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The Diagnostic Value of Near-Infrared Spectroscopy to Predict Delayed Cerebral Ischemia and Unfavorable Outcome After Subarachnoid Hemorrhage

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■ OBJECTIVE: **Near-infrared spectroscopy (NIRS) is a noninvasive tool to monitor cerebral regional oxygen saturation. Impairment of microvascular circulation with subsequent cerebral hypoxia during delayed cerebral ischemia (DCI) is associated with poor functional outcome after subarachnoid hemorrhage (SAH). Therefore, NIRS could be useful to predict the risk for DCI and functional outcome. However, only limited data are available on NIRS regional cerebral tissue oxygen saturation (rSO_2) distribution in SAH. The aim of this study was to compare the distribution of NIRS rSO_2 values in patients with nontraumatic SAH with the occurrence of DCI and functional outcome at 2 months. In addition, the predictive value of NIRS rSO_2 was compared with the previously validated SAFIRE grade (derived from Size of the aneurysm, Age, FIsher grade, World Federation of Neurosurgical Societies after REsuscitation).**

■ METHODS: **In this study, the rSO_2 distribution of patients with and without DCI after SAH was compared. The optimal cutoff points to predict DCI and outcome were assessed, and its predictive value was compared with the SAFIRE grade.**

■ RESULTS: **Of 41 patients, 12 developed DCI, and 9 had unfavorable outcome at 60 days. Prediction of DCI with NIRS had an area under the curve of 0.77 (95% confidence interval 0.62–0.92; $P = 0.0028$) with an optimal cutoff point of 65% (sensitivity 1.00; specificity 0.45). Prediction of favorable outcome with NIRS had an area under the curve of 0.86 (95% confidence interval 0.74–0.98; $P = 0.0003$) with an optimal cutoff point of 63% (sensitivity 1.00; specificity 0.63). Regression analysis showed that NIRS rSO_2 score is complementary to the SAFIRE grade.**

■ CONCLUSIONS: **NIRS rSO_2 monitoring in patients with SAH may improve prediction of DCI and clinical outcome after SAH.**

INTRODUCTION

Subarachnoid hemorrhage (SAH) is a dreaded neurovascular disorder with high mortality and morbidity.[1] Approximately 85% of nontraumatic SAHs are due to an intracranial

Key words
- Delayed cerebral ischemia
- Functional outcome
- Modified Rankin scale
- Near-infrared spectroscopy
- rSO_2
- SAFIRE grade
- Subarachnoid hemorrhage

Abbreviations and Acronyms
aSAH: Aneurysmal subarachnoid hemorrhage
AUC: Area under the curve
CI: Confidence interval
CT: Computed tomography
CTA: Computed tomography angiography
CTP: Computed tomography perfusion
CW: Continuous wave
DCI: Delayed cerebral ischemia
mRS: Modified Rankin scale
NIRS: Near-infrared spectroscopy
OR: Odds ratio
ROC: Receiver operator characteristic
rSO_2: Regional cerebral tissue oxygen saturation
rWFNS: World Federation of Neurosurgical Societies grading after resuscitation
SAFIRE grade: Size aneurysm, Age, FIsher grade, World Federation of Neurosurgical Societies grading after REsuscitation
SAH: Subarachnoid hemorrhage
TCD: Transcranial Doppler

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aneurysm (aSAH). The other 15% consist of perimesencephalic SAH or are due to a variety of underlying diseases (amyloid angiopathy, vasculitis, arteriovenous malformations/fistulas).[2] The incidence of aSAH is 9 in 100,000 persons per year. Despite many improvements in treatment and subsequently better clinical outcomes over the recent decades, case fatality is approximately 35%, and one-third of survivors have a poor outcome. The societal and personal burden of aSAH is therefore high, given that aSAH occurs in relatively young patients (mean age 55 years).[3]

Functional outcome after nontraumatic SAH is determined by complications such as hydrocephalus, secondary vasospasm, delayed cerebral ischemia (DCI), rebleeding, hyponatremia, and electrocardiographic changes.[2] Diagnosis, prevention, and treatment of DCI are complex but highly relevant, as DCI may result in irreversible cerebral infarction.[4,5] The pathophysiology of DCI is much debated. In the past, theories were mainly focused on a direct relation with macrovascular vasospasm. Nowadays, multifactorial causes such as micro- and macrovascular dysfunction, microthrombosis, cortical spreading depolarization, and neuroinflammation are considered important.[6,7] Imaging techniques to capture the microvasculature are digital subtraction angiography and computed tomography perfusion (CTP), by measuring cerebral circulation time or related indicators as mean transit time and time to peak.[7] Since microvascular supply is essential to deliver oxygen and glucose, this metabolic demand also can be measured with techniques such as positron emission tomography and single-photon emission computed tomography. Another way to measure metabolic demand is brain tissue oxygen monitoring and microdialysis, both however having the disadvantage of their invasiveness.[8]

Near-infrared spectroscopy (NIRS) is a light-spectroscopy technique that uses the relation between absorbed light in tissue and the regional cerebral tissue oxygen saturation (rSO_2). In continuous-wave (CW) NIRS, the venous, capillary respectively arterial ratios are assumed to be 70% respectively 30%. NIRS thus significantly reflects changes in rSO_2 in the cerebral venous system. It is a noninvasive tool with a high temporal resolution. Its measurement is applicable at the bedside and independent of technician skills, but the main disadvantage of NIRS is its low spatial resolution and possible contamination of the signal from extracerebral sources.[9,10] A strong relationship between metabolic demand and microvasculature status has been established and is also apparent from the strong correlation between CTP and NIRS.[11]

The purpose of the present study was to compare the distribution of NIRS rSO_2 values in patients with nontraumatic SAH with the occurrence of DCI and functional outcome at 2 months. In addition, the predictive value of NIRS rSO_2 was compared with the previously validated SAFIRE grade (derived from Size of the aneurysm, Age, FIsher grade, world federation of neurosurgical societies after REsuscitation [rWFNS]).[12]

METHODS

Data Availability Statement

The data supporting the conclusions of this article will be made available by the corresponding author upon reasonable request.

