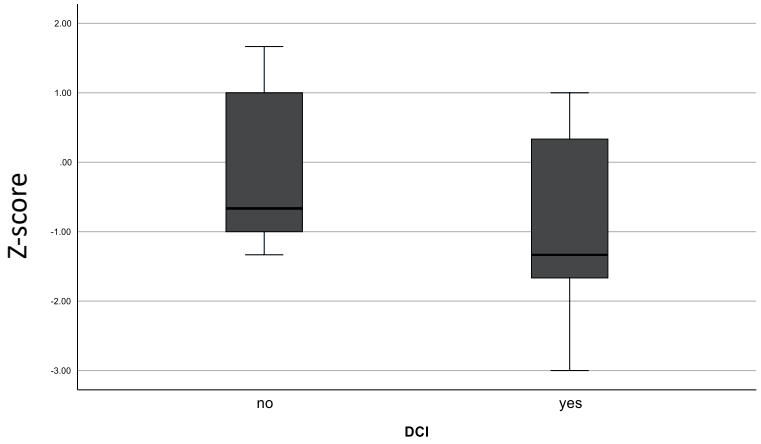


Table 14.11. WMS-III / word list I, in all patients, mean -0,56 (SD 1,03), n = 12

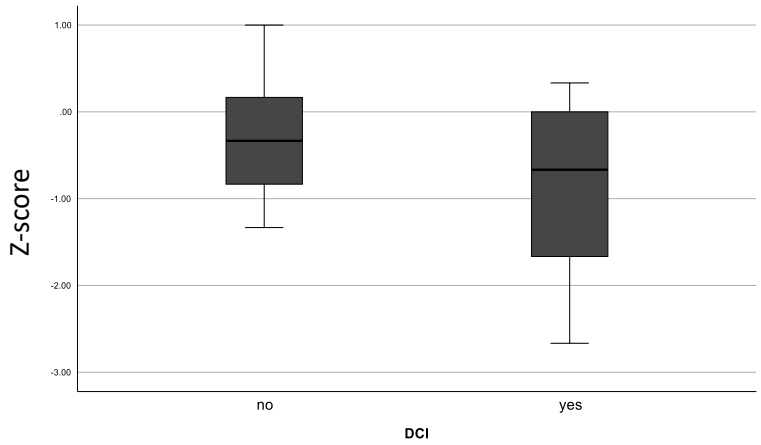


Table 14.12. WMS-III / word list II, in all patients, mean -0,75 (SD 1,33), n = 12

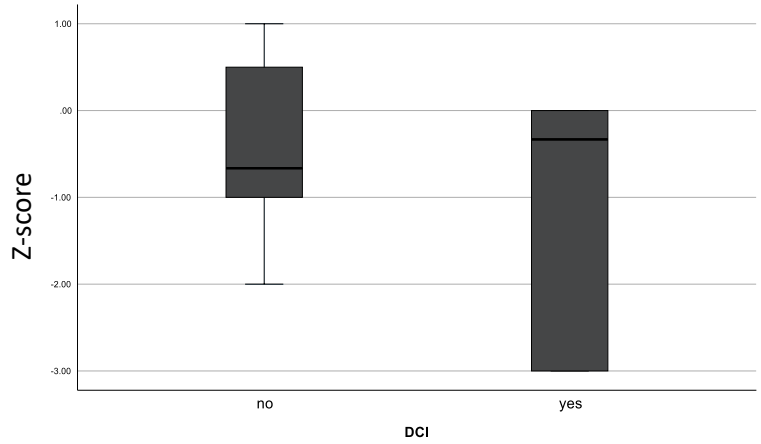


Table 14.13. WMS-III / word list, recognition, in all patients, mean 0,41 (SD 1,23), n = 9

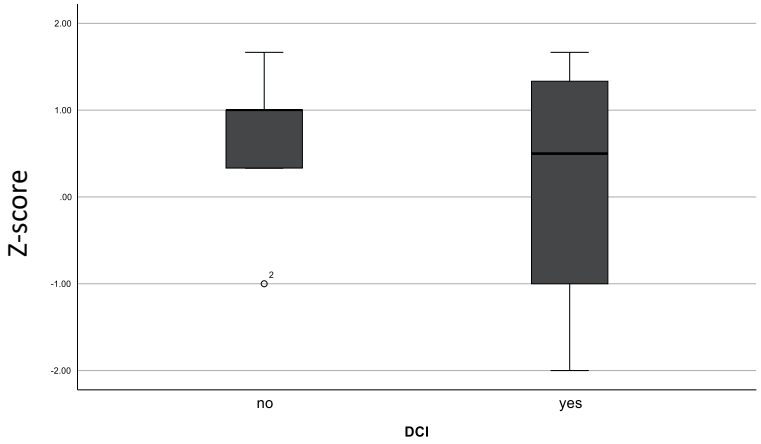


Table 14.14. WMS-III / visual memory I, in all patients, mean 0,06 (SD 1,20), n = 6

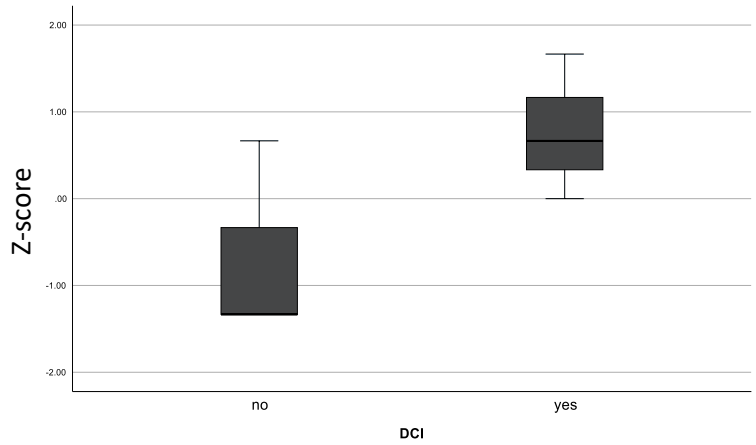


Table 14.15. WMS-III / visual memory II, in all patients, mean -0,50 (SD 1,50), n = 6

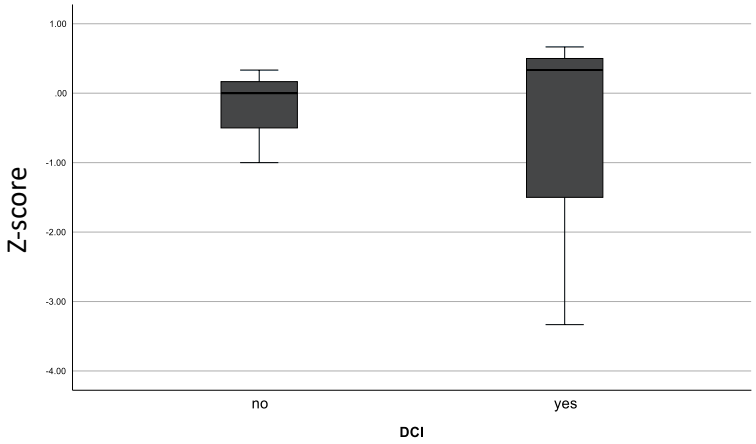


Table 14.16. WMS-III / digit span, in all patients, mean 0,09 (SD 0,92), n = 23

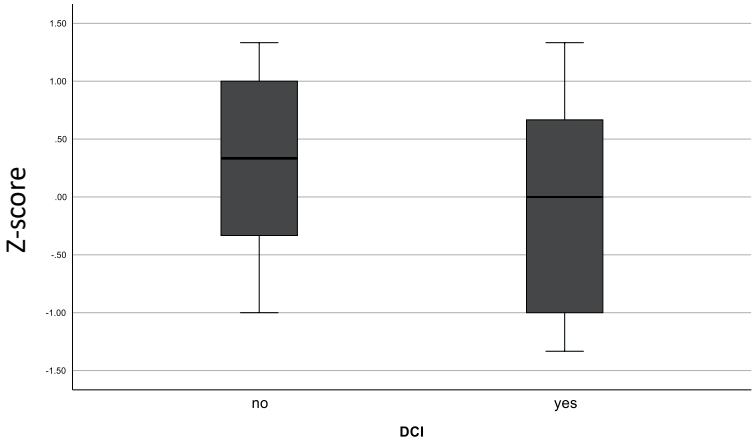


Table 14.17. WMS-III / digit span forward, in all patients, mean 0,55 (SD 0,70), n = 19

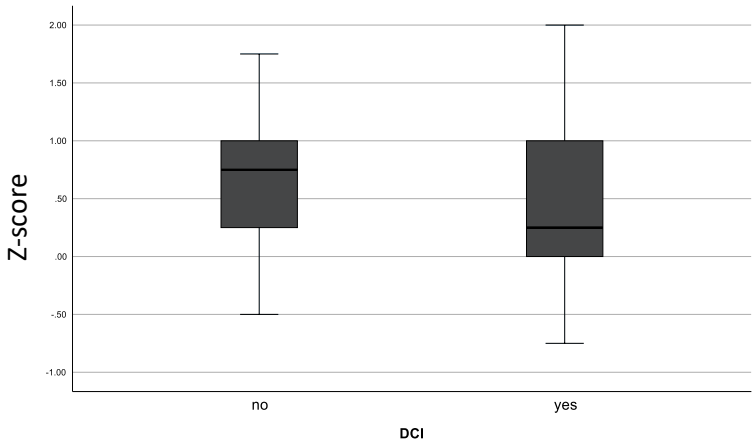


Table 14.18. WMS-III / digit span backward, in all patients, mean -0,42 (SD 1,32), n = 19

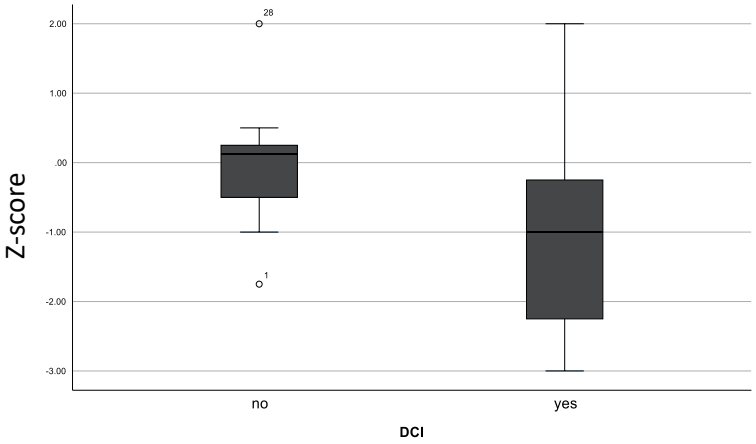


Table 14.19. Verbal fluency / animal-words, in all patients, mean -1,06 (SD 1,28), n = 21

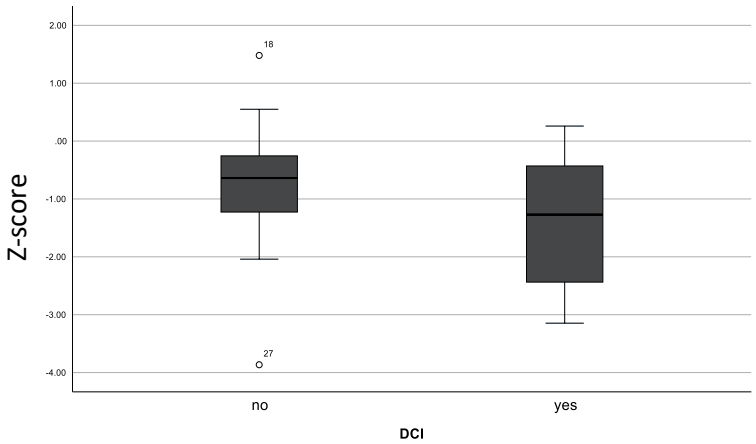


Table 14.20. Verbal fluency / s-words, in all patients, mean -0,71 (SD 1,53), n = 17

