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COMPUTED TOMOGRAPHY PERFUSION EXAMINATION CAN DETECT THE IMPAIRMENT OF CEREBRAL CIRCULATION AND MAY HELP PREDICT THE OUTCOME OF PATIENTS WITH ANEURYSMAL SUBARACHNOID HEMORRHAGE

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Abstract
Aneurysmal subarachnoid hemorrhage (aSAH) rapidly elevates intracranial pressure and disrupts intracerebral blood perfusion. As the objective evaluation of cerebral circulation is seldom performed due to the instability of the patient's condition, we investigated the utility of measuring two indices of disturbed cerebral perfusion in the acute-stage of aSAH-regional cerebral blood flow (rCBF) and regional mean transit time (rMTT)-with computed tomography perfusion (CTP) to predict unfavorable outcomes of patients of aSAH. We enrolled 55 patients within the first 3 days of the onset of aSAH and used their modified Rankin Scale (mRS) scores to classify them into favorable (mRS, 0-2) and unfavorable (mRS, 3-6) outcome groups : 38 and 17 patients, respectively. The univariate analysis identified the following risk factors for unfavorable outcomes : age ($p=0.004$), World Federation of Neurological Society (WFNS) grade ($p=0.005$), presence of hydrocephalus ($p=0.026$) and delayed ischemic neurological deficit ($p=0.005$), and prolongation of rMTT of the cortex (rMTT-CTX ; $p=0.014$) and basal ganglia (rMTT-BG ; $p=0.003$). The significance of higher WFNS grade (odds ratio [OR]=2.063, $p=0.018$), presence of delayed ischemic neurological deficit (OR=8.048, $p=0.019$), and rMTT-BG (OR=3.476, $p=0.013$) remained following multivariate analysis. Hence, CTP-derived parameters, especially rMTT, at admission can help to predict unfavorable outcomes in patients.

Key words : Computed tomography perfusion, Regional cerebral blood flow, Regional mean transit time, Aneurysmal subarachnoid hemorrhage

Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is a life-threatening disease associated with high mortality and morbidity rates ; approximately one-third of the patients with aSAH die, and only about one-half can live an independent life[1)]. In particular, damage owing to a rapid and marked increase in the intracranial pressure (ICP) by repeated bleeding worsens the clinical outcome of the patients with aSAH ; therefore, hemostatic therapy of ruptured aneurysms with either surgical clipping or endovascular coil embolization and immediate control of ICP are highly recommended[2)]. However, these treatments are invasive and expensive ; therefore, surgical indications should be identified according to the accurate estimates of the outcome.

As one of the prognostic factors of aSAH, the concept

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of early brain injury (EBI), mainly caused by the rupture of a cerebral aneurysm and the subsequent hemodynamic impairment of cerebral circulation, has recently attracted attention[3]. In aSAH, arterial hemorrhage rapidly spreads in the closed subarachnoid cisternal space ; and, because of the sudden increase in ICP, it interferes with the blood supply to the brain, largely affecting the microcirculation or metabolism[4]. The concept of EBI may explain the relationship between permanent neuronal injury after aSAH and cerebral perfusion impairment in the early stages. One hypothesis to explain the pathogenesis of EBI is that the increase in ICP, followed by cerebral ischemia, may consequently induce apoptosis, inflammation, and cerebral metabolic disturbance, which have been implicated in short- and long-term complications after aSAH[3,5-7]. To investigate the pathogenesis of EBI, it is necessary to evaluate the hemodynamic impairment of cerebral circulation in the early stages of aSAH.

Intracerebral perfusion dynamics has mainly been measured using the modalities of nuclear medicine[8-10], and computed tomography perfusion (CTP) is a recently established evaluation method[11-13]. Nuclear medicine methods are advantageous because of the high accuracy in detecting ischemic regions and estimating oxygen metabolism. However, these modalities may be ineligible for use in emergency settings because of their complexity[11,12]. Meanwhile, CTP examination can be performed immediately after three-dimensional computed tomography angiography (3D-CTA), which is an essential preoperative examination for aSAH to detect ruptured aneurysms and obtain their accurate morphological images[14]. The pairing of these modalities may help to avoid subjecting patients with aSAH to further invasiveness in the acute stage and to detect cerebral circulatory disturbances.

This study assessed the CTP-derived intracerebral perfusion parameters in the early stage of aSAH and examined the association between the early-stage disturbed cerebral circulation and patient outcomes.

Patients and Methods

Patient characteristics

From January 2013 to December 2018, 209 patients with ruptured aneurysms in the anterior circulation were surgically treated within 72 hours of onset at Akita Cerebrospinal and Cardiovascular Center. The hemostatic surgical procedures, such as surgical clipping or endovascular coiling, were determined by the judgment of the neurosurgeons in charge. Of the 209 patients, 61 underwent CTP examination prior to the surgical treatment. With reference to the results of transthoracic echocardiography, six patients were excluded because they had cardiac hypofunction with an ejection fraction <50% or Takotsubo cardiomyopathy. Fifty-five patients were eventually enrolled in this retrospective case-control study. This study complies with the principles of the Declaration of Helsinki. The Ethics Committee of Akita Cerebrospinal and Cardiovascular Center approved this study (approval Number 19-14). Written informed consent was obtained from the patients or nearest family relatives.

Using patient records, we retrospectively investigated 55 patients with respect to the following parameters : age, sex, size and location of the aneurysm, World Federation of Neurosurgical Societies (WFNS) grade, Glasgow Coma Scale score on admission, modified Fisher computed tomography (CT) group, relative bicaudate index (RBCI)[15], surgical approach for hemostatic therapy, the occurrence of delayed ischemic neurological deficit (DIND), and the outcome at discharge evaluated using the modified Rankin scale (mRS). Non-enhanced CT performed concurrently with CTP showed no extensive initial damage extending to the brain parenchyma and brainstem in any patient. The patients who developed ischemic symptoms from 4 to 14 days after the onset of SAH were diagnosed with DIND. The overall characteristics of the patients included in the study are summarized in Table 1.

Scanning protocol for CT perfusion study

We used the Aquilion ONE® CT scanner (Canon Medical Systems Corporation, Otawara, Tochigi, Japan), and 3D-CTA and CTP examination were simultaneously performed using a test bolus tracking method. In total, 70 mL of the non-ionic iodinated contrast agent (Iopamidol®, Bracco, Milan, Italy) was intravenously administered at the injection rate of 5 mL/s by an automatic in-

Table 1. Clinical profile of patients showing the total number of patients and the number of patients in the favorable and unfavorable outcome groups

Patients' characteristics	Total (N=55)	Favorable outcome group (N=38)	Unfavorable outcome group (N=17)	p value
Age (years), median (IQR)	64 (56–72)	60 (52–69)	71 (66–77)	0.001
Sex, *n* (%)				0.735
Male	12 (21.8)	9 (27.3)	3 (17.6)	
Female	43 (78.2)	29 (76.3)	14 (82.4)	
Aneurysm size (mm), median (IQR)	5.6 (4.0–7.5)	4.6 (3.6–6.8)	7.5 (5.2–9.0)	0.020
Location of the aneurysm, *n* (%)				0.166
ICA	20 (36.4)	11 (28.9)	9 (52.9)	
ACA	17 (30.9)	12 (31.6)	5 (29.4)	
MCA	18 (32.7)	15 (39.5)	3 (17.6)	
WFNS grade, *n* (%)				0.019
1	27 (49.1)	22 (57.9)	5 (29.4)	
2	10 (18.2)	8 (21.1)	2 (11.8)	
3	5 (9.1)	4 (10.5)	1 (5.9)	
4	10 (18.2)	3 (7.9)	7 (41.2)	
5	3 (5.5)	1 (2.6)	2 (11.8)	
Modified Fisher CT group, *n* (%)				0.083
1	6 (10.9)	5 (13.2)	1 (5.9)	
2	2 (3.6)	2 (5.3)	0 (0)	
3	33 (60.0)	25 (65.8)	8 (47.1)	
4	14 (25.5)	6 (15.8)	8 (47.1)	
Intraventricular hematoma, *n* (%)				0.062
Present	16 (29.1)	8 (21.1)	8 (47.1)	
Absent	39 (70.9)	30 (78.9)	9 (52.9)	
RBCI, median (IQR)	0.86 (0.74–0.97)	0.86 (0.80–0.94)	0.86 (0.67–1.06)	0.820
Hydrocephalus (RBCI>1.0)				0.033
Present	12 (21.8)	5 (13.2)	7 (41.2)	
Absent	43 (78.2)	33 (86.8)	10 (58.8)	
Therapeutic approach, *n* (%)				0.435
Clipping	46 (83.6)	33 (86.8)	13 (76.5)	
Coiling	9 (16.4)	5 (13.2)	4 (23.5)	
DIND, *n* (%)				0.005
Present	12 (21.8)	4 (10.5)	8 (47.1)	
Absent	43 (78.2)	34 (89.5)	9 (52.9)	
mRS at discharge, *n* (%)				<0.001
0		23 (41.8)	0 (0)	
1		9 (16.4)	0 (0)	
2		6 (10.9)	0 (0)	
3		0 (0)	5 (9.1)	
4		0 (0)	6 (10.9)	
5		0 (0)	6 (10.9)	
6		0 (0)	0 (0)	

Abbreviations : IQR : interquartile range, ICA : internal carotid artery, ACA : anterior cerebral artery, MCA : middle cerebral artery, WFNS : World Federation of Neurosurgical Societies, CT : computed tomography, RBCI : relative bicaudate index, DIND : delayed ischemic neurologic deficits, mRS : modified Rankin scale

jector (Dual Shot GX®, Nemoto Kyorindo, Tokyo, Japan). The start time of scanning was determined by a test bolus injection, and dynamic imaging was performed for approximately 40–50 s starting at 5 s before the contrast agent's arrival. The imaging conditions were set as follows : tube voltage was 120 kV, tube current was 300 mA (CTA) or 30 mA (CTP), tube speed was 1.0 s/rot, and imaging range was 140 mm (slice thickness 0.5 mm×

280 slices) covering the whole brain. The image was reconstructed at 1 mm thickness. The medical imaging workstation, Ziostation2® (Ziosoft, Inc., Tokyo, Japan), was used for analysis.

CTP examination was performed under adequate sedation, and blood pressure was controlled to ensure the stability of the patient's condition and to prevent rebleeding. Specifically, flunitrazepam and pentazocine were intravenously administered until the consciousness level reached somnolence and the patient remained at rest. Moreover, continuous intravenous administration of nicardipine was done to maintain the systolic blood pressure between 110 mm Hg and 140 mm Hg.

Regions of interest for the analysis of CTP-derived perfusion parameters

The CTP-derived parameters were evaluated using the standard singular value decomposition analysis method. The arterial input function was calculated using the regions of interest (ROIs) set on the internal carotid artery at the carotid siphon of each side. The ROI of the brain parenchyma was placed as described in the axial sections.

To evaluate the perfusion of the middle cerebral artery, we placed three ROIs on the cerebral cortex (CTX) perfused by the middle cerebral artery, as well as a single ROI at the basal ganglia (BG) on each hemispheric side in the axial slice, at the site of the bilateral Monroe foramen. When a hematoma existed, the ROI was placed in the region to minimize the influence of the hematoma. All ROIs were elliptical, and the cortical ROI was 20 mm (semimajor axis) × 8 mm (semiminor axis), whereas the ROI for the BG was 15 mm (semimajor axis) × 10 mm (semiminor axis) (Figure 1). The CTP-derived perfusion parameters, namely the regional cerebral blood flow (rCBF) and regional mean transit time (rMTT), were calculated in each ROI. Furthermore, the parameters in the cortex were calculated as the average of six cortical ROIs and described as rCBF-CTX and rMTT-CTX. The parameters in the BG were the average values from both sides and were defined as rCBF-BG and rMTT-BG.

Figure 2 illustrates the cerebral perfusion color maps generated from the CTP examination of two representative cases.

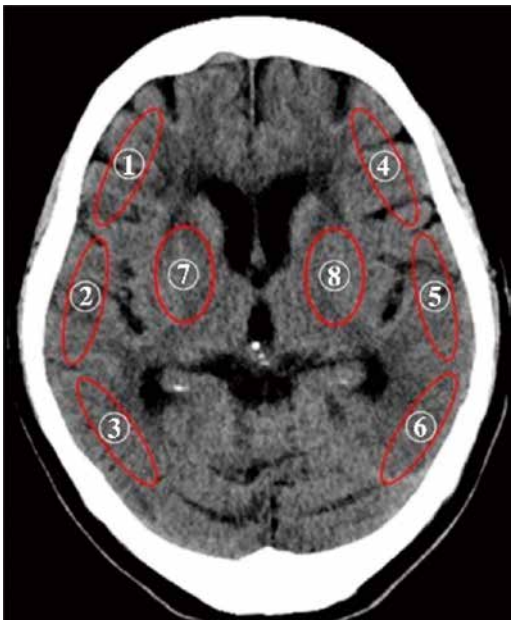

Figure 1. Setting of the regions of interests for computed tomography perfusion analysis
We placed three ROIs on each hemispheric side in the axial slice ; overall, six ROIs (1, 2, 3, 4, 5, and 6) indicated the perfused areas of the middle cerebral artery. These ROIs were in an elliptical shape of 20 mm×8 mm (semimajor and semiminor axis, respectively). The parameters for the cortex were calculated using the average of these six ROIs. In addition, two ROIs were set in the axial slice, which could clearly recognize structures of the BG (7 and 8) and bilateral Monroe foramen. ROIs for the BG were elliptical [15 mm (semimajor axis)×10 mm (semiminor axis)].
ROI : region of interest, CTP : computed tomography perfusion, BG : basal ganglia

Statistical analyses

The patients whose outcome at discharge was independent (mRS, 0-2) were grouped into the favorable outcome group, while those whose outcome at discharge was dependent (mRS, 3-6) were categorized into the unfavorable outcome group. Baseline characteristics were compared between the two groups using Fisher's exact test or Pearson's chi-squared test for categorical variables and Mann-Whitney U test for continuous variables.

To analyze the diagnostic accuracy of CTP-derived perfusion parameters for predicting the unfavorable outcome, we plotted the receiver operating characteristic

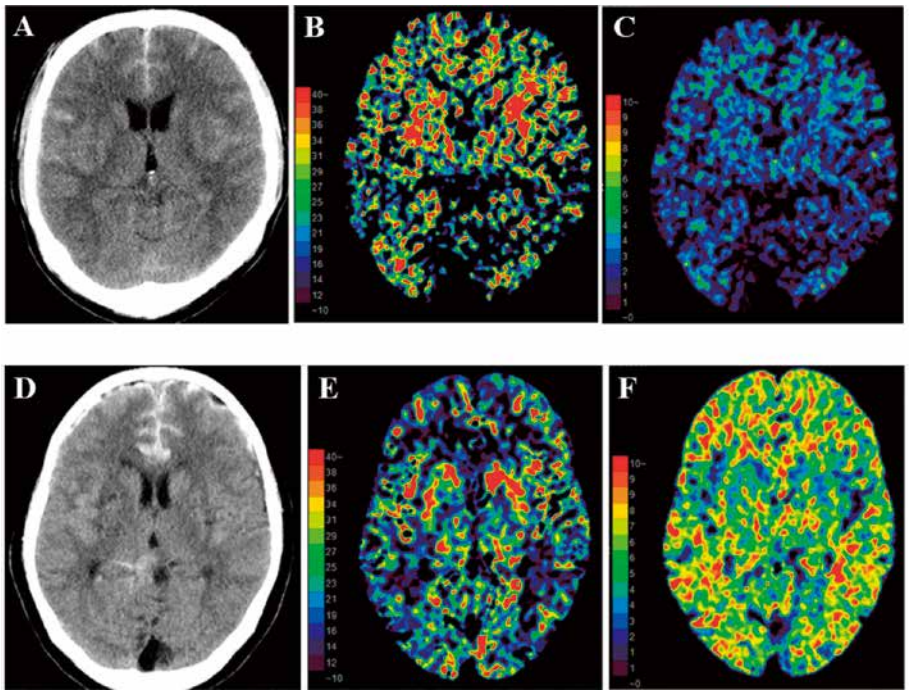

Figure 2. Color maps generated from the CTP examination of two representative cases
Figures A, B, and C demonstrate the conventional CT image, and color maps of CBF and MTT, respectively, of a 51-year-old patient presenting with aneurysmal subarachnoid hemorrhage with a WFNS clinical grade of 4. The outcome at discharge was favorable. Figures D, E, and F demonstrate the conventional CT image, and color maps of CBF and MTT, respectively, of a 68-year-old patient presenting with aneurysmal subarachnoid hemorrhage with a WFNS clinical grade of 4. The outcome at discharge was unfavorable. Figures B and E, and C and F, are demonstrated with the same color grading scale, respectively, where red indicates higher values and blue indicates lower values. CTP: computed tomography perfusion, CT: computed tomography, CBF: cerebral blood flow, MTT: mean transit time, WFNS: World Federation of Neurosurgical Societies

(ROC) curve. Moreover, we evaluated the optimal cutoff values of rCBF and rMTT using Youden's index and subsequently investigated the sensitivity, specificity, positive likelihood ratio (LR+), negative likelihood ratio (LR−), and diagnostic odds ratio (DOR) at the optimal cutoff point.

The independent variables of the multiple logistic regression analysis were selected using the forward-stepwise method and analyzed to identify patient characteristics that were most closely associated with the unfavorable outcome. These independent variables were selected according to the likelihood ratio test score probability (p in=0.05 and p out=0.10). Among the patient characteristics, the following were regarded as the candidate variables, which were the prognostic indicators of a poor outcome after aSAH: age[16-20], WFNS grade[16-22], the presence of acute hydrocephalus (RBCI >1.0)[23], the severity of the hemorrhage (modified Fisher CT groups 3 and 4 as well as the presence of intraventricular hemorrhage)[19-21,24,25], aneurysm size[19,20], DIND occurrence[2,20,26], and CTP-derived perfusion parameters. Regarding CTP-derived parameters, representative parameters with larger areas under the curve (AUCs) in the ROC analyses were introduced into the model to avoid multicollinearity.

Statistical analyses were done using SPSS software, version 26 (SPSS Inc., Chicago, IL, USA). The differences with p value less than 5% were considered statistically significant.

Results

Patient background and general clinical data

Overall, 55 patients were included, of whom 38 and 17 were classified into the favorable and unfavorable outcome groups, respectively. Table 1 summarizes the patient background and clinical data. Patients with unfavorable outcomes were older and had larger aneurysms, higher WFNS grade, hydrocephalus, and DIND.

Relationship between CTP-derived perfusion parameters and unfavorable outcomes

In the ROC analysis for CTP-derived perfusion parameters related to unfavorable outcomes, the AUC values of rMTT-CTX and rMTT-BG were >0.70 (0.72 and 0.77, respectively), suggesting that both had moderate diagnostic power. The optimal cutoff values estimated according to Youden's index were 6.2 s and 4.9 s for rMTT-CTX and rMTT-BG, respectively. For rMTT-CTX at the cutoff point of 6.2 s, the sensitivity, specificity, LR+, LR−, and DOR values were 0.41, 0.97, 15.85, 0.60, and 26.25, respectively, whereas for rMTT-BG at the cutoff point of 4.9 s, the values were 0.88, 0.58, 2.10, 0.20, and 10.28, respectively. Table 2 summarizes these results.

Relationship between the clinical features of aSAH and unfavorable outcomes

In the univariate analysis, the risk factors for unfavorable outcomes were age, WFNS grade, presence of hydrocephalