Prediction of clinical outcome in subacute subarachnoid hemorrhage using diffusion tensor imaging

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OBJECTIVE Clinical outcome in nontraumatic subarachnoid hemorrhage (SAH) is multifactorial and difficult to predict. Diffusion tensor imaging (DTI) findings are a prognostic marker in some diseases such as traumatic brain injury. The authors hypothesized that DTI parameters measured in the subacute phase of SAH can be associated with a poor clinical outcome.

METHODS Diffusion tensor imaging was prospectively performed in 54 patients at 8–10 days after nontraumatic SAH. Logistic regression analysis was performed to evaluate the association of fractional anisotropy (FA) and apparent diffusion coefficient (ADC) values with a poor clinical outcome (modified Rankin Scale score ≥ 3) at 3 months.

RESULTS At 8–10 days post-SAH, after adjusting for other variables associated with a poor outcome, an increased ADC at the frontal centrum semiovale was associated with a poor prognosis (OR estimate 1.29, 95% CI 1.04–1.60, $p = 0.020$). Moreover, an increase of 0.1 in the FA value at the corpus callosum at 8–10 days after SAH corresponded to 66% lower odds of having a poor outcome ($p = 0.002$).

CONCLUSIONS Decreased FA and increased ADC values in specific brain regions were independently associated with a poor clinical outcome after SAH. This preliminary exploratory study supports a potential role for DTI in predicting the outcome of SAH.

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KEYWORDS subarachnoid hemorrhage; diffusion tensor imaging; clinical outcome; vascular disorders

SPONTANEOUS subarachnoid hemorrhage (SAH) has high mortality and morbidity.¹⁹ Most prognostic factors are present on admission, and others develop a few days later, for example, hydrocephalus or delayed cerebral ischemia (DCI).^{15,17,29–31}

Magnetic resonance imaging (MRI), in particular diffusion tensor imaging (DTI), is a sensitive noninvasive tool for detecting neuronal injury. The measurement of parameters such as fractional anisotropy (FA) and apparent diffusion coefficient (ADC) allows for indirect evaluation of white matter integrity and the presence of cytotoxic

edema, respectively.²⁶ Diffusion tensor imaging evaluation has proved to be a valuable tool for predicting prognosis in traumatic brain injury, in which reductions in FA have been associated with an unfavorable long-term outcome,⁴⁰ as well as in small vessel disease.²⁷

Changes in FA values over time have been reported in patients with SAH, especially in those who develop DCI.¹⁰ Although a reduction in ADC values in the cerebral white matter has been described in the vasospasm period,⁴ other studies have found an increase in ADC values in normal-appearing white matter in both the acute³⁸ and the sub-

ABBREVIATIONS ADC = apparent diffusion coefficient; AUC = area under the ROC curve; DCI = delayed cerebral ischemia; DTI = diffusion tensor imaging; DWI = diffusion-weighted imaging; FA = fractional anisotropy; GCS = Glasgow Coma Scale; HH = Hunt and Hess; MRI = magnetic resonance imaging; mRS = modified Rankin Scale; PLIC = posterior limb of internal capsule; ROC = receiver operating characteristic; ROI = region of interest; SAH = subarachnoid hemorrhage; WFNS = World Federation of Neurosurgical Societies.

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acute²⁵ phase, suggesting the presence of vasogenic edema. However, the relation of these changes to prognosis has been less studied: one analysis has suggested that very early changes in DTI parameters are independent predictors of outcome,⁹ and another study has supported a potential role for DTI as a predictor of late mortality in patients with severe SAH.³³

In this study, we hypothesized that DTI parameters measured in the subacute phase of SAH may add a prognostic indication for clinical outcome in SAH patients.

