

University of Groningen

## Long-term Course of Cognitive Functioning After Aneurysmal and Angiographically Negative Subarachnoid Hemorrhage

Khosdelazad, Sara; Jorna, Lieke S; Rakers, Sandra E; Koffijberg, Ralf; Groen, Rob J M; Spikman, Jacoba M; Buunk, Anne M

*Published in:*  
Neurosurgery

*DOI:*  
[10.1227/neu.0000000000002559](https://doi.org/10.1227/neu.0000000000002559)

**IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.**

*Document Version*  
Publisher's PDF, also known as Version of record

*Publication date:*  
2023

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*

Khosdelazad, S., Jorna, L. S., Rakers, S. E., Koffijberg, R., Groen, R. J. M., Spikman, J. M., & Buunk, A. M. (2023). Long-term Course of Cognitive Functioning After Aneurysmal and Angiographically Negative Subarachnoid Hemorrhage. *Neurosurgery*, 93(6), 1235-1243.  
<https://doi.org/10.1227/neu.0000000000002559>

### Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

### Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

# Long-term Course of Cognitive Functioning After Aneurysmal and Angiographically Negative Subarachnoid Hemorrhage

Sara Khosdelazad, MSc<sup>1</sup>, Lieve S. Jorna, MSc<sup>1</sup>, Sandra E. Rakers, PhD<sup>1</sup>, Ralf Koffijberg, MSc<sup>2</sup>, Rob J. M. Groen, PhD<sup>3</sup>,  
Jacoba M. Spikman, PhD<sup>1</sup>, Anne M. Buunk, PhD<sup>1,5</sup>

<sup>1</sup>Department of Neurology, Unit Neuropsychology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; <sup>2</sup>Department of Medical Psychology, Medical Center Leeuwarden, Leeuwarden, The Netherlands; <sup>3</sup>Department of Neurosurgery, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

This material was presented as an poster abstract at the 2022 International Neuropsychological Society (INS) Meeting in Barcelona, Spain, July 8, 2022.

**Correspondence:** Sara Khosdelazad, MSc, Department of Neurology (AB51), University Medical Center Groningen, P.O. Box 30.001, Groningen, 9700RB, The Netherlands. Email: s.khosdelazad@umcg.nl Twitter: @SaraKhosdelazad

**Received,** December 19, 2022; **Accepted,** April 17, 2023; **Published Online,** June 5, 2023.

© Congress of Neurological Surgeons 2023. All rights reserved.

**BACKGROUND AND OBJECTIVES:** Cognitive impairment is a common consequence of subarachnoid hemorrhage (SAH), negatively affecting everyday functioning. This study is the first to investigate the long-term course of cognitive functioning after SAH and its associations with long-term well-being (ie, anxiety and depression), cognitive complaints, and return to work, separately for patients with aneurysmal SAH (aSAH) and angiographically negative SAH (anSAH) in a longitudinal design.

**METHODS:** Cognitive functioning was measured at 2 time points (T1: 3-6 months post-SAH; T2: 2-4 years post-SAH) in 58 patients with aSAH and 22 patients with anSAH with neuropsychological tests for (working) memory, psychomotor speed, and attention/executive functioning. Questionnaires were used to measure cognitive complaints and well-being at T1 and T2 and return to work at T2.

**RESULTS:** At T2, patients with aSAH only showed improvements in memory and on an executive functioning and psychomotor speed subtest, whereas in contrast, patients with anSAH had significantly poorer scores on tests for psychomotor speed. A significant amount of patients with aSAH and anSAH still reported cognitive complaints, anxiety, and depression in the chronic stage. Cognitive functioning was not significantly associated with cognitive complaints in both SAH groups. On the other hand, cognitive complaints were related to well-being at the long-term in both SAH groups. More cognitive complaints were also associated with more difficulties in return to work in patients with aSAH.

**CONCLUSION:** Patients with aSAH and anSAH have cognitive impairments at the subacute stage post-SAH, and these impairments persist into the chronic stage. Moreover, both SAH groups still reported decreased well-being in the chronic stage post-SAH, related to cognitive complaints but not to cognitive impairment. For clinical practice, an early neuropsychological assessment will already provide relevant information to estimate long-term cognitive impairment, but in addition, it is important to pay attention to psychological distress at the long-term.

**KEY WORDS:** Cognition, Long-term outcome, Subarachnoid hemorrhage, Well-being, Neuropsychology

Neurosurgery 00:1–9, 2023

<https://doi.org/10.1227/neu.0000000000002559>

**ABBREVIATIONS:** **15WT DR**, 15 Words Test Delayed Recall; **15WT IR**, 15 Words Test Immediate Recall; **anSAH**, angiographically negative subarachnoid hemorrhage; **DSB**, digit span backward; **DSF**, digit span forward; **EF**, executive functioning; **ELD**, external lumbar drainage; **EVD**, external ventricular drainage; **HADS-A**, Hospital Anxiety and Depression Scale Anxiety; **HADS-D**, Hospital Anxiety and Depression Scale Depression; **LF**, letter fluency; **M**, mean; **RRL-RTW**, role resumption list return to work; **StroopC**, Stroop Color-Word Test color; **StroopC-W**, Stroop Color-Word Test color-word; **StroopW**, Stroop Color-Word Test word; **T1**, subacute stage; **T2**, chronic stage; **TMT**, Trail Making Test; **TMT-A**, Trail Making Test, part A; **TMT-B**, Trail Making Test, part B; **UMCG**, University Medical Center Groningen; **VP shunt**, ventriculo-peritoneal shunt; **WFNS**, World Federation of Neurological Surgeons.

Supplemental digital content is available for this article at [neurosurgery-online.com](https://neurosurgery-online.com).

A spontaneous subarachnoid hemorrhage (SAH) accounts for approximately 3%–5% of all stroke types, with a yearly incidence rate in the Netherlands of 7 cases per 100,000 individuals.<sup>1</sup> In most cases, SAH is caused by the rupture of an intracranial aneurysm, defined as aneurysmal SAH (aSAH). By contrast, in angiographically negative SAH (anSAH), usually considered as a more benign condition, there is no visible cause for the hemorrhage.<sup>2,3</sup> SAH can result in emotional, cognitive, and behavioral disturbances, negatively interfering with everyday life functioning, activities, and responsibilities, and consequently, with quality of life.<sup>4–7</sup> Hence, it is clinically relevant to investigate not only which cognitive, emotional, and behavioral problems patients encounter after SAH but even more if and to which extent such impairments change over time.

Several studies conducted in the subacute stage (ie,  $\geq 6$  months post-SAH) after aSAH revealed neurocognitive deficits in psychomotor speed, attention, memory, executive functions, and social cognition.<sup>8-11</sup> Cognitive deficits, mainly in attention and executive functioning (EF), are also found in the anSAH group, although on average milder than in the aSAH group.<sup>9,12,13</sup> Until now, the course of cognitive functioning has been investigated in patients with aSAH only, with a short time course of up to 12–15 months post-SAH.<sup>14-18</sup> Hence, it is unknown whether cognitive deficits change or persist at a longer term and whether this applies to both aSAH and anSAH.

Despite a lack of knowledge regarding cognitive change in the long-term after SAH, several studies investigated other aspects of recovery, such as well-being. Anxiety and depression are common and persistent after aSAH, even in patients with good clinical outcome.<sup>19,20</sup> Regarding anSAH, studies investigated only depression with inconsistent results: 2 studies reported high rates of persistent symptoms of depression<sup>21,22</sup>, whereas 1 study found no indication for clinical depression.<sup>12</sup> A pending question is whether the presence of cognitive deficits after SAH is related to post-SAH anxiety or depression. Although some studies identified cognitive deficits as a risk factor for post-SAH depression<sup>23,24</sup>; others did not.<sup>25,26</sup> To the best of our knowledge, there are no studies investigating the association between cognitive deficits and anxiety.

In addition, both patients with aSAH and anSAH report cognitive complaints that may persist in the long-term, such as forgetfulness, concentration difficulties, or difficulties with organization and planning.<sup>11,22,27,28</sup> Studies in several patient groups with other types of brain injuries (ie, traumatic brain injury and stroke) demonstrated that cognitive complaints are not related to cognitive impairment, but mainly to mental distress.<sup>29,30</sup> In addition, in the SAH patient group, studies found weak<sup>11</sup> or no significant associations<sup>26</sup> between cognitive deficits and cognitive complaints. Consequently, patients may report cognitive complaints as a sign of decreased well-being. Indeed, cognitive complaints are found to be associated with anxiety and depression in the SAH patient group.<sup>11,31,32</sup> To summarize, within the scope of long-term well-being after SAH, there may be complex relations between the presence of cognitive deficits, cognitive complaints, and depression and anxiety. To date, there is no clear picture of whether and how these factors are interrelated nor whether these profiles are similar for patients with aSAH and anSAH in the chronic stage.

This study is the first to investigate longitudinally the long-term course of cognitive functioning after SAH, separately for patients with aSAH and anSAH. In addition, we examined in both SAH groups whether cognitive functioning in the chronic stage is related to long-term well-being (ie, anxiety and depression), cognitive complaints, and the ability to return to work.

## METHODS

### Participants

All patients with a spontaneous SAH admitted between 2009 and 2012 at the University Medical Center Groningen (UMCG) were eligible

for participation in this study. Inclusion criteria were older than 18 years, sufficient proficiency of the Dutch language, and absence of neurological or serious psychiatric diseases that requested inpatient treatment (such as bipolar disorder or schizophrenia) at the time of SAH. SAH diagnosis was determined using computed tomography (CT) on admission, combined with CT angiography and/or digital subtraction angiography to validate the presence (aSAH) or absence (anSAH) of an intracranial aneurysm. Information regarding demographics (age and sex), clinical severity of SAH (World Federation of Neurological Surgeons),<sup>33</sup> and medical data (time since SAH, type of SAH, and treatment) was collected.

This study was approved by the Medical Ethical Committee of UMCG. All participants were treated according to the Declaration of Helsinki and gave written informed consent.

### Neuropsychological Measures

Patients underwent a battery of neuropsychological tests at both the subacute (3–6 months, T1) and chronic stage (2–4 years, T2) post-SAH, measuring a broad range of cognitive domains (ie, memory, working memory, psychomotor speed, attention, and EF). The tests administered were the Dutch version of the Rey Auditory Verbal Learning Test (15 Words Test, Immediate Recall and Delayed Recall [15WT IR, 15WT DR]),<sup>34</sup> The Digit Span (subtest of the Wechsler Adult Intelligence Scale)<sup>35</sup> Forward and Backward (DSF, DSB), Trail Making Test parts A and B (TMT-A, TMT-B),<sup>36,37</sup> Stroop Color-Word Test (word [StroopW], color [StroopC], color-word [StroopC-W]),<sup>38,39</sup> Zoo Map Test,<sup>40</sup> and the Dutch version of the Controlled Oral Word Association Test,<sup>41</sup> Letter Fluency (LF).

### Self-Report Measures for Long-Term Well-Being and Return to Work

Patients completed self-report questionnaires regarding long-term well-being at T1 and T2 and the ability to return to work at T2. Cognitive complaints were assessed with a semistructured interview using a brain injury symptom checklist (used previously in SAH),<sup>31</sup> which is an extended version of the Head Injury Symptom Checklist.<sup>42</sup> The total score ranged from 0 to 34. The Hospital Anxiety and Depression Scale<sup>43</sup> measures anxiety and depression separately, with 14 items for each subscale, resulting in total scores ranging from 0 to 21. A score of 8 or higher reflects symptomatology indicative of anxiety or depression. Return to work was rated on a 5-point scale, using the Role Resumption List,<sup>44</sup> whereby a score of 0 indicates that “former work has been resumed without changes,” and a score of 4 indicates “not working at all.” Scores were dichotomized into “return to work completely” (0) and “return to work not completely” (1–4).