Patient Selection

This study retrospectively analyzed prospectively kept data of patients with nontraumatic SAH admitted to the university neurovascular unit (tertiary care) from August 2013 to August 2015. Adult patients aged 18 and older were included if they had at least 1 NIRS measurement of sufficient quality and if follow-up data (functional outcome and DCI) were available. The research ethical board approved the study. Due to its retrospective nature, it met the requirements for waiving informed consent. The no objection register was consulted for each patient. NIRS measurements were performed on different follow-up days, depending on request of transcranial Doppler (TCD) within regular patient care NIRS measurement were performed subsequently.

All patients were treated according to national SAH-management guidelines, based on American Heart Association guidelines and European Stroke Organization Guidelines.[13,14] The protocol included oral nimodipine, fluid management to prevent hypovolemia, and frequent evaluation of the neurologic condition. DCI was determined upon exclusion of other causes of neurologic deterioration, such as hydrocephalus, rebleeding, seizures, and metabolic disturbances. If DCI was suspected, blood pressure augmentation was induced in the intensive care unit.[15]

NIRS Assessment

The INVOS 5100C oximeter device (Somanetics Corp., Detroit, Michigan, USA) was used for measuring 2 channels rSO_2 with a sampling frequency of 0.2 Hz. Two adhesive somatic sensors (optodes) were placed on each side of the forehead according to the manufacturer's recommendations. NIRS measurements were usually repeated 1–3 times, depending on the clinical condition. Raw NIRS data from the INVOS 5100C oximeter device were analyzed in MATLAB, version R2021a (MathWorks, Natick, Massachusetts, USA). Artifacts were removed. A moving average filter of 15 backward samples was used to smooth the signals (**Figure 1**). After editing, the mean and standard deviation were calculated over the whole measurement.

Clinical and Radiologic Assessment

Baseline characteristics sex, age, hypertension, smoking, rWFNS,[12] modified Fisher scale, aneurysm location, type SAH, size aneurysm (millimeters), DCI and modified Rankin Scale (mRS) were available variables in the institutional neurovascular database. The previous SAFIRE study also was based on this database, which includes a total of 1839 patients with nontraumatic SAH. The rWFNS was determined by the best neurologic WFNS score after neurologic resuscitation, within 12 hours after the intervention.[12] Modified Fisher scale was based on computed tomography (CT) of the head on admission grading from 0 for scans without SAH to 4 depending on the degree of SAH and the presence of intraventricular hemorrhage.[16] Location of an aneurysm, if applicable, was dichotomized in the anterior and posterior circulation. Main vessels and their branches defined as anterior circulation were the internal carotid artery, middle cerebral artery, anterior cerebral artery, anterior communicating artery, and carotid branches (ophthalmic artery and anterior choroidal artery). Posteriorly located

vessels and their branches were the posterior communicating artery, posterior cerebral artery, basilar artery, superior cerebellar artery, anterior inferior cerebellar artery, posterior inferior cerebellar artery, and vertebral artery.[17] Type of nontraumatic SAH included aneurysmal-type or perimesencephalic SAH.

Predictive Variable

In addition to the rSO_2, the SAFIRE grading scale was used to predict outcome. The SAFIRE grade is a composite score consisting of a points system on variables available within the baseline characteristics. The variables counted in the SAFIRE are size aneurysm, age, Fisher grade, and rWFNS (ranging from 0 to 22 points). These points determine the SAFIRE grade, where a greater grade has a greater likelihood of an unfavorable outcome.[12]

Outcome Variables

DCI and functional outcome measured with mRS were used as outcome variables. DCI was defined by reduced consciousness or focal neurologic deficits or new infarction on follow-up imaging (CT or magnetic resonance imaging of the head) by the exclusion of other causes such as epilepsy, hydrocephalus, and systemic factors.[5] Assessment of DCI on imaging was established by an experienced radiologist on CT or magnetic resonance imaging performed within 6 months after SAH. Functional outcome was obtained with mRS score at 2 months after SAH, or mRS score at discharge (if mRS at 2 months was not available). The mRS score was dichotomized into mRS ≤ 3, representing favorable functional outcome, and mRS >3, representing unfavorable functional outcome.[18]

Statistical Analysis

Statistical analysis was performed in R (version 4.0; R Foundation for Statistical Computing, Vienna, Austria) under RStudio 2021 (version 1.4). Given the small sample size and non-Gaussian distribution, medians of groups were compared with Mann–Whitney U test. For categorical data, contingency tables with the Fisher exact test were used. Receiver operator characteristic (ROC) analyses were used to determine the diagnostic value of NIRS and SAFIRE Grading Scale. The area under the curve (AUC) quantifies diagnostic accuracy. The Youden index for rSO_2 predicting DCI and functional outcome set the optimal cutoff value. The optimal cutoff value was used to assess diagnostic accuracy with contingency analysis, including sensitivity, specificity, positive predictive value, negative predictive value, and accuracy ([true positive + true negative]/total number of cases). Statistical significance was determined by a 2-sided probability value of <0.05. The results of the univariate analysis were used to select independent variables with a $P < 0.1$ for multivariate logistic regression analysis. Variables that are part of the SAFIRE grading scale are not separately included in the multivariate logistic regression analysis. Because of the separation of this relatively small sample, Firth's correction is used within the regression analysis. Firth's correction reduces the bias of maximum likelihood. Important for this relatively small sample Firth's correction estimates parameters with infinity to finiteness by penalized maximum likelihood estimation.[19] Confidence intervals were set at 95%.

RESULTS

Study Population

In this study, 41 patients were included. Twelve patients developed DCI, and 9 had an unfavorable functional outcome (mRS >3). The baseline characteristics are presented in Table 1.

Outcome

Univariate statistical analysis of baseline characteristics of patients with and without DCI showed a significant difference for smoking. The rWFNS score and the Modified Fisher scale were both significantly different in patients with favorable and unfavorable functional outcome. In the group of 29 patients without DCI, 3 (10%) had an unfavorable functional outcome (mRS >3). Of the 12 patients with DCI, 6 (50%) had unfavorable functional outcomes. Of the 9 patients with unfavorable functional outcome, 6 (67%) had DCI, and of the 32 patients with favorable functional outcome, 6 (19%) had DCI (Supplementary Table 1 and Supplementary Figure 1).

NIRS rSO_2 and SAFIRE Grade

The median rSO_2 was significantly lower for patients with DCI ($P = 0.006$; Table 2 and Figure 1). In addition, the median rSO_2 was lower for patients with an unfavorable functional outcome ($P = 0.001$; Table 2 and Figure 1). The median interval between the ictus and NIRS measurements was 8.2 days, which did not differ significantly between groups ($P = 0.80$ and $P = 0.61$; Table 2). For the whole group, the median number of subsequent NIRS measurements was 2 and the median samples per measurement were 418. For functional outcome, subsequent measurements and samples did not differ significantly between groups ($P = 0.75$ and $P = 0.92$). Patients with DCI had significantly more measurements and samples than those without DCI ($P = 0.003$ and $P = 0.005$; Table 2).

In patients with DCI, median SAFIRE grade was significantly greater compared with patients without DCI ($P = 0.027$; Table 2). For unfavorable functional outcome, median SAFIRE grade was significantly greater compared with favorable functional outcome ($P = 0.025$; Table 2).

ROC Curve Analysis and Contingency Table Analysis

Predicting DCI. Panel E of Figure 1 shows the ROC curve for predicting DCI. The AUC of NIRS rSO_2 was 0.77 (95% confidence interval [CI] 0.62–0.92; $P = 0.0028$) and for the SAFIRE grade 0.66 (95% CI 0.48–0.87; $P = 0.040$) for predicting DCI. The optimal rSO_2 cutoff point for predicting DCI estimated by the Youden index was 65%, with a sensitivity of 1.00 and a specificity of 0.45 (see also positive predictive value, negative predictive value, and accuracy in Table 3 and Supplementary Table 2).

Predicting Functional Outcome. For predicting unfavorable functional outcome, the AUC of NIRS rSO_2 was 0.86 (95% CI 0.74–0.98; $P = 0.0003$) and for the SAFIRE grade 0.75 (95% CI 0.55–0.96; $P = 0.012$; Figure 1F). The optimal rSO_2 cutoff point for predicting functional outcome estimated by the Youden index was 63%. This cutoff yields a sensitivity of 1.00 and specificity of 0.63 (see also Table 3 and Supplementary Table 3).

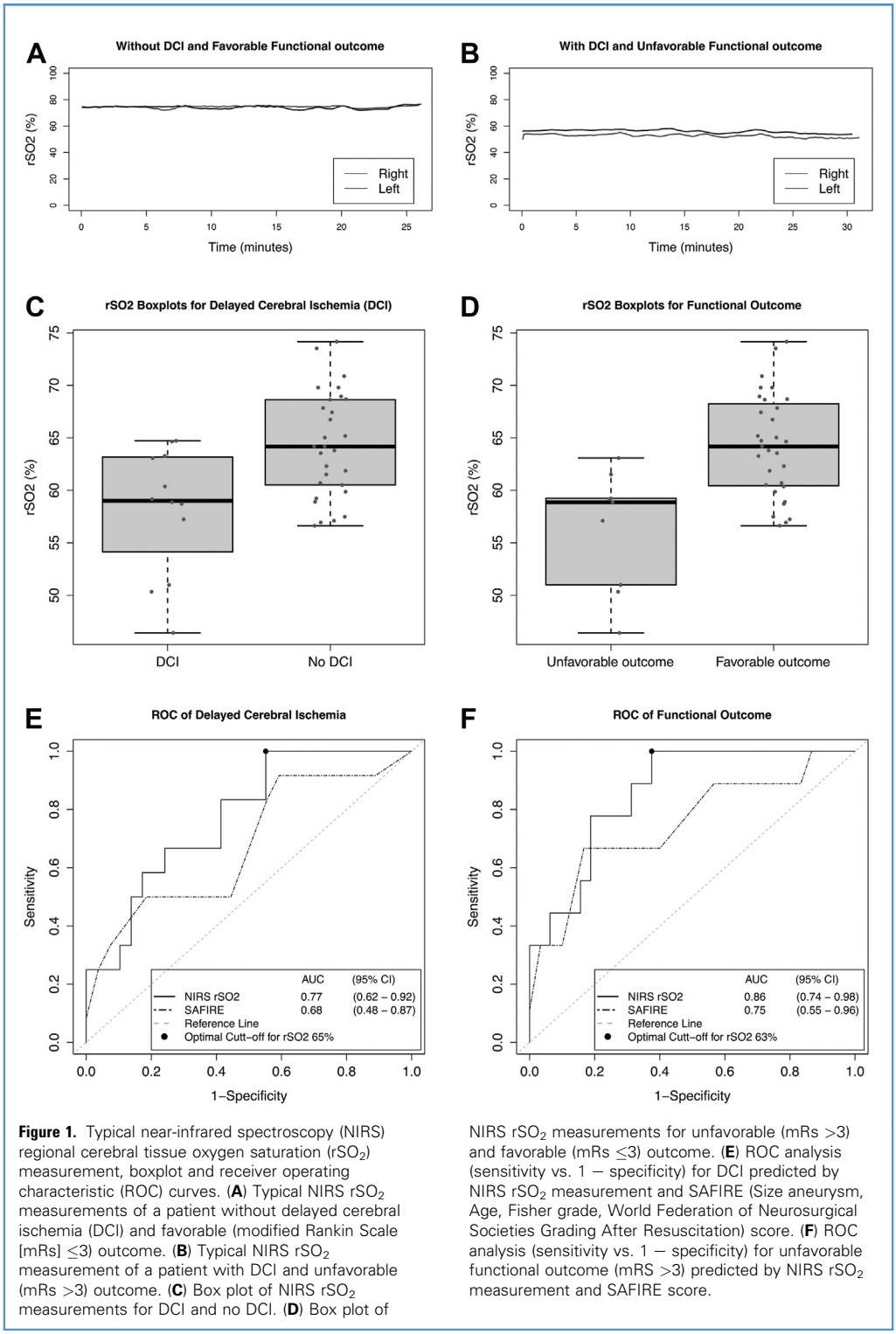

Figure 1. Typical near-infrared spectroscopy (NIRS) regional cerebral tissue oxygen saturation (rSO_2) measurement, boxplot and receiver operating characteristic (ROC) curves. (**A**) Typical NIRS rSO_2 measurements of a patient without delayed cerebral ischemia (DCI) and favorable (modified Rankin Scale [mRs] ≤3) outcome. (**B**) Typical NIRS rSO_2 measurement of a patient with DCI and unfavorable (mRs >3) outcome. (**C**) Box plot of NIRS rSO_2 measurements for DCI and no DCI. (**D**) Box plot of NIRS rSO_2 measurements for unfavorable (mRs >3) and favorable (mRs ≤3) outcome. (**E**) ROC analysis (sensitivity vs. 1 − specificity) for DCI predicted by NIRS rSO_2 measurement and SAFIRE (Size aneurysm, Age, Fisher grade, World Federation of Neurosurgical Societies Grading After Resuscitation) score. (**F**) ROC analysis (sensitivity vs. 1 − specificity) for unfavorable functional outcome (mRS >3) predicted by NIRS rSO_2 measurement and SAFIRE score.

Logistic Regression Analysis. In multivariable logistic regression analysis, $rSO_2 < 65$ (odds ratio [OR] 14.06; 95% CI 1.18–2103.54; $P = 0.034$), SAFIRE grade (OR per grade increase 2.36; (95% CI 1.00–7.14; $P = 0.050$) and smoking (OR 11.34; 95% CI 1.30–92.10; $P = 0.026$) were associated with DCI. For unfavorable outcome (mRS >3), logistic regression analysis revealed $rSO_2 < 63$ (OR

Table 1. Patient Characteristics

	Overall, $n = 41$
Female	27 (66%)
Age, years, median (IQR)	61 (51, 68)
Hypertension	16 (39%)
Smoking	6 (17%)
World Federation of Neurosurgical Societies grading after neurological resuscitation	
I	20 (49%)
II	14 (34%)
IV	5 (12%)
V	2 (4.9%)
Modified Fisher scale	
0	0 (0%)
1	11 (27%)
2	15 (37%)
3	7 (17%)
4	8 (20%)
Location aneurysm, type SAH, and size aneurysm	
Anterior	20 (49%)
Posterior	17 (41%)
Perimesencephalic	4 (9.8%)
Size aneurysm, mm, median (IQR)	6.0 (4.0, 8.2)
Treatment	
None*	6 (15%)
Coiling	29 (71%)
Clipping	6 (15%)

IQR, interquartile range; SAH, subarachnoid hemorrhage.
*Two patients with aneurysm were not treated, one because very old age with severe comorbidity and the other because complex treatment would for a very small aneurysm resulting in high treatment risk compared natural history. The other 4 patients had perimesencephalic hemorrhage.

23.07; 95% CI 2.44–3091; P = 0.003) and the SAFIRE grade (OR per grade increase 1.93; 95% CI 0.91–4.69; P = 0.087) as significant predictors (Figure 2).

DISCUSSION

In this single-center study, we found that a decrease in NIRS rSO_2 below 65/63% reliably predicted DCI and unfavorable outcome.