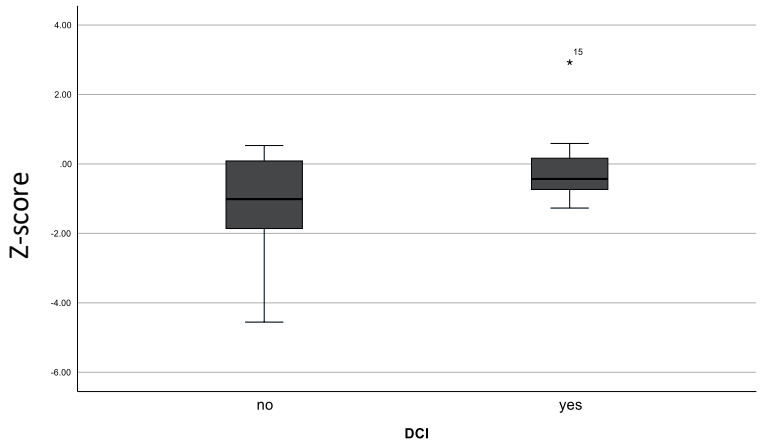


Table 14.21. Trail-Making A (TMA), in all patients, mean -2,23 (SD 6,65), n = 20

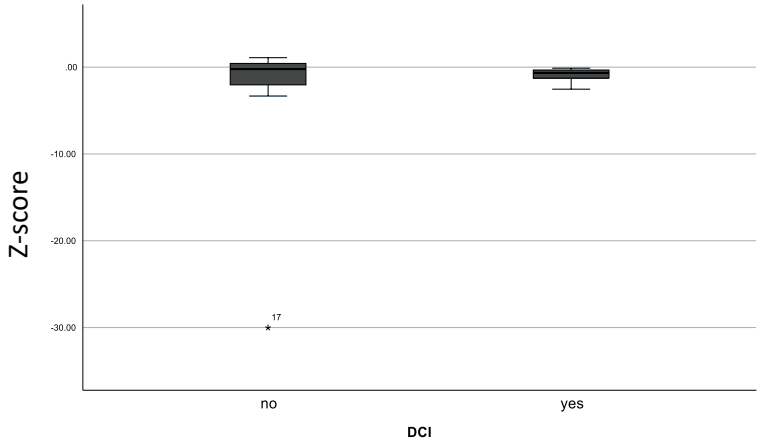


Table 14.22. Trail-Making B (TMB), in all patients, mean -1,56 (SD 3,43), n = 21

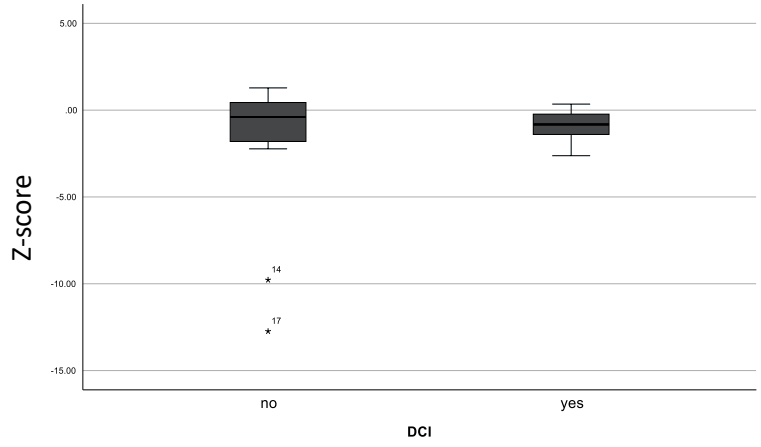


Table 14.23. WAIS-IV / coding, in all patients, mean -0,52 (SD 0,91), n = 22

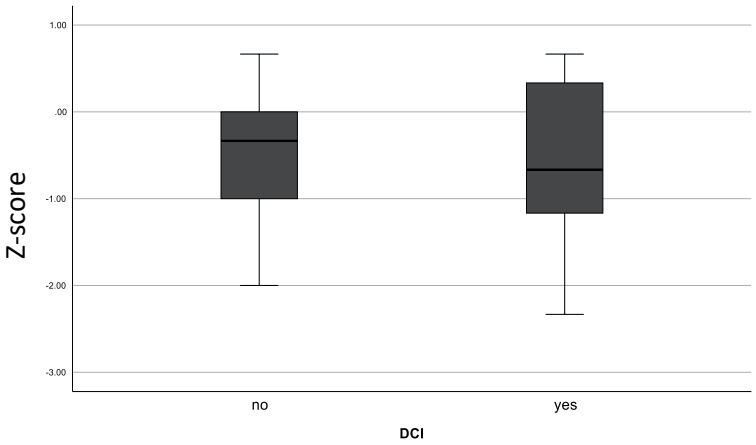
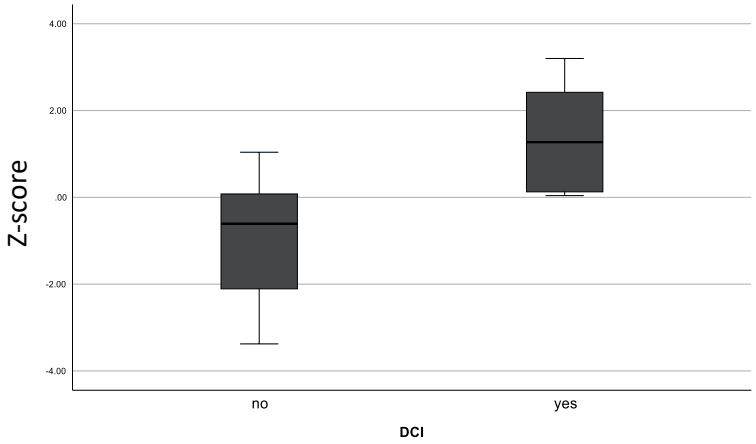


Table 14.24. Stroop / 45s, in all patients, mean 0,05 (SD 1,82), n = 14



4 DISCUSSION

In this study 20 % of the patients died because of aSAH, which is less than expected mortality rate of 25–40 % (1, 4). This is mostly caused by excluding patients with no expectation of surviving at least 120 hours. The percentage of surviving patients diagnosed with DCI 44 % was mildly higher than expected amount 30–40 % (1, 3, 8). In this study, there were no association between DCI and poor neurological outcome, unlike in previous studies where the risk for poor neurological outcome was up to 5-fold higher in patients with DCI (11).

In neuropsychological studies the mean Z-scores were close to the age standards: most were between -1 and 0 and some a bit above 0. In attentiveness and executive functions patients of this study were mostly below the age standards, especially in both Trail-Making tests. There are some previous studies with similar results concerning both general neuropsychological outcome and attentiveness and executive functions. However,

these studies included also non-aneurysmal subarachnoid hemorrhages (18, 19, 20, 21). In one study concerning aSAH, attention deficits were also reported but general neuropsychological outcome was poorer (22).

In this study there was no obvious difference in neuropsychological outcome between patients with DCI and without DCI. At some tests patients diagnosed with DCI performed better than patients without DCI. I could not find any previous studies where the neuropsychological outcome of DCI patients would not have been poorer. In one study though the difference between DCI and non-DCI patients narrowed during 3 months follow-up (23). In earlier studies DCI patients have had up to 5-fold risk for neuropsychological deficits including mood disorders, fatigue and sleep disturbances (11, 12). DCI patients have also been more likely to be left with cognitive impairment based on MMSE scores (6).

There are several limitations in this study. One main problem is that different test patterns for neuropsychological evaluation were used, which makes it difficult to compare patients' neuropsychological outcomes. There were notable differences even within the same health care district. Still, it is understandable that all tests can't be used to all patients. However, this is probably not the only reason. In future, it would be preferable to use the same set of tests in all patients. Other option is to write more detailed referrals, so the neuropsychologists would know which tests would be most useful.