### Statistical Analysis

Statistical analyses were conducted using Statistical Package for the Social Sciences (IBM), version 23.0. The educational level was scored on a 7-point scale, ranging from 1 (no primary school) to 7 (university degree), dichotomized into low (1–4) and high (5–7). Impairments were defined as test performances below the 10th percentile, compared with sex, age, and education matched normative values.<sup>45</sup> Descriptive statistics were calculated to describe general patient characteristics; for interval variables, means and SDs were used, and for categorical variables, numbers and percentages were used. Differences on neuropsychological tests and questionnaires between patients with aSAH and anSAH were tested, using Mann-Whitney *U* and independent *t*-tests. Differences

between neuropsychological test scores, anxiety and depression, and cognitive complaints at T1 and T2 were tested using the Student paired sample *t*-test or Wilcoxon signed-rank test. Effect sizes (Cohen's *d*, *r*) were calculated.<sup>46</sup> Four cognitive domain scores were calculated based on Z-scores from the T2 neuropsychological measures: Memory (15WT IR, 15WT DR), Working Memory (DSF, DSB), Psychomotor Speed (TMT-A, StroopW, StroopC), and Attention/EF (TMT-B, StroopC-W, Zoo Map Test, LF). Spearman rank correlations were calculated between these 4 composite scores with anxiety, depression, cognitive complaints, and return to work. The alpha level was set at .05, and Bonferroni Holm<sup>47</sup> corrections were used for all analyses to minimize the possibility of type 1 errors.

## RESULTS

From a total of 203 patients with SAH who were hospitalized at the UMCG between 2009 and 2012, 119 were eligible and took part in this study at T1. The flowchart of patients is presented in Figure 1. Eventually, 80 patients were included in this study at T2. No significant differences (all *P*s > .05) were found between the 39 drop-outs and the 80 patients at T2 for age (*t* = 0.41), sex ( $X^2$  = 2.0), or World Federation of Neurological Surgeons grade ( $X^2$  = 2.62). The demographic and SAH characteristics of the patients are listed in Table 1.

## The Course of Cognitive Functioning Between T1 and T2

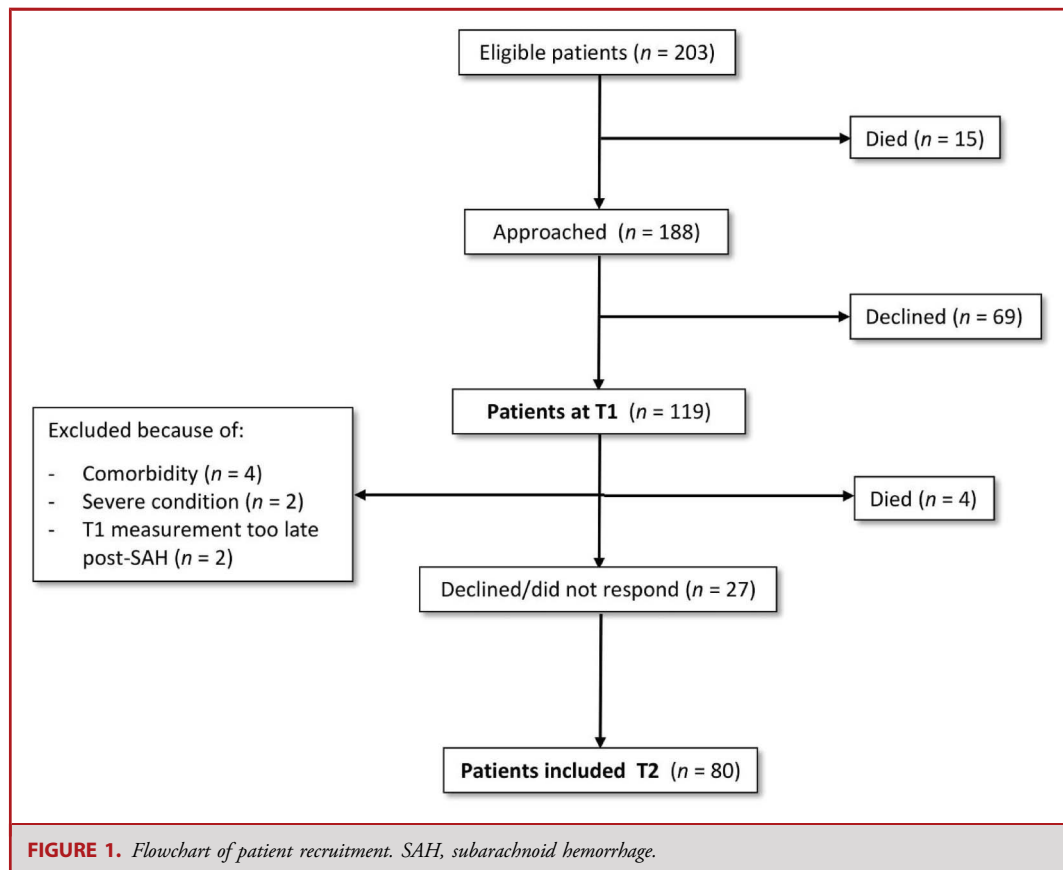
Table 2 presents mean scores on all neuropsychological tests, tested for differences between T1 and T2. At T2, patients with aSAH had significantly higher scores on both subtests of the 15WT, with moderate effect sizes, and significantly better scores on the StroopW and the Zoo Map test, with weak effect sizes.

By contrast, patients with anSAH showed significantly worse scores on 3 measures of psychomotor speed (TMT-A, StroopW, StroopC) at T2, with moderate to strong effect sizes, but no other significant differences were found.

## Differences Between SAH Groups and Cognitive Impairments

We found no significant differences in test performances at T1 nor T2 between patients with aSAH and anSAH (all *P*s > .05).

Table 2 presents percentages of patients with SAH with impaired neuropsychological test performance at T1 and T2. Higher percentages were found for patients with aSAH; however,  $X^2$  tests did not reveal significant differences in these percentages between the 2 SAH groups (all *P*s > .05). At T2, 84% of patients with aSAH and 86% of patients with anSAH were impaired on at least 1 cognitive subtest.



## The Course of Well-Being and Cognitive Complaints Between T1 and T2

Table S1 presents the mean scores for anxiety, depression, and cognitive complaints, tested for differences between T1 and T2. No significant differences for any of the measures were found between the 2 SAH groups at both T1 and T2 (Table S1, <http://links.lww.com/NEU/D846>).

### Cognitive Complaints

Both SAH groups report, on average, more cognitive complaints at T2 compared with T1, although these differences were not significant. Figure 2 shows that 52 patients with aSAH (89.7%) and 20 patients with anSAH (95.2%) reported at least 3 cognitive complaints at T2.

### Anxiety and Depression

No significant differences were found in the presence of symptoms of anxiety and depression between T1 and T2 for both patients with aSAH and anSAH.