Clinical Implications

Thus, with a sensitivity of 1.00, all patients with DCI had rSO_2 values less than 65% and for unfavorable outcome below 63%. The positive predictive value of 0.43 for DCI and unfavorable functional outcome implies that 57% of the patients do not have DCI or unfavorable outcome when rSO_2 is below the estimated cutoff values. The specificity of, respectively, 0.45 and 0.63 shows that not all patients without DCI and with favorable outcome have rSO_2 values greater than 63% and 65%. As such, these cutoff values can be useful as a screening tool to select those patients with SAH at risk for DCI. Early detection of DCI can potentially avoid irreversible brain damage for patients with risk of developing DCI and unfavorable functional outcome. This includes decisions such as whether to keep patients with SAH admitted or discharged, guiding extra diagnostics, monitoring or not, and directing (future) treatments.

The rSO_2 measurements described in this study were in good agreement with available literature. The median rSO_2 value of 64% (interquartile range 61–68) for patients without DCI and good functional outcomes were comparable with cardiac patients in a preoperative setting, in whom rSO_2 values of 65%–75% are considered normal.[20] In a study of 14 patients with aSAH without vasospasm, rSO_2 values measured 73.9% ± 1.8, and after vasospasm, 64.1% ± 2.5.[21] The rSO_2 values in this cohort tend to be greater, particularly before vasospasm. This study considered macrovascular vasospasm as an outcome measure, which is questionable since macrovascular vasospasm has no strong relation with DCI and functional outcome.[5,15] A study by Yousef et al.[22] used a cutoff point of rSO_2 <50% to predict DCI and functional outcome but did not explain why the rSO_2 of 50% was chosen. They showed that a rSO_2 <50% gave an OR of 3.25 (CI 1.58–6.69) for DCI and an OR of 2.72 (CI 1.02–7.20) for unfavorable outcome. In our study, the OR at estimated cutoff values tends to be greater with a large CI.

Other studies use NIRS to assess cerebral autoregulation. However, these complex methods do not appear to predict DCI better.[23] A recent study by Park et al.,[10] including 54 patients with aSAH, is very consistent with the values found in our study. They showed that rSO_2 values for patients with DCI decreased to 59.5% (56.9%–64.5%), whereas the non-DCI group did not get below 63.3% (59.7%–68.7%). Their study used percent changes as a predictor of vasospasm with day 1 as the reference standard. From that level, a decrease of rSO_2 with >12.7% predicted DCI with a sensitivity of 94% (95% CI 73%–100%) and a specificity of 71% (95% CI 52%–85%). The sensitivity was comparable with our study, with greater specificity. The crucial difference with our study is that the study we present uses an absolute cutoff point. The advantage of an absolute cutoff value is that it is readily available without baseline measurement, requires no calculations, and is easy to interpret. On the other hand, a disadvantage of absolute cutoff values is that our study has a lower specificity (45%), although this also has other explanations, e.g., fewer measurements.

Advantages of NIRS

Compared with other modalities such as digital subtraction angiography, computed tomography angiography (CTA), and CTP, NIRS predicts DCI and functional outcome quite accurately. These other modalities have a sensitivity and specificity of 70%–80%.[8] In our previous study, we found an even lower sensitivity and specificity for CTA and TCD in predicting DCI and functional outcome (CTA sensitivity 81%, specificity 7%; TCD sensitivity

Table 2. NIRS and SAFIRE Grading Scale in Patients with DCI and without DCI, and with Unfavorable Functional Outcome and Favorable Functional Outcome

	Overall, $n = 41$	DCI, $n = 12$	No DCI, $n = 29$	*P* Value	mRS >3, $n = 9$	mRS ≤3, $n = 32$	*P* Value
Day of NIRS measurements	8.2 (5.0, 11.0)	7.8 (6.4, 10.4)	8.4 (5.0, 11.0)	0.80	10.0 (5.6, 11.1)	8.2 (5.0, 10.9)	0.61
NIRS measurements	2 (1, 3)	3 (2, 4)	1 (1, 2)	**0.003**	2 (1, 2)	2 (1, 3)	0.75
rSO_2 samples	418 (220, 752)	654 (554, 1,077)	312 (182, 538)	**0.005**	482 (212, 680)	394 (240, 772)	0.92
rSO_2	63.1 (58.9, 66.7)	59.0 (55.7, 63.1)	64.2 (60.5, 68.6)	**0.006**	58.9 (51.0, 59.2)	64.2 (60.5, 68.0)	**<0.001**
SAFIRE grade	2.0 (1.0, 3.0)	2.5 (2.0, 4.00)	2.0 (1.0, 2.5)	**0.027**	3.0 (2.0, 4.0)	2.0 (1.0, 2.0)	**0.025**

Median with interquartile range (IQR). $P < 0.05$ was considered significant (indicated in bold).
NIRS, near-infrared spectroscopy; SAFIRE, Size Aneurysm, Age, Fisher grade, World Federation of Neurosurgical Societies Grading After Resuscitation; DCI, delayed cerebral ischemia; mRS, modified Rankin Scale; rSO_2, regional cerebral tissue oxygen saturation; IQR, interquartile range.