Methods

Sample

Patients with acute spontaneous SAH admitted to our institution between May 2013 and November 2014 were consecutively enrolled in a prospective cohort study. Institutional review board approval was obtained. Patients were included in the study if they 1) had an age > 18 years, 2) had acute nontraumatic SAH diagnosed by CT or lumbar puncture, 3) had imaging studies (CT or MRI) performed within the first 72 hours of SAH onset, and 4) provided informed consent either from themselves or a legal representative. Exclusion criteria were as follows: poor clinical condition (Glasgow Coma Scale [GCS] score < 3), pregnancy, renal insufficiency, any contraindication to performing MRI, or time for onset of SAH unknown. For the current analysis, we included patients who had undergone MRI at 8–10 days after SAH.

Clinical and Imaging Data

Demographic and clinical presentation data were collected from the patient medical records, such as hydrocephalus, vasospasm on transcranial Doppler ultrasonography, DCI, aneurysm, and surgical and/or endovascular treatment. The GCS,³⁴ World Federation of Neurosurgical Societies (WFNS) scale,⁶ and Hunt and Hess (HH) scale²⁰ were used to assess neurological status at admission. The modified Fisher scale¹² and the Hijdra scale for cisternal and intraventricular hemorrhage¹⁸ were used to quantify the amount of blood on admission brain CT. Hydrocephalus was defined as a bicaudate index above the 95th percentile for age, at any time between admission and discharge.³⁵ The presence of cerebral vasospasm was defined by a Lindegaard index²⁴ above 3 (moderate/severe vasospasm) on transcranial Doppler ultrasonography studies after the 4th day post-SAH. Patients were classified as having DCI if 1) they presented with a new focal neurological deficit and/or a decrease in their level of consciousness not attributable to other causes (for example, hydrocephalus, seizures, metabolic derangement, infection, or sedation), 2) there was a new infarct on follow-up CT or MRI after 4 days after ictus, or 3) both 1 and 2.^{13,36}

MRI Protocol

Magnetic resonance imaging was performed on days 8–10 after SAH. All MRI was performed on the same 1.5-T scanner (Magnetom Avanto, Siemens Medical Systems) with an imaging protocol that included T1, T2, T2*, FLAIR, and DTI sequences. In the DTI sequence, for each of the 20 noncollinear diffusion-sensitizing gradients, we

acquired 84 contiguous slices. Imaging parameters were as follows: matrix 128 × 128, FOV 230 mm, TE 95 msec, TR 2800 msec, EPI factor 128, b = 1000 sec/mm², NEX 1, and slice thickness 5 mm.

Postprocessing

Regions of interest (ROIs) of 20 mm² were selected using OLEA software, at the following locations: frontal centrum semiovale, parietal centrum semiovale, posterior limb of internal capsule (PLIC), lentiform nucleus, thalamus, genu and splenium of corpus callosum, mid pons, and subcortical cerebellar hemispheres, bilaterally and symmetrically (Fig. 1). All measurements were performed by the same observer, who was blinded to the clinical data and had 10 years' experience in neuroradiology. No significant differences were found between the 2 sides, and an average of the left and right ROIs for each anatomical location was analyzed. Mean FA and ADC were measured for each ROI. Whole-brain mean FA and ADC values were calculated from total ROIs.

Outcome

We aimed to assess the association between DTI measurements and the modified Rankin Scale (mRS) score at 3 months,² as a clinical outcome. The mRS was applied at 3 months via in-person or telephone interview by 2 physicians with experience in stroke (A.P.N., P.F.) and who were blinded to the clinical and MRI data.²¹ Clinical outcome was dichotomized as good (mRS score < 3) and poor (mRS score ≥ 3).