### Long-Term Well-Being, Cognitive Complaints, and Associations With Cognition at T2

Table 3 presents that there are no significant correlations between the composite cognitive scores with cognitive complaints or anxiety and depression at T2 in both SAH groups.

### Return to Work at T2

Thirty-eight (65.5%) patients with aSAH and 7 (36.8%) patients with anSAH were not able to return to work completely at T2. Significantly, more patients with aSAH had problems with return to work than patients with anSAH ( $X^2 = 5.25$ ,  $P = .02$ ). Return to work was not significantly associated with cognitive functioning in both SAH groups (Table 3).

### Associations Between Cognitive Complaints, Well-Being, and Return to Work at T2

Table 4 presents significant low to moderate positive correlations for patients with aSAH and moderate to high positive correlations for patients with anSAH between cognitive complaints and anxiety and depression. This indicates that patients who have more symptoms of anxiety and depression also report more cognitive complaints. Return to work is significantly positively correlated with cognitive complaints in patients with aSAH only, indicating that those patients who are unable to return to work completely also report more cognitive complaints.

## DISCUSSION

This is the first study that longitudinally investigated the long-term course of cognitive functioning across different domains (ie, memory, working memory, psychomotor speed, and attention/EF) between the subacute stage (3-6 months post-SAH) and

**TABLE 1. Patient Characteristics**

Characteristics	aSAH (n = 58)	anSAH (n = 22)
Sex, women, n (%)	38 (65.5%)	11 (50%)
Mean age at the time of SAH, y (SD)	52.8 (9.9)	53.4 (9.7)
Time since SAH, mo, mean T1 (range)	4.6 (2-8)	5.1 (3-7)
Time since SAH, mo, mean T2 (range)	30.1 (15-39)	43.1 (22-56)
<b>Educational level</b>		
Low (1-4)	21 (36.2%)	6 (27.3%)
High (5-7)	37 (63.8%)	16 (72.7%)
<b>WFNS</b>		
Low (1-3)	46 (79.3%)	21 (95.5%)
High (4-5)	12 (20.7%)	1 (4.5%)
<b>CSF drainage</b>		
Acute (ELD/EVD)	45 (77.6%)	10 (45.5%)
Chronic (VP-shunt)	12 (20.7%)	1 (4.5%)
<b>Treatment</b>		
Clipping	16 (27.6%)	
Coiling	41 (70.7%)	
Other	1 (1.7%)	

aSAH, aneurysmal subarachnoid hemorrhage; anSAH, angiographically negative subarachnoid hemorrhage; CSF, cerebrospinal fluid; ELD, external lumbar drainage; EVD, external ventricular drainage; SAH, subarachnoid hemorrhage; T1, subacute stage; T2, chronic stage; VP shunt, ventriculo-peritoneal shunt; WFNS, World Federation of Neurological Surgeons.

chronic stage (2-4 years post-SAH), separately for patients with aSAH and anSAH. Overall, this study did not yield evidence for substantial change at the long-term in cognitive functioning after SAH. Both SAH groups still showed cognitive impairments at T2. Furthermore, it was investigated whether cognitive functioning in the long-term chronic stage post-SAH was associated with high levels of cognitive complaints, feelings of anxiety and depression, and the ability to return to work. For all cognitive domains, there was no significant relation with well-being, cognitive complaints, and return to work, but in contrast, cognitive complaints were significantly associated with the presence of anxiety and depression.

In patients with aSAH, we found only for a few measures (15WT, Stroop Word, Zoo map) a small improvement. Moreover, 84% of these patients still were impaired on at least 1 neuropsychological subtest in the chronic stage. A previous study conducted by our research group found cognitive deficits at 3 to 6 months after aSAH as well as lower neurocognitive performances in patients with anSAH compared with healthy controls.<sup>9</sup> This study shows that this pattern also exists in the chronic stage

**TABLE 2. Course of Cognitive Functioning Between the Subacute Stage (T1) and Chronic Stage (T2)**

Measure	aSAH							anSAH						
	T1 raw scores (M ± SD)	T2 raw scores (M ± SD)	T1 impaired, n (%)	T2 impaired, n (%)	t/Z <sup>a</sup>	P	d/r <sup>b</sup>	T1 raw scores (M ± SD)	T2 raw scores (M ± SD)	T1 impaired, n (%)	T2 impaired, n (%)	t/Z <sup>c</sup>	P	d/r <sup>b</sup>
<b>Memory</b>														
15WT IR	39.1 ± 9.6	42.1 ± 10.2	25 (43.1)	21 (36.2)	-3.15	<b>0.003<sup>d</sup></b>	-0.41	40.6 ± 12.2	41.8 ± 12.2	10 (45.5)	5 (22.7)	-0.79	0.44	-0.17
15WT DR	7.8 ± 3.0	9.0 ± 3.2	7 (12.1)	4 (6.9)	-3.51	<b>0.000<sup>d</sup></b>	-0.46	8.6 ± 2.5	8.5 ± 3.5	7 (31.8)	2 (9.1)	-0.15	0.88	-0.03
<b>Working memory</b>														
DSF	5.5 ± 1.4	8.1 ± 2.1	12 (20.7)	14 (24.1)	-1.40	0.16	0.18	5.6 ± 1.0	8.5 ± 1.5	3 (13.6)	2 (9.1)	-1.36	0.19	-0.29
DSB	4.1 ± 1.2	5.3 ± 1.8	23 (39.7)	20 (34.5)	-0.53	0.60	-0.07	4.5 ± 1.1	6.2 ± 1.8	1 (4.5)	3 (13.6)	-1.20	0.24	-0.26
<b>Psychomotor speed</b>														
TMT-A	37.4 ± 14.3	37.3 ± 16.8	6 (10.3)	2 (3.4)	-1.59	0.11	-0.21	32.8 ± 14.9	38.2 ± 13.8	1 (4.5)	3 (13.6)	-2.61	<b>0.009<sup>d</sup></b>	-0.56
Stroop Word	53 ± 16.1	49.6 ± 9.9	21 (36.2)	15 (25.9)	-2.47	<b>0.01<sup>d</sup></b>	-0.32	48.4 ± 8.0	53.6 ± 10.1	7 (31.8)	11 (50)	-2.61	<b>0.02<sup>d</sup></b>	-0.56
Stroop Color	65.8 ± 17.2	64.5 ± 13.9	16 (27.6)	11 (19)	-1.05	0.30	-0.14	56.9 ± 10.4	62.7 ± 11.4	3 (13.6)	4 (18.2)	-3.52	<b>0.002<sup>d</sup></b>	-0.75
<b>Attention/EF</b>														
TMT-B	90.6 ± 43	83.6 ± 35.2	6 (10.3)	4 (6.9)	-2.29	0.03	-0.29	73.2 ± 53.8	65.1 ± 16.6	1 (4.5)	0	-0.93	0.35	-0.20
Stroop Color-Word	105.7 ± 29.9	100.9 ± 23.8	10 (17.2)	2 (3.4)	-1.18	0.24	-0.16	90.6 ± 30.8	93.1 ± 26.5	3 (13.6)	3 (13.6)	-1.56	0.12	-0.33
Zoo Map Test	7.1 ± 6.1	10.0 ± 4.9	22 (37.9)	9 (15.5)	-2.87	<b>0.004<sup>d</sup></b>	-0.38	7.4 ± 5.9	11.2 ± 3.5	7 (31.8)	1 (4.5)	-2.34	0.02	-0.50
LF	30.8 ± 10.3	33.8 ± 11.3	12 (20.7)	10 (17.2)	-2.47	0.02	-0.32	35.3 ± 9.9	37.8 ± 10.2	2 (9.1)	2 (9.1)	-1.51	0.15	-0.32

aSAH, aneurysmal subarachnoid hemorrhage; anSAH, angiographically negative subarachnoid hemorrhage; DSB, Digit Span Backward; DSF, digit span forward; EF, executive functioning; LF, letter fluency; M, mean; TMT, Trail Making Test; 15WT IR, 15 Words Test Immediate Recall; 15WT DR, 15 Words Test Delayed Recall.

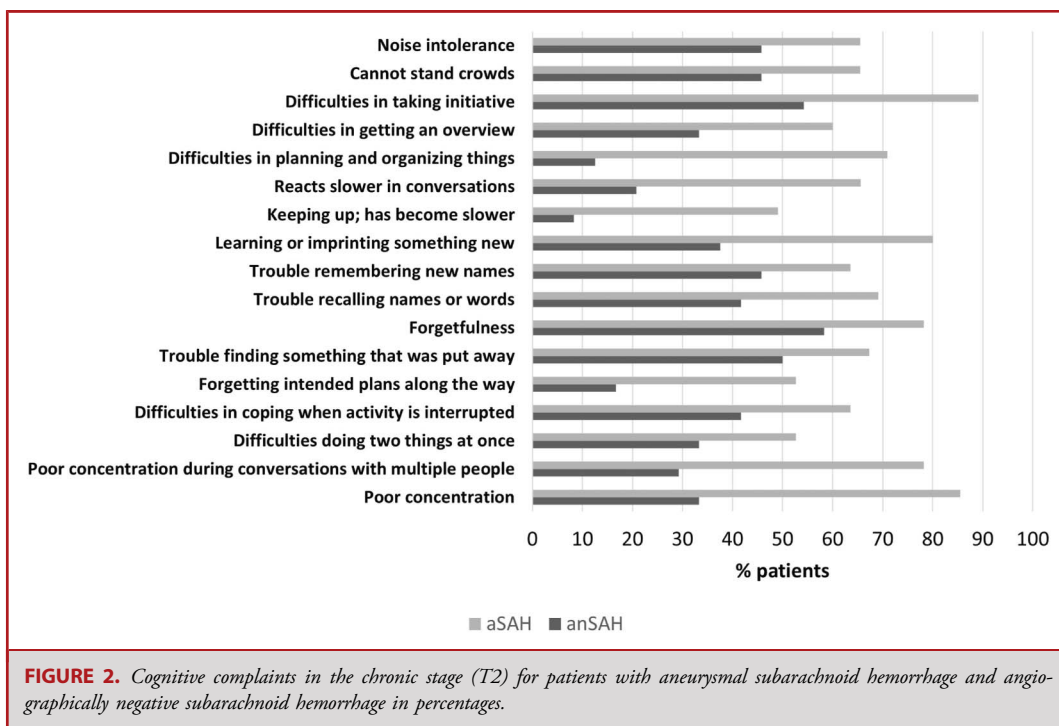
<sup>a</sup>Paired t-test: 15WT IR, LF; Wilcoxon signed-rank test: TMT-A, Stroop Word, Stroop Color, DSF, 15WT DR, DSB, TMT-B, Stroop Color-Word, Zoo map test.

<sup>b</sup>Cohen's d, effect size; r = Z/√N, effect size.

<sup>c</sup>Paired t-test: Stroop Word, Stroop Color, DSF, 15WT IR, 15WT DR, DSB, LF; Wilcoxon signed-rank test: TMT-A, TMT-B, Stroop Color-Word, Zoo map test.

<sup>d</sup>Bold indicates statistical significance after Bonferroni-Holm corrections.

Downloaded from http://journals.lww.com/neurosurgery by BHDMSepHKav1Zeum1QIN4at+KLLHEZqbsH04XIM0h  
CvWCX1AWNvQpIIQhD3i3D00dRyITV5F14C13V1C1y0abgQZxdtwIKZB7Yms= on 08/01/2023



after SAH. The anSAH group performed on most tests at T2 on a similar level as at T1. Moreover, in the chronic stage, 86% of patients with anSAH still showed impaired performances on at least 1 neuropsychological test. Remarkably though, on the tests that measure psychomotor speed (TMT-A, StroopC, StroopW), and accordingly, require extra mental effort, they even performed significantly worse at T2. Thus, the overall picture is that patients with aSAH and anSAH show little or no change in cognitive functioning in the long-term, and impairments seem to be persistent. This implies that the measurement of cognition at the subacute stage post-SAH is a reliable indication of cognitive

functioning in the long-term in most patients with SAH. In clinical care, it is therefore of great importance to perform a detailed neuropsychological examination in the SAH patient group 3 to 6 months after the bleeding. Interestingly, we found no significant differences between patients with aSAH and anSAH regarding their neuropsychological performances nor regarding the percentage of impairments. Hence, this warrants that cognitive deficits should not be underestimated in the anSAH group, as also demonstrated in previous research.<sup>9,12</sup>

In the chronic stage post-SAH, the prevalence of cognitive complaints was high in both patients with aSAH (90%) and

**TABLE 3. Spearman Correlations of the Composite Neuropsychological Scores and Well-Being, Cognitive Complaints, and Return to Work at the Chronic Stage (T2)**

Cognitive domain	aSAH				anSAH			
	HADS-A	HADS-D	Cognitive complaints	RRL-RTW	HADS-A	HADS-D	Cognitive complaints	RRL-RTW
Memory	-0.05	0.06	-0.16	-0.19	-0.06	-0.10	-0.04	-0.04
Working memory	-0.06	0.03	-0.19	0.05	-0.10	-0.37	-0.40	-0.07
Psychomotor speed	0.12	0.002	-0.30	-0.02	-0.19	-0.13	-0.30	-0.20
Attention/EF	0.11	0.07	-0.17	0.10	-0.15	-0.28	-0.34	-0.23

aSAH, aneurysmal subarachnoid hemorrhage; anSAH, angiographically negative subarachnoid hemorrhage; HADS-A, Hospital Anxiety and Depression Scale Anxiety; HADS-D, Hospital Anxiety and Depression Scale Depression; RRL-RTW: Role Resumption List Return To Work; SAH, subarachnoid hemorrhage.

**TABLE 4. Spearman Correlations Between Cognitive Complaints, Anxiety and Depression, and the Ability to Return to Work at the Chronic Stage (T2)**

Measure	Cognitive complaints—aSAH	Cognitive complaints—anSAH
HADS-A	<b>0.38<sup>a</sup></b>	<b>0.56<sup>a</sup></b>
HADS-D	<b>0.60<sup>a</sup></b>	<b>0.76<sup>a</sup></b>
RRL-RTW	<b>0.35<sup>a</sup></b>	0.45

aSAH, aneurysmal subarachnoid hemorrhage; anSAH, angiographically negative subarachnoid hemorrhage; HADS-A, Hospital Anxiety and Depression Scale Anxiety; HADS-D, Hospital Anxiety and Depression Scale Depression; RRL-RTW: role resumption list return to work.

<sup>a</sup>Bold indicates statistical significance after Bonferroni-Holm corrections.

anSAH (95%). We did not find significant associations of these numbers of cognitive complaints with all cognitive domains in both SAH groups. Cognitive functioning also was not related to return to work for both SAH groups, while for patients with aSAH, more cognitive complaints were associated with more difficulties in returning to work. Almost one-third of patients with aSAH and almost one-quarter of patients with anSAH experienced symptoms of anxiety and/or depression in the subacute stage which lasted in the chronic stage. These persistent symptoms were not related to cognitive functioning, but to cognitive complaints in both SAH groups. Complaints and feelings of depression or anxiety may result from distress related to changes in everyday life functioning after SAH, but anxiety and depression may also be a direct effect of brain damage, as earlier described for patients with stroke.<sup>48</sup> It is therefore of great importance that, next to cognitive deficits, symptoms of anxiety and depression are timely identified and monitored after SAH.

This is the first study to demonstrate that in the chronic stage, a significant part of patients with aSAH and anSAH still, to a similar extent, experience decreased well-being, which is related to the presence of cognitive complaints, but not to cognitive impairment. Interestingly, we found no differences in the amount of cognitive complaints nor anxiety and depression between patients with aSAH and anSAH, indicative of similar long-term well-being patterns. Cognitive complaints should therefore be interpreted as an indication of reduced well-being, and not of cognitive change as measured by neuropsychological tests.

### Limitations

Some limitations to this study need to be acknowledged. First, no alternate test versions were used; thus, possible retest effects cannot be excluded, although these were not deemed likely given the large interval between T1 and T2. Second, the group size of patients with anSAH is relatively small compared with the aSAH group. For this reason, we did not differentiate between perimesencephalic anSAH and nonperimesencephalic anSAH, of which the latter is known to have better clinical outcome,<sup>49</sup> and did not take into account the presence of cerebrospinal fluid

drainage. Several studies found an association between acute hydrocephalus and poor cognitive functioning in patients with aSAH.<sup>10,50</sup> Further research is needed to clarify the impact of these factors on long-term cognitive outcome after both aSAH and anSAH. Third, we did not include a control group to compare the neuropsychological performances of the patients, but we used normative data to compare performances to determine cognitive deficits in both SAH groups. Finally, we did not take into account fatigue, which is known to be a frequent and long-term persisting symptom after SAH and other types of acquired brain injury and is associated with cognitive deficits, mainly attention, but also with complaints and mental distress.<sup>11,32,51,52</sup>

### CONCLUSION

This study shows little to no change of cognitive functioning, between the subacute and long-term chronic stage in patients with aSAH and anSAH. Importantly, in both SAH groups, most patients still demonstrated cognitive impairments and reported decreased well-being in this chronic phase, up to 4 years after SAH. Contrary to the current view, we found that patients with anSAH have similar sequelae as patients with aSAH. In the existing literature, anSAH is considered the “harmless type” of SAH, given that there is no need for endovascular or neurosurgical treatment, the risk of a rebleed is lower, and patients are considered to have a more favorable neurological prognosis.<sup>3,53,54</sup> However, cognitive deficits also exist in this patient group, and this study now adds to the literature that these deficits do not recover either in the long-term. In addition, we found no differences in neuropsychological performances, cognitive complaints, and anxiety and depression symptoms in the long-term between patients with aSAH and anSAH. It is therefore questionable whether it is correct to label anSAH as a benign condition. Communicating to patients with anSAH that they suffered a “benign hemorrhage” may create certain expectations regarding their recovery that cannot be met. These unmet expectations may, in turn, result in increased reporting of complaints or level of distress in this patient group. However, future research in a larger sample of patients with anSAH is needed to elucidate this important topic further. For clinical practice, we therefore recommend that patients with aSAH and anSAH receive equal psychosocial follow-up, with a timely (ie, in the subacute stage post-SAH) neuropsychological assessment including measures of well-being to make patients aware of possible deficits and to offer tailor-made treatment.

### Funding

This study did not receive any funding or financial support.

### Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article. Jacoba M.



Spikman and Anne M. Buunk have a financial relationship with Stichting Catharina Heerd.