44%, and specificity 67%).[15] The CTA vasospasm score showed a clear added value and resulted in a sensitivity of 71% and specificity of 62% for predicting DCI, although not superior than the current NIRS study, which underlines the importance of monitoring the microvascular status. Microvascular status is reported to be directly related to macrovascular status and cerebral autoregulation.[24] Therefore, macrovascular vasospasm may be absent in the presence of microvascular vasospasm and vice versa, which illustrates the complexity of the pathophysiology of DCI.[6,7] All in all, microvascular dysfunction appears to be a better predictor of DCI.[7,10,21]

Limitations

In general, NIRS measurements have several limitations. First, most devices have only limited channels, monitoring a restricted area of the brain. Our INVOS 5100C device has 2 channels with optodes placed on the forehead in accordance with the manufacturer's recommendation.[10] Our measurements mainly focused on watershed border zones between anterior cerebral artery and middle cerebral artery.[25] Hence, due to the limited number of channels, our measurement were less sensitive to microvascular problems in other vascular supplies.[25-27] That the risk of DCI can be derived from one vascular territory even when hemorrhage is not located in this territory can probably explained by the fact that the whole brain shows signs of vascular dysfunction. This vascular dysfunction is related to an increased risk of developing DCI. Vascular dysfunction in SAH is related to a more generalized process related to reduced cerebrovascular autoregulation, spreading depolarizations and inflammation. These processes occur throughout the brain and are phenomena not limited to one single vascular territory.[28] This is consistent with a study from our group, where poor outcome often was associated with generalized vasospasm on CTA, although the severity may differ depending on a measurement location.[29] The pattern of diffuse vasospasm in SAH is also supported, given the strong correlation of frontal NIRS with CTP[11] and autoregulation coefficients based on frontal NIRS which shows to be related to other measures of autoregulation and outcome.[23]

Second, various confounders affect light attenuation, influencing rSO_2 measurements, including extracranial tissue (skull), ratios of arterial/venous oxyhemoglobin influencing relative rSO_2 estimation, and motion artifacts.[27] If patients had a craniotomy, tissue composition is changed, significantly influencing rSO_2 measurements. Therefore, rSO_2 measurements should preferably not be taken on the side of craniotomy.[10,11] Third, from a theoretical point of view, the absolute rSO_2 values in CW-NIRS should be interpreted cautiously because these rSO_2 values are approximated based on a calibrated algorithm. Approximations induce errors that can be reduced by looking at rSO_2 changes, trends, and comparison with baseline,[9,30] in contrast to the more complex devices using multiple wavelengths in frequency or time domain (i.e., FD-NIRS and TD-NIRS) that can determine an absolute absorption coefficient.[9]

This study also has specific limitations. First, NIRS data were retrospectively analyzed with the risk of selection bias. Second, NIRS measurements were not taken at fixed times but at the discretion of clinicians. Also, snapshot measurements were used for analysis. Continuous measurements could have provided more information about trends. Besides, establishing a baseline rSO_2 early in the course of the disease would possibly also be of added value. Nevertheless, we did find a relationship between rSO_2 measurements and outcome. Third, the relatively small sample size and determination of the optimal cutoff point with the Youden index have led to the fact that there were no false-negative patients. The cutoff point based on the Youden index resulted in a maximum sensitivity of 1.00 for which the cut-off values were not specifically aimed (**Table 2**, **Supplementary Tables 2** and **3**). This makes the CI of the maximum odds ratios very large (nonconvergence due to complete separation). Fourth, the SAFIRE grade was validated to predict functional outcome. In addition, in the current study, the SAFIRE grade also was used to predict DCI, for which the SAFIRE grade was not validated. Fifth, our outcome measures DCI and functional outcome have been determined during the disease; however, it cannot be excluded that these outcome events occurred already before a NIRS measurement took place. Sixth, our cutoff values of rSO_2 were optimized for the present study data and the used NIRS device, the INVOS 5100C oximeter. Optimal absolute cutoff values may need to be determined per device, especially in the

Table 3. Diagnostic Accuracy with Contingency Analysis for rSO_2 Predicting DCI and Functional Outcome

	AUC	95% CI	*P* Value	Cut-off	Sen	Spe	PPV	NPV	AC
DCI	0.77	0.62—0.92	<0.01	65	1.00	0.45	0.43	1.00	0.61
Functional outcome*	0.86	0.74—0.98	<0.01	63	1.00	0.63	0.43	1.00	0.71

rSO_2, regional cerebral tissue oxygen saturation; DCI, delayed cerebral ischemia; AUC, area under curve; CI, confidence interval; Sen, sensitivity Spe, specificity; PPV, positive predictive value; NPV, negative predictive value; AC, accuracy; mRS, modified Rankin Scale.
*Functional outcome is dichotomized in unfavorable outcome mRS >3 and favorable outcome mRS ≤3.

CW-NIRS devices, since rSO_2 is approximated through an algorithm that may vary between manufacturers (see the second limitation of this study).

Our study shows that the most basic rSO_2 value of a 2-channel NIRS gives valuable information about the condition of patients with nontraumatic SAH predicting the risk of developing DCI and unfavorable functional outcome. Currently, NIRS is only used to a limited extent in daily practice for monitoring patients with SAH, although NIRS is easy to apply bedside and is also very usable for long-term monitoring. The limited use may be partly caused by often extra calculations applied to interpret rSO_2 values, whereas our study shows that this is not necessarily necessary. This finding requires confirmation in a larger prospectively collected sample of patients with nontraumatic SAH. In addition, the subject of further studies can be continuous NIRS monitoring or even use as standard care instead of other monitoring modalities like TCD measurements, which usefulness for this purpose is a matter of debate. The subsequent step can be to use NIRS to target and monitor therapeutic choices.

CONCLUSIONS

NIRS rSO_2 values below estimated cutoff values appear to be a risk factor for DCI and unfavorable outcome. As such, NIRS rSO_2 showed a clear added value to known patient characteristics and the SAFIRE score.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript.

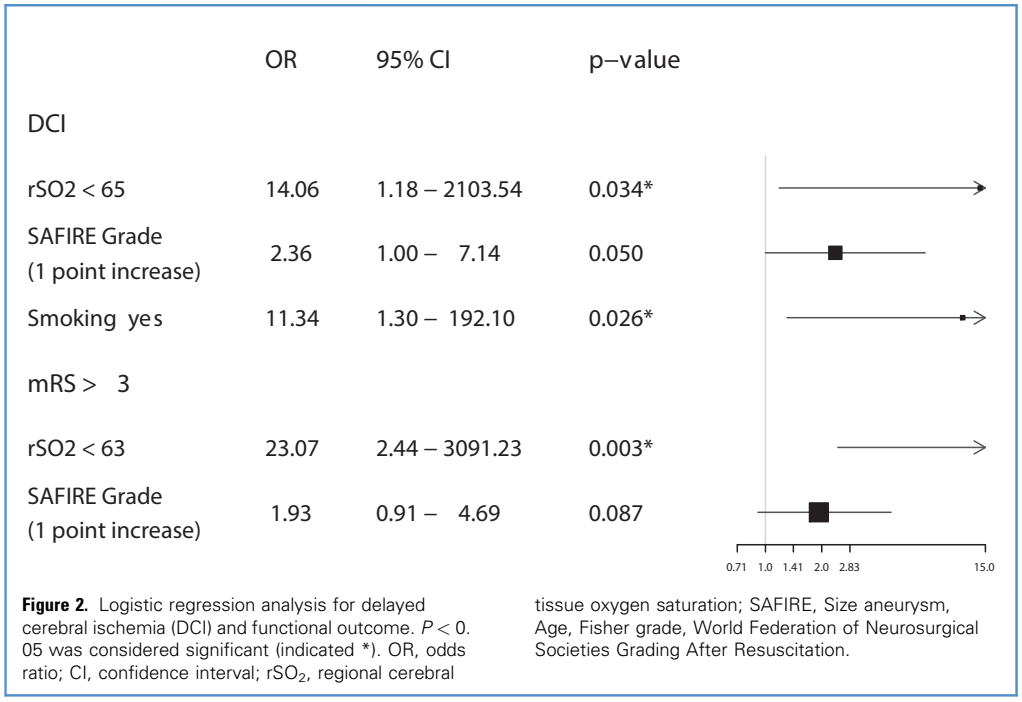

Figure 2. Logistic regression analysis for delayed cerebral ischemia (DCI) and functional outcome. $P < 0.05$ was considered significant (indicated *). OR, odds ratio; CI, confidence interval; rSO_2, regional cerebral tissue oxygen saturation; SAFIRE, Size aneurysm, Age, Fisher grade, World Federation of Neurosurgical Societies Grading After Resuscitation.

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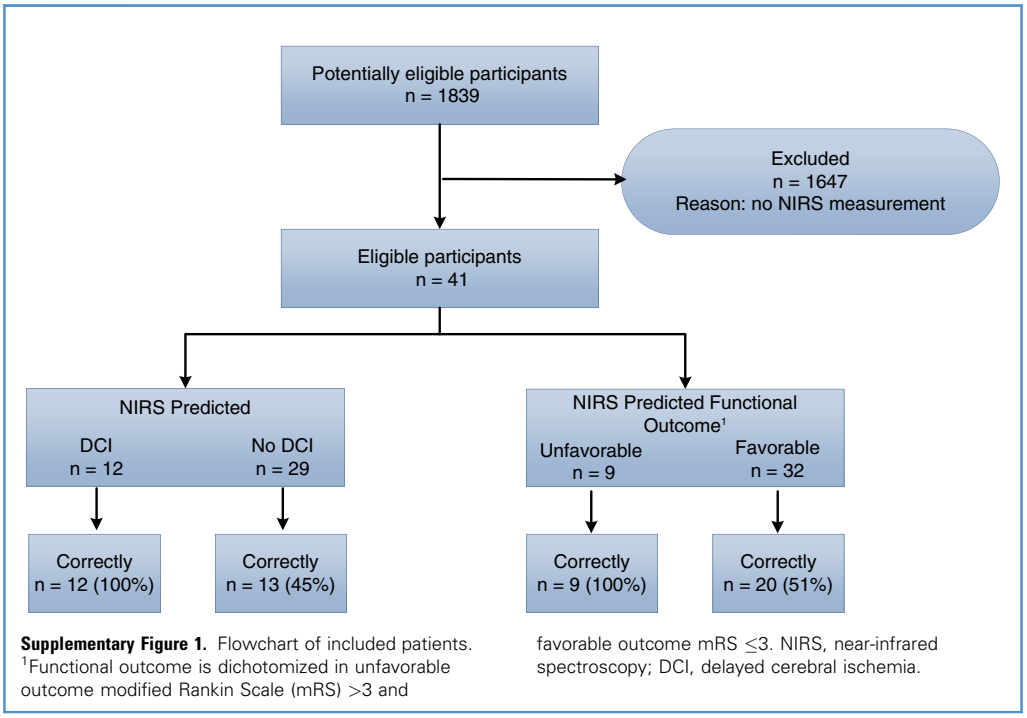
SUPPLEMENTARY DATA



Supplementary Figure 1. Flowchart of included patients. [1]Functional outcome is dichotomized in unfavorable outcome modified Rankin Scale (mRS) >3 and favorable outcome mRS ≤3. NIRS, near-infrared spectroscopy; DCI, delayed cerebral ischemia.

Supplementary Table 1. Patient Characteristics for DCI and Functional Outcome

	Overall	DCI	No DCI		mRS > 3	mRS ≤3	
	n = 41	*n* = 12	*n* = 29	*P* Value	*n* = 9	*n* = 32	*P* Value
Female	27 (66%)	9 (75%)	18 (62%)	0.49	6 (67%)	21 (66%)	>0.99
Age, years, median (IQR)	61 (51, 68)	62 (56, 64)	61 (48, 70)	0.82	63 (54, 68)	61 (48, 67)	0.36
Hypertension	16 (39%)	7 (58%)	9 (31%)	0.16	3 (33%)	13 (41%)	>0.99
Smoking	6 (17%)	4 (40%)	2 (8.0%)	**0.043**	3 (38%)	3 (11%)	0.12
rWFNS				0.051			**0.005**
I	20 (49%)	4 (33%)	16 (55%)		3 (33%)	17 (53%)	
II	14 (34%)	3 (25%)	11 (38%)		1 (11%)	13 (41%)	
IV	5 (12%)	4 (33%)	1 (3.4%)		4 (44%)	1 (3.1%)	
V	2 (4.9%)	1 (8.3%)	1 (3.4%)		1 (11%)	1 (3.1%)	
Modified Fisher scale				0.067			**0.003**
0, No SAH or IVH	0 (0%)	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
1, Thin SAH no IVH	11 (27%)	1 (8.3%)	10 (34%)		0 (0%)	11 (34%)	
2, Thin SAH with IVH	15 (37%)	3 (25%)	12 (41%)		2 (22%)	13 (41%)	
3, Thick SAH no IVH	7 (17%)	4 (33%)	3 (10%)		5 (56%)	2 (6.2%)	
4, Thick SAH with IVH	8 (20%)	4 (33%)	4 (14%)		2 (22%)	6 (19%)	
Location aneurysm, type SAH, and size aneurysm				0.88			>0.99
Anterior	20 (49%)	5 (42%)	15 (52%)		4 (44%)	16 (50%)	
Posterior	17 (41%)	6 (50%)	11 (38%)		4 (44%)	13 (41%)	
Perimesencephalic	4 (9.8%)	1 (8.3%)	3 (10%)		1 (11%)	3 (9.4%)	
Size aneurysm, mm, median (IQR)	6.0 (4.0, 8.2)	6.0 (5.5, 8.5)	6.0 (3.0, 8.0)	0.19	8.0 (6.0, 10.8)	5.5 (4.0, 7.2)	0.12
Treatment				>0.99			0.58
None	6 (15%)	1 (8%)	5 (17%)		2 (22%)	4 (13%)	
Coiling	29 (71%)	9 (75%)	20 (69%)		5 (56%)	24 (75%)	
Clipping	6 (15%)	2 (17%)	4 (14%)		2 (22%)	4 (13%)	
Functional outcome (dichotomized mRS)				**0.011**			–
mRS >3 9 (22%)		6 (50%) 3 (10%)			–	–	
mRS ≤3 32 (78%)		6 (50%) 26 (90%)			–	–	
DIC				–			**0.011**
DCI 12 (29%)		–			6 (67%)	6 (19%)	
No DCI 29 (71%)		–			3 (33%)	26 (81%)	
Modified Rankin Scale				**0.013**			**<0.001**
0, No symptoms		6 (15%)	0 (0%)	6 (21%)	0 (0%)	6 (19%)	
1, No significant disability		14 (34%)	1 (8.3%)	13 (45%)	0 (0%)	14 (44%)	
2, Slight disability		7 (17%)	3 (25%)	4 (14%)	0 (0%)	7 (22%)	
3, Moderate disability		5 (12%)	2 (17%)	3 (10%)	0 (0%)	5 (16%)	
4, Moderately severe		5 (12%)	3 (25%)	2 (6.9%)	5 (56%)	0 (0%)	
5, Severe disability		1 (2.4%)	1 (8.3%)	0 (0%)	1 (11%)	0 (0%)	
6, Dead		3 (7.3%)	2 (17%)	1 (3.4%)	3 (33%)	0 (0%)	

$P < 0.05$ was considered significant (indicated in bold). Where applicable, medians with IQR are presented.
DCI, delayed cerebral ischemia; mRS, modified Rankin Scale; IQR, interquartile range; rWFNS, World Federation of Neurosurgical Societies grading scale after neurological resuscitation; SAH, subarachnoid hemorrhage; IVH, Intraventricular hemorrhage.

Supplementary Table 2. Contingency Table for NIRS Predicting DCI

NIRS	DCI	No DCI	Total
rSO_2 <65	12 (29%)	16 (39%)	28 (68%)
rSO_2 ≥65	0 (0%)	13 (32%)	13 (32%)
Total	12 (29%)	29 (71%)	41 (100%)

Fisher exact test, $P = 0.007$.
NIRS, near-infrared spectroscopy; DCI, delayed cerebral ischemia; rSO_2, regional cerebral tissue oxygen saturation.

Supplementary Table 3. Contingency Table for NIRS Predicting Functional Outcome

NIRS	mRS >3	mRS ≤3	Total
rSO_2 <63	9 (22%)	12 (29%)	21 (51%)
rSO_2 ≥63	0 (0%)	20 (49%)	20 (49%)
Total	9 (22%)	32 (78%)	41 (100%)

Fisher exact test, $P = 0.001$.
NIRS, near-infrared spectroscopy; mRS, modified Rankin Scale; rSO_2, regional cerebral tissue oxygen saturation.