Statistical Analysis

Demographic and clinical characteristics of patients were described as frequencies (percentages), the mean ± standard deviation, or the median (minimum–maximum range), as appropriate. To compare FA and ADC ROI values between the left and right hemispheres, the Wilcoxon signed-rank test was used. Logistic regression models were used to study the association between DTI parameters and clinical outcome. Discriminative and predictive abilities of the final multivariable models were assessed using the area under the receiver operating characteristic (ROC) curve (AUC) and the Hosmer-Lemeshow test, respectively. The following variables were considered in the univariable analyses: age, sex, GCS score, WFNS grade (I vs II–V), HH grade (I vs II, III, IV–V), modified Fisher grade (2–3 vs 4), cisternal Hijdra grading, ventricular Hijdra grading, SAH location (perimesencephalic vs nonperimesencephalic), vasospasm (yes/no), hydrocephalus (yes/no), DCI (yes/no), treatment (nonaneurysmal SAH, clipped aneurysm, coiled aneurysm), and DTI parameters measured in all ROIs. Variables that attained a p value ≤ 0.25 were considered for multivariable analysis.

Generalized additive models were applied to model the association between age and poor clinical outcome. The level of significance was considered to be $\alpha = 0.05$. Data were analyzed using Stata 13.0 (StataCorp LP) and R software (R: A language and environment for statistical computing, R Core Team, R Foundation for Statistical Computing, <http://www.R-project.org>).

FIG. 1. Transverse FA and ADC maps show ROIs drawn bilaterally in the brain parenchyma. **Upper and lower left:** Regions of interest in the pons and cerebellar white matter. **Upper and lower center:** Regions of interest in the lentiform nucleus, thalamus, PLIC, and splenium and genu of corpus callosum. **Upper and lower right:** Regions of interest in the frontal and parietal centrum semiovale. From *Neuroradiology*, Evolution of diffusion tensor imaging parameters after acute subarachnoid haemorrhage: a prospective cohort study, 59, 2017, 13–21, Fragata I, Canhão P, Alves M, Papoila AL, Canto-Moreira N. With permission from Springer. Figure is available in color online only.

Results

Demographic and Clinical Data

During the inclusion period, 129 patients with nontraumatic SAH were admitted to our institution. Eighty patients fulfilled the inclusion criteria for the prospective cohort. Of these, 10 patients were excluded from the analysis because MRI could not be performed. Another 16 patients were excluded because their images were degraded by artifacts, leaving a total of 54 patients eligible for the current analysis (Fig. 2).

The median patient age was 60 years (range 35–86 years), and 63% of the patients were female. The median HH grade was II (range I–V), 29 patients had WFNS grade I SAH, and 6 patients had GCS score < 8 on admission (Table 1). A total of 15 patients (27.8%) developed DCI. At 3 months, 15 patients (28%) were dependent (mRS score ≥ 3 ; Table 2). The mortality rate at 3 months was 3.7% (2 patients).

Univariable regression analysis of clinical variables identified age, clinical grade on admission (WFNS grade and GCS score), amount of blood on admission CT (modified Fisher and Hijdra scales), hydrocephalus, aneurysmal

SAH, and SAH location as candidates in the multivariable model (Table 2). A nonlinear association of patient age with poor outcome was identified, as younger and older patients had higher odds of a poor outcome. Accordingly, age was modeled with splines through a generalized additive model (Fig. 3) and was dichotomized into 2 categories: age 42–67 years and ages < 42/> 67 years.

Fractional Anisotropy in Subacute SAH as an Indicator of Poor Clinical Outcome

Univariable analysis concerning FA (Table 3) yielded the frontal centrum semiovale, parietal centrum semiovale, lentiform nucleus, corpus callosum, subcortical cerebellum, and pons as candidates for the multivariable model (Fig. 4A). An association between whole-brain FA and poor clinical outcome was also found in the univariable analysis (OR 0.41, 95% CI 0.01–0.036, $p = 0.004$) but was not included in the multivariable model to avoid redundancy since whole-brain FA was calculated from the mean of all ROIs.

In the multivariable analysis, only FA at the corpus callosum (OR 0.34, 95% CI 0.17–0.68, $p = 0.002$) and age

FIG. 2. Flowchart with the number of patients admitted, excluded, and enrolled in the present study. h = hours; IV = intravenous.