## REFERENCES

- Risselada R, De Vries LM, Dippel DWJ, et al. Incidence, treatment, and case-fatality of non-traumatic subarachnoid haemorrhage in The Netherlands. *Clin Neurol Neurosurg.* 2011;113(6):483-487.
- Kapadia A, Schweizer TA, Spears J, Cusimano M, Macdonald RL. Nonaneurysmal perimesencephalic subarachnoid hemorrhage: diagnosis, pathophysiology, clinical characteristics, and long-term outcome. *World Neurosurg.* 2014;82(6):1131-1143.
- van Gijn J, Kerr RS, Rinkel GJ. Subarachnoid haemorrhage. *Lancet.* 2007;369(9558):306-318.
- Buunk AM, Spikman JM, Metzemaekers JDM, van Dijk JMC, Groen RJM. Return to work after subarachnoid hemorrhage: the influence of cognitive deficits. *PLoS One.* 2019;14(8):e0220972.
- Persson HC, Carlsson L, Sunnerhagen KS. Life situation 5 years after subarachnoid haemorrhage. *Acta Neurol Scand.* 2018;137(1):99-104.
- Sonesson B, Kronvall E, Säveland H, Brandt L, Nilsson OG. Long-term reintegration and quality of life in patients with subarachnoid hemorrhage and a good neurological outcome: findings after more than 20 years. *J Neurosurg.* 2018;128(3):785-792.
- Springer MV, Schmidt JM, Wartenberg KE, Frontera JA, Badjatia N, Mayer SA. Predictors of global cognitive impairment 1 year after subarachnoid hemorrhage. *Neurosurgery.* 2009;65(6):1043-1051.
- Nussbaum ES, Mikoff N, Paranjape GS. Cognitive deficits among patients surviving aneurysmal subarachnoid hemorrhage. A contemporary systematic review. *Br J Neurosurg.* 2021;35(4):384-401.
- Buunk AM, Groen RJM, Veenstra WS, et al. Cognitive deficits after aneurysmal and angiographically negative subarachnoid hemorrhage: memory, attention, executive functioning, and emotion recognition. *Neuropsychology.* 2016;30(8):961-969.
- Haug Nordenmark T, Karic T, Sorteberg W, Sorteberg A. Predictors of cognitive function in the acute phase after aneurysmal subarachnoid hemorrhage. *Acta Neurochir (Wien).* 2019;161(1):177-184.
- Passier PECA, Visser-Meily JMA, Van Zandvoort MJE, Post MWM, Rinkel GJE, Van Heugten C. Prevalence and determinants of cognitive complaints after aneurysmal subarachnoid hemorrhage. *Cerebrovasc Dis.* 2010;29(6):557-563.
- Boerboom W, Heijenbrok-Kal MH, Khajeh L, Kooten F, Ribbers GM. Differences in cognitive and emotional outcomes between patients with perimesencephalic and aneurysmal subarachnoid haemorrhage. *J Rehabil Med.* 2014;46(1):28-32.
- Burke T, Hughes S, Carr A, Javadpour M, Pender N. A systematic review of cognitive outcomes in angiographically negative subarachnoid haemorrhage. *Neuropsychol Rev.* 2018;28(4):453-469.
- Frazer D, Ahuja A, Watkins L, Cipolotti L. Coiling versus clipping for the treatment of aneurysmal subarachnoid hemorrhage: a longitudinal investigation into cognitive outcome. *Neurosurgery.* 2007;60(3):434-442.
- Hasan TF, Haranhalli N, Mbabu N, et al. Aneurysmal subarachnoid hemorrhage: a pilot study for using longitudinal cognitive and neuropsychological testing for functional outcomes. *Clin Neurol Neurosurg.* 2020;194:105941.
- Haug T, Sorteberg A, Sorteberg W, Lindegaard KF, Lunder T, Finset A. Cognitive outcome after aneurysmal subarachnoid hemorrhage: time course of recovery and relationship to clinical, radiological, and management parameters. *Neurosurgery.* 2007;60(4):649-657.
- Koivisto T, Vanninen R, Hurskainen H, Saari T, Hernesniemi J, Vapalahti M. Outcomes of early endovascular versus surgical treatment of ruptured cerebral aneurysms: a prospective randomized study. *Stroke.* 2000;31(10):2369-2377.
- Samra SK, Giordani B, Caveney AF, et al. Recovery of cognitive function after surgery for aneurysmal subarachnoid hemorrhage. *Stroke.* 2007;38(6):1864-1872.
- Ackermark PY, Schepers VPM, Post MWM, Rinkel GJE, Passier PECA, Visser-Meily JMA. Longitudinal course of depressive symptoms and anxiety after aneurysmal subarachnoid hemorrhage. *Eur J Phys Rehabil Med.* 2017;53(1):98-104.
- Visser-Meily JA, Rhebergen ML, Rinkel GJE, Van Zandvoort MJ, Post MWM. Long-term health-related quality of life after aneurysmal subarachnoid hemorrhage relationship with psychological symptoms and personality characteristics. *Stroke.* 2009;40(4):1526-1529.
- Madureira S, Canhão P, Guerreiro M, Ferro JM. Cognitive and emotional consequences of perimesencephalic subarachnoid hemorrhage. *J Neurol.* 2000;247(11):862-867.
- Marquardt G, Niebauer T, Schick U, Lorenz R. Long term follow up after perimesencephalic subarachnoid haemorrhage. *J Neurol Neurosurg Psychiatry.* 2000;69(1):127-130.
- Fertl E, Killer M, Eder H, Linzmayer L, Richling B, Auff E. Long-term functional effects of aneurysmal subarachnoid haemorrhage with special emphasis on the patient's view. *Acta Neurochir.* 1999;141(6):571-577.
- Wong GKC, Lam S, Ngai K, et al. Evaluation of cognitive impairment by the Montreal Cognitive Assessment in patients with aneurysmal subarachnoid haemorrhage: prevalence, risk factors and correlations with 3 month outcomes. *J Neurol Neurosurg Psychiatry.* 2012;83(11):1112-1117.
- Brand S, Zimmerer S, Kalak N, et al. Compared to controls, patients with ruptured aneurysm and surgical intervention show increase in symptoms of depression and lower cognitive performance, but their objective sleep is not affected. *World J Biol Psychiatry.* 2015;16(2):96-105.
- Ørbo M, Waterloo K, Egge A, Isaksen J, Ingebrigtsen T, Romner B. Predictors for cognitive impairment one year after surgery for aneurysmal subarachnoid hemorrhage. *J Neurol.* 2008;255(11):1770-1776.
- Ravnik J, Starovasnik B, Šešok S, et al. Long-term cognitive deficits in patients with good outcomes after aneurysmal subarachnoid hemorrhage from anterior communicating artery. *Croat Med J.* 2006;47(2):253-263.
- Toomela A, Pulver A, Tomberg T, Orasson A, Tikk A, Asser T. Possible interpretation of subjective complaints in patients with spontaneous subarachnoid haemorrhage. *J Rehabil Med.* 2004;36(2):63-69.
- Anderson JFI. Cognitive complaint and objective cognition during the post-acute period after mild traumatic brain injury in pre-morbidly healthy adults. *Brain Inj.* 2021;35(1):103-113.
- van Rijsbergen MWA, Mark RE, Kop WJ, de Kort PLM, Sitskoorn MM. Course and predictors of subjective cognitive complaints during the first 12 months after stroke. *J Stroke Cerebrovasc Dis.* 2020;29(3):104588-104589.
- Buunk AM, Groen RJM, Veenstra WS, Spikman JM. Leisure and social participation in patients 4-10 years after aneurysmal subarachnoid haemorrhage. *Brain Inj.* 2015;29(13-14):1589-1596.
- Boerboom W, van Zandvoort MJE, van Kooten F, et al. Long-term fatigue after perimesencephalic subarachnoid haemorrhage in relation to cognitive functioning, mood and comorbidity. *Disabil Rehabil.* 2017;39(9):928-933.
- Teasdale GM, Drake CG, Hunt W, et al. A universal subarachnoid hemorrhage scale: report of a committee of the World Federation of Neurological Societies. *J Neurol Neurosurg Psychiatry.* 1988;51(11):1457.
- Deelman BG, Brouwer WH, Van Zomeren AH, Saan RJ. Functiestoornissen na trauma capitis. In A Jennekens-Schinkel, J Diamant, H Diesfeldt, R Haaxma (EDS.). *Neuropsychologie in Nederland.* Deventer, the Netherlands: Van Loghum Slaterus. 1980: 253-281.
- Stinissen J, Willems PJ, Coetsier P, Hulsman WLL. *Handleiding bij de Nederlandstalige bewerking van de Wechsler Adult Intelligence Scale (WAIS) (manual of the Dutch edition of the WAIS).* Lisse: Swets & Zeitlinger; 1970.
- Reitan RM. Validity of the trail making test as an indicator of organic brain damage. *Perceptual Mot Skills.* 1958;8(7):271-276.
- Arbuthnott K, Frank J. Trail making test, part B as a measure of executive control: validation using a set-switching paradigm. *J Clin Exp Neuropsychol.* 2000;22(4):518-528.
- Golden CJ. *Stroop Color and Word Test: A Manual for Clinical and Experimental Uses.* Wood Dale, Illinois: Stoelting Company; 1978.
- Stroop JR. Studies of interference in serial verbal reactions. *J Exp Psychol.* 1935;18(6):643-662.
- Wilson BA, Alderman N, Burgess PW, Emslie H, Evans JJ. *BADS: Behavioural Assessment of the Dysexecutive Syndrome.* London, England: Pearson; 1996.
- Benton AL, Hamsher KD, Sivan AB. *Multilingual Aphasia Examination.* Lutz, FL: Psychological Assessment Resources, Inc.; 1994.
- de Koning ME, Gareb B, El Mounni M, et al. Subacute posttraumatic complaints and psychological distress in trauma patients with or without mild traumatic brain injury. *Injury.* 2016;47(9):2041-2047.
- Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatrica Scand.* 1983;67(6):361-370.
- Spikman JM, Boelen DH, Lamberts KF, Brouwer WH, Fasotti L. Effects of a multifaceted treatment program for executive dysfunction after acquired brain injury on indications of executive functioning in daily life. *J Int Neuropsychol Soc.* 2010;16(1):118-129.