Using private services to do neuropsychological testing might otherwise be as good option as public healthcare but while doing studies it seems to be harder to get the original test results needed for analysis. Other test relating factors concerning this study are human errors when copying data between multiple files and different age ranges in different tests. For example, with some tests the oldest age range with Z-scores was over 45 and with other tests the oldest was over 85. In addition, all tests did not take account of patients' gender.

Our patient sample, 60 or 59, was relatively small, especially when we got the test results from 29. Of course, also poor outcome for 16 patients (death or poor neuropsychological state caused by aSAH) is also a finding. From those 16 patients 7 (44 %) were diagnosed with DCI. Besides the sample size being small, for some patients the tests were done less than a month after the aSAH and for some patients they were done after almost two years. This gives some patients much more time to recover from aSAH which can affect the results.

It might be useful to standardize which test are used to evaluate patients after SAH. At least that could lead to better understanding on differences between DCI and non-DCI patients. There is also a need for studies, which asses the most valid tests to use in SAH patients. A larger study, where the same set of tests would be performed to each surviving patient within the determined time limit, could provide better and more reliable information.

In conclusion, in this study all patients with aSAH performed close to age-standards in neuropsychological testing, mostly mildly under. In this study, DCI did not lead to poor neuropsychological outcome as often than expected (3,5). The differences in neuropsychological test results between DCI patients and non-DCI patients were minor. This issue needs further evaluations with larger study populations and validated, widely used test patterns.

5 ACKNOWLEDGEMENTS

Special thanks to neuropsychologist Eija Rosti-Otajärvi for sharing her knowledge and expertise with neuropsychological studies. Thanks should also go to my supervisor Eija Junttila for support and great feedback every step of the writing process.

REFERENCES

1. **Macdonald, R. Loch and Schweizer, Tom A.** Spontaneous subarachnoid haemorrhage. *Lancet.* 2017. 389: 655-66. doi: 10.1016/S0140-6736(16)30668-7.

2. **D'Souza, Stanlies.** Aneurysmal Subarachnoid Hemorrhage. *J Neurosurg Anesthesiol.* 2015 Jul. 27(3): 222–240. doi: 10.1097/ANA.0000000000000130.

3. **Flynn, Liam and Andrews, Peter.** Advances in the understanding of delayed cerebral ischaemia after aneurysmal subarachnoid haemorrhage. *F1000Res.* 2015. 4: 1200. doi: 10.12688/f1000research.6635.1.

4. **Macdonald, R. Loch.** Delayed neurological deterioration after subarachnoid haemorrhage. *Nat. Rev. Neurol.* 2014. 10: 44-58. doi: 10.1038/nrneurol.2013.246.

5. **Dorhout Mees, Sanne M. et al.** Occurrence and impact of delayed cerebral ischemia after coiling and after clipping in the International Subarachnoid Aneurysm Trial (ISAT). *J Neurol.* 2012 Apr. 259(4): 679–683. doi: 10.1007/s00415-011-6243-2.

6. **Eagles, Matthew E., Tso, Michael K. and Macdonald, R. Loch.** Cognitive Impairment, Functional Outcome, and Delayed Cerebral Ischemia After Aneurysmal Subarachnoid Hemorrhage. *World Neurosurg.* 2019 Apr. 124: e558-e562. doi: 10.1016/j.wneu.2018.12.152.

7. **Francoeur, Charles L. and Mayer, Stephan A.** Management of delayed cerebral ischemia after subarachnoid haemorrhage. *Crit Care.* 2016. 20: 277. doi: 10.1186/s13054-016-1447-6.

8. **Muniz, C. F., Shenoy, A. V. et al.** Clinical development and implementation of an institutional guideline for prospective EEG monitoring and reporting of delayed cerebral ischemia. *J Clin Neurophysiol.* 2016 Jun. 33(3): 217–226. doi: 10.1097/WNP.0000000000000281.

9. **Vergouwen, Mervyn D. I., Vermeulen, Marinus et al.** Definition of Delayed Cerebral Ischemia After Aneurysmal Subarachnoid Hemorrhage as an Outcome Event in Clinical Trials and Observational Studies. Proposal of a Multidisciplinary Research Group. *Stroke.* 2010 Oct. 41(10):2391-5. doi: 10.1161/STROKEAHA.110.589275.

10. **Royal College of Physicians and Surgeons of Glasgow.** Glasgow Coma Scale. [Online] [Viitattu: 2. October 2022.] https://www.glasgowcomascale.org/.

11. **Stienen, Martin N., Smoll, Nicolas R. et al.** Delayed Cerebral Ischemia Predicts Neurocognitive Impairment Following Aneurysmal Subarachnoid Hemorrhage. *World Neurosurg.* 2014 Nov. 82(5): e599-605. doi: 10.1016/j.wneu.2014.05.011.

12. **Macdonald, R. L., Al-Khindi, T. and Schweizer, T. A.** Cognitive and functional outcome after aneurysmal subarachnoid hemorrhage. *Stroke.* s.l. : American Heart Association, Inc., 2010. 41(8): e519–36. doi: 10.1161/STROKEAHA.110.581975.

13. **Hunt, William E. ja Hess, Robert M.** Surgical risk as related to time of intervention in the repair of intracranial aneurysms. *J Neurosurg.* 1968 Jan. 28(1):14-20. doi: 10.3171/jns.1968.28.1.0014.

14. **Ahn, Sung-Ho et al.** The Subarachnoid Hemorrhage Early Brain Edema Score Predicts Delayed Cerebral Ischemia and Clinical Outcomes. *Neurosurgery.* 2018 Jul. 1;83(1):137-145. doi: 10.1093/neuros/nyx364.

15. **Fisher, C. M., Kistler, J. P. and Davis, J. M.** Relation of cerebral vasospasm to subarachnoid hemorrhage visualized by computerized tomographic scanning. *Neurosurgery.* 1980 Jan. 6(1):1-9. doi: 10.1227/00006123-198001000-00001.

16. **Wilson, L. et al.** A Manual for the Glasgow Outcome Scale-Extended Interview. *J Neurotrauma.* 2021 Sep. 1;38(17):2435-2446. doi: 10.1089/neu.2020.7527.

17. **Connolly, E. S. et al.** Guidelines for the Management of Aneurysmal Subarachnoid Hemorrhage: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke.* 2012. 43(6): 1711-37. doi: 10.1161/STR.0b013e3182587839.

18. **Krajewski, Kara et al.** Neuropsychological assessments in patients with aneurysmal subarachnoid hemorrhage, perimesencephalic SAH, and incidental aneurysms. *Neurosurg Rev.* 2014 Jan. 37(1):55-62. doi: 10.1007/s10143-013-0489-3.

19. **Koso, Maida and Dizdarevic, Kemal.** Attention and executive functions in microsurgically treated patients after subarachnoid hemorrhage. *Asian J Neurosurg.* 2015 Oct-Dec. 10(4):260-5. doi: 10.4103/1793-5482.162683.

20. **Buunk, Anne M. et al.** Return to work after subarachnoid hemorrhage: The influence of cognitive deficits. *PLoS One.* 2019 Aug. 9;14(8):e0220972. doi: 10.1371/journal.pone.0220972.

21. **Mukerji, Nitin et al.** Neuropsychologic impact of treatment modalities in subarachnoid hemorrhage: clipping is no different from coiling. *World Neurosurg.* 2010 Jul. 74(1):129-38. doi: 10.1016/j.wneu.2010.05.009.

22. **Buunk, Anne M. et al.** Cognitive deficits after aneurysmal and angiographically negative subarachnoid hemorrhage: Memory, attention, executive functioning, and emotion recognition. *Neuropsychology.* 2016 Nov. 30(8):961-969. doi: 10.1037/neu0000296.

23. **Stienen, Martin N., Germans, Menno R. et al.** Longitudinal neuropsychological assessment after aneurysmal subarachnoid hemorrhage and its relationship with delayed cerebral ischemia: a prospective Swiss multicenter study. *J Neurosurg.* 2022 Apr. 29;137(6):1742-1750. doi: 10.3171/2022.2.JNS212595.