(OR 17.6, 95% CI 2.31–134.1, $p = 0.006$) showed an association with poor outcome at 3 months after SAH. For each increase of 0.1 in the FA value measured at the corpus callosum, there was a 66% reduction in the odds of having a poor clinical outcome. Younger and older patients (age < 42 and > 67 years, respectively) had 17-fold increased odds of a poor outcome. The ROC curve had an AUC of 0.88 (95% CI 0.79–0.98, good discriminative ability), and the Hosmer-Lemeshow goodness-of-fit test showed good calibration ($p = 0.665$).

TABLE 1. Demographic, clinical, and imaging characteristics of 54 patients with nontraumatic SAH

Characteristic	Value
Median age in yrs (range)	60 (35–86)
No. of females (%)	34 (63)
No. w/ comorbidities (%)	
Hypertension	24 (44)
Smoking	11 (20)
Diabetes	2 (4)
Clinical grade at admission	
Median GCS score (range)	15 (4–15)
WFNS grade (no. [%])	
I	29 (54)
II	10 (19)
III	1 (2)
IV	9 (17)
V	5 (9)
HH grade (no. [%])	
I	19 (35)
II	11 (20)
III	13 (24)
IV	4 (7)
V	7 (13)
Imaging at admission	
Modified Fisher grade (no. [%])	
2	6 (11)
3	14 (26)
4	34 (63)
Median Hijdra grade (range)	
Cisternal	14 (2–26)
Ventricular	2 (0–12)
Aneurysmal SAH (no. [%])	40 (74)
Ant circulation	33 (83)
Pst circulation	7 (17)
Nonaneurysmal SAH (no. [%])	14 (26)
Perimesencephalic SAH	12 (86)
Nonperimesencephalic SAH	2 (14)
Hydrocephalus (no. [%])	8 (15)
Clipped aneurysm (no. [%])	11 (28)
Coiled aneurysm (no. [%])	30 (75)

Ant = anterior; pst = posterior.

Apparent Diffusion Coefficient in Subacute SAH as an Indicator of Poor Clinical Outcome

In the univariable analysis for ADC (Table 3), the frontal centrum semiovale, lentiform nucleus, thalamus, PLIC, subcortical cerebellum, and pons were selected for the multivariable model (Fig. 4B). An association between whole-brain ADC and poor clinical outcome was also found in the univariable analysis but again was not included in the multivariable model to avoid redundancy.

Multivariable analysis showed that ADC measured at the frontal centrum semiovale was associated with a poor

TABLE 2. Univariable regression analysis results for a poor clinical outcome

Variable	mRS Score <3	mRS Score ≥3	OR Estimate (95% CI)	p Value*
No. of patients	39	15		
Median age in yrs (range)	53 (35–84)	69 (35–86)	1.08 (1.02, 1.13)	0.006
Male sex (no. [%])	15 (38.5)	5 (33.3)	0.80 (0.23, 2.80)	0.727
Median GCS score (range)	15 (4–15)	10 (4–15)	0.65 (0.50, 0.83)	0.001
WFNS grades II–V (no. [%])	11 (28.2)	14 (93.3)	35.64 (4.17, 304.50)	0.001
HH grade (no. [%])†				
II	11 (28.2)	0 (0.0)		
III	8 (20.5)	5 (33.3)		
IV–V	2 (5.1)	9 (60.0)		
Modified Fisher grade 4 (no. [%])	22 (56.4)	13 (86.7)	5.02 (1.00, 25.32)	0.051
Median Hijdra grade (range)				
Cisternal	12 (2–26)	20 (6–26)	1.18 (1.06, 1.32)	0.003
Ventricular	2 (0–10)	4 (0–12)	1.46 (1.13, 1.89)	0.003
Perimesencephalic SAH location (no. [%])	11 (28.2)	1 (6.7)	0.16 (0.03, 1.83)	0.159
Vasospasm (no. [%])	17 (43.6)	4 (26.7)	0.471 (0.13, 1.74)	0.259
Hydrocephalus (no. [%])	2 (5.1)	6 (40.0)	12.33 (2.13, 71.57)	0.005
DCI (no. [%])	11 (28.2)	4 (26.7)	0.45 (0.11, 1.86)	0.267
Treatment (no. [%])				
Clipped aneurysm	7 (17.9)	3 (20.0)	1.57 (0.25, 10.09)	0.634
Coiled aneurysm	20 (51.3)	9 (60.0)	1.65 (0.37, 7.39)	0.513

* The p values were obtained by logistic regression models. Reference categories: female sex, GCS score <8, WFNS grade I, HH grade I, modified Fisher grade 2–3, SAH location: nonperimesencephalic SAH, treatment: nonaneurysmal SAH/no treatment.

† Computational problems emerging from a quasi-complete separation problem due to the small sample size (poor clinical outcome is perfectly determined by HH grade).

outcome at 3 months (OR 1.29, 95% CI 1.04–1.60, $p = 0.020$); for each increase of 10 units in the ADC value, an increase of 29% in the odds of a poor outcome was found.

Additionally, for each unit increase in the cisternal Hijdra grade, there was a 21% increase in the odds of a poor outcome (OR 1.21, 95% CI 1.00–1.47, $p = 0.050$), and for each increase of 1 unit in the GCS score, there was a 53% decrease in the odds of a poor outcome (OR 0.47, 95% CI 0.30–0.74, $p = 0.001$). The ROC curve had an AUC of 0.95 (95% CI 0.90–1.00, excellent discriminative ability), and the Hosmer-Lemeshow goodness-of-fit test showed good calibration ($p = 0.960$).

Discussion

In this prospective study, we found an association between the FA and ADC values measured in the subacute stage of SAH and clinical outcome. Increased ADC values at the subcortical frontal white matter and reduced FA values at the corpus callosum were independent predictors of a poor outcome at 3 months. In accordance with what has been established in other SAH cohorts,^{12,31,35,39} a higher blood burden on admission CT, lower clinical scores on admission, and patient age were strongly associated with a poor clinical outcome in our patients.

The pathophysiological mechanisms causing cerebral injury in SAH are not fully understood. Immediately after hemorrhage, drastic changes can occur, including an increase in intracranial pressure, the loss of autoregulation,

cortical spreading depolarization, blood-brain barrier opening, and neuronal apoptosis, leading to early brain injury.³² After the initial insult, other complications may ensue—for example, hydrocephalus, vasospasm, and ultimately DCI—and contribute to brain injury and influence the prognosis. Vasospasm, one of the most serious complications of SAH, usually starts after the 4th day, has a peak around 8–10 days, and can persist until around 3 weeks after SAH.^{8,23} Delayed cerebral ischemia is eventually the result of vasospasm, although it is also thought to reflect the early brain injury occurring in the first days after SAH.³¹

The role of MRI in predicting prognosis in SAH has been addressed,^{5,11,37} with most studies characterizing the diffusion-weighted imaging (DWI) and FLAIR lesion burden and focusing on poor-grade patients, whose prognosis is difficult to determine. Acute ischemic injury after SAH detectable on DWI has been shown to be proportional to neurological impairment on admission^{5,37} and to be associated with long-term outcome.¹¹ However, few studies have sought to identify DTI markers of prognosis in SAH, as has been done for other diseases such as traumatic brain injury⁴⁰ and small vessel disease.²⁷

Fractional anisotropy and ADC represent different physiological mechanisms.^{22,26} Fractional anisotropy is used as a measure of axonal integrity^{26,28} and can be reduced even without visible lesions on conventional MRI sequences, functioning as a subtle marker of the microstructural integrity of white matter. We found that patients

FIG. 3. Influence of age on outcome at 3 months (solid curve) and corresponding 95% confidence intervals (dashed curves), showing a nonlinear association that led to a dichotomization into 2 categories: age 42–67 years and ages < 42/> 67 years.

with better outcomes had globally higher FA values (both in individual regions and in whole-brain measurements) and that FA measured at the corpus callosum in the sub-

acute phase was an independent predictor of a good clinical outcome. Our results are somewhat in line with those of Sener and colleagues,³³ who demonstrated, in a cohort of 23 SAH patients, the association between reduced whole-brain FA at 12 days post-SAH and decreased survival at 6 months. However, these results were not adjusted for other variables influencing prognosis. An axonal lesion occurring in SAH—eventually due to early brain injury in the first hours after SAH or secondary to complications after the acute phase such as hydrocephalus, vasospasm, or DCI—may explain these findings: FA will be reduced in patients with more extensive parenchymal injury, and it can be a biomarker of a worse prognosis.

Apparent diffusion coefficient reflects the diffusion of water molecules across cell membranes. Early ischemia leads to cytotoxic edema secondary to an energetic failure at the cell membrane, reducing ADC.⁷ On the contrary, the facilitated diffusion of water molecules in vasogenic edema leads to an increase in ADC. Most studies reporting on early MRI in acute SAH have focused on acute ischemic lesions on DWI, with a corresponding reduced ADC.^{4,5,11} However, a recent study by Weimer et al. described a global increase in the ADC values in normal-appearing parenchyma as early as the first 72 hours post-SAH,³⁸ but these authors did not assess the relation of this finding to prognosis. In a previous study,⁹ we found that early increases in ADC values in normal-appearing white matter, mea-

TABLE 3. Univariable regression analysis results for a poor clinical outcome, considering the DTI parameters obtained on MRI at 8–10 days post-SAH

Parameter	mRS Score <3	mRS Score ≥3	OR Estimate (95% CI)	p Value
No. of patients	39	15		
FA				
FCSO	0.50 (0.07)	0.45 (0.07)	0.42 (0.17, 1.00)	0.049
PCSO	0.48 (0.05)	0.45 (0.08)	0.49 (0.18, 1.29)	0.149
Lentiform nucleus	0.19 (0.05)	0.21 (0.07)	2.08 (0.68, 6.38)	0.200
Thalamus	0.30 (0.05)	0.29 (0.05)	0.72 (0.20, 2.58)	0.613
PLIC	0.65 (0.05)	0.66 (0.06)	1.51 (0.46, 4.98)	0.498
G&S of corpus callosum	0.73 (0.09)	0.60 (0.14)	0.38 (0.21, 0.69)	0.001
Cerebellum	0.39 (0.06)	0.35 (0.07)	0.30 (0.10, 0.87)	0.026
Mid pons	0.36 (0.11)	0.31 (0.11)	0.63 (0.34, 1.18)	0.147
Whole brain	0.45 (0.05)	0.42 (0.04)	0.41 (0.01, 0.36)	0.004
ADC				
FCSO	706.4 (45.5)	738.8 (74.0)	1.13 (0.99, 1.30)	0.071
PCSO	732.5 (49.4)	738.9 (62.9)	1.02 (0.91, 1.15)	0.698
Lentiform nucleus	725.9 (68.2)	779.8 (110.4)	1.08 (1.00, 1.17)	0.053
Thalamus	756.8 (51.7)	821.2 (115.4)	1.11 (1.02, 1.21)	0.019
PLIC	697.8 (47.5)	725.7 (71.4)	1.10 (0.98, 1.24)	0.120
G&S of corpus callosum	766.2 (93.8)	807.6 (191.7)	1.03 (0.98, 1.08)	0.302
Cerebellum	666.5 (42.3)	698.6 (66.1)	1.15 (1.00, 1.32)	0.053
Mid pons	666.7 (57.7)	695.2 (47.7)	1.10 (0.98, 1.23)	0.110
Whole brain	714.8 (34.8)	750.8 (55.9)	1.24 (1.04, 1.47)	0.016

FCSO = frontal centrum semiovale; G&S = genu and splenium; PCSO = parietal centrum semiovale.

Values expressed as the mean (standard deviation). The p values were obtained using logistic regression models; variables attaining a p value ≤ 0.25 were considered for multivariable analysis.

FIG. 4. Odds ratio estimates and corresponding 95% confidence intervals obtained by logistic regression models for a poor clinical outcome in each ROI. **A:** Fractional anisotropy at 8–10 days post-SAH. **B:** Apparent diffusion coefficient at 8–10 days post-SAH. C = cerebellum; FCSO = frontal centrum semiovale; GSCC = genu and splenium of corpus callosum; L = lentiform nucleus; P = pons; PCSO = parietal centrum semiovale; T = thalamus.

sured within 72 hours after SAH, were associated with a worse prognosis. According to our present results, these changes also seem to occur in the subacute phase of SAH. Liu et al.²⁵ described a mild diffusely increased ADC of the subcortical white matter but did not analyze its impact on prognosis. Our results are in line with their findings and add a prognostic value of the ADC measurements in the subacute phase of SAH, helping to predict the clinical outcome.

The pathophysiological mechanisms explaining this increase in ADC in the subacute phase of SAH possibly start as early as the first 72 hours and are probably multifactorial: altered cerebral autoregulation, effects of treatment (hypervolemia), and disruption of the blood-brain barrier,²⁵ the latter peaking at 48 hours post-SAH.¹⁴ All of these factors together may negatively impact clinical prognosis.

Modifications of FA and ADC reflect different mechanisms, and although we found some significant associations with outcome, the pathophysiological meaning of these associations remains undetermined.

The finding of an association between a younger age and a worse outcome is surprising. Besides the higher frequency of vasospasm in this age group, we hypothesize that the increased intracranial pressure may also be more harmful in younger patients. Older patients, with their higher degree of cerebral atrophy leading to an increase in the extraaxial compartments, seem to better tolerate increases in intracranial pressure, as is known, for example, in malignant edema after ischemic stroke.¹⁶

We acknowledge some limitations to our study. The small size of the study population probably explains the selective association of certain ROIs since other regions of the parenchyma showed similar associations in the univariable analysis but did not reach statistical significance in the multivariable analysis. Limitations of DTI measurements, mainly affecting FA, are known given that crossing the white matter fibers can modify FA values.²⁸ Moreover,

the reliability of measurements of DTI parameters may be questioned. However, in a study by Brander et al.,³ intraobserver agreement was acceptable in most anatomical regions, with the best agreement found at the genu and splenium of the corpus callosum and the lowest agreement at the centrum semiovale.

One of the limitations of this study was that some patients in very poor neurological condition, for example, those with severe vasospasm and a decreased level of consciousness, did not undergo MRI at 8–10 days after SAH. This may have led to a selection bias, meaning that we imaged patients in better clinical condition. On the other hand, this underlines the value of our finding that DTI may provide incremental value in prognostication in these patients.

The lack of a negative control group is a limitation as well. Long-term follow-up MRI would be important to determine if the observed FA and ADC changes persist in time or are limited to the subacute phase of SAH. Moreover, global and anatomical volumetric evaluations of brain structures would be interesting to correlate with DTI measurements since there are described changes in cerebral volume in the chronic stage of SAH.¹

Finally, to confirm our preliminary results, larger studies and the inclusion of additional patients, such as poor-grade SAH patients, are needed.

Conclusions

A poor clinical outcome after SAH was independently associated with DTI parameters in specific regions of the brain. Decreased FA and increased ADC may reflect different mechanisms occurring in the subacute phase of SAH, influencing the clinical prognosis of patients. Larger studies are needed to confirm the results of this exploratory study and to establish the utility of DTI as a prognostic tool in SAH.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Fragata, Canhão. Acquisition of data: Fragata, Ferreira, Nunes. Analysis and interpretation of data: Fragata, Alves, Papoila, Canhão. Drafting the article: Fragata, Alves, Papoila. Critically revising the article: Alves, Papoila, Canto-Moreira, Canhão. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Fragata. Statistical analysis: Alves, Papoila. Study supervision: Fragata, Canhão.

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