45. Lezak MD, Howieson DB, Loring DW, Hannay HJ, Fischer JS. *Neuropsychological Assessment (4th ed.)*. New York: Oxford University Press; 2004.
46. Rosenthal JA. Qualitative descriptors of strength of association and effect size. *J Soc Serv Res*. 1996;21(4):37-59.
47. Holm S. A simple sequentially rejective multiple test procedure. *Scand J Stat*. 1979; 6(2):65-70.
48. Klingbeil J, Brandt ML, Wawrzyniak M, et al. Association of lesion location and depressive symptoms poststroke. *Stroke*. 2021;52(3):830-837.
49. Conzen C, Weiss M, Albanna W, et al. Baseline characteristics and outcome for aneurysmal versus non-aneurysmal subarachnoid hemorrhage: a prospective cohort study. *Neurosurg Rev*. 2022;45(2):1413-1420.
50. Stienen MN, Smoll NR, Weisshaupt R, et al. Delayed cerebral ischemia predicts neurocognitive impairment following aneurysmal subarachnoid hemorrhage. *World Neurosurg*. 2014;82(5):e599–e605.
51. Buunk AM, Groen RJM, Wijbenga RA, et al. Mental versus physical fatigue after subarachnoid hemorrhage: differential associations with outcome. *Eur J Neurol*. 2018;25(11):1313–e113.
52. Rakers SE, Timmerman ME, Scheenen M, et al. Trajectories of fatigue, psychological distress, and coping styles after mild traumatic brain injury: a 6-month prospective cohort study. *Arch Phys Med Rehabil*. 2021;102(10):1965-1971.e2.
53. Konczalla J, Platz J, Schuss P, Vatter H, Seifert V, Güresir E. Non-aneurysmal non-traumatic subarachnoid hemorrhage: patient characteristics, clinical outcome and prognostic factors based on a single-center experience in 125 patients. *BMC Neurol*. 2014;14:140-148.
54. Rinkel GJ, Wijdicks EF, Franke C, et al. Outcome in patients with subarachnoid haemorrhage and negative angiography according to pattern of haemorrhage on computed tomography. *Lancet*. 1991;338(8773):964-968.

---

**Supplemental digital content** is available for this article at [neurosurgery-online.com](http://neurosurgery-online.com).

**Table S1.** Course of well-being and cognitive complaints between the subacute (T1) and chronic (T2) stage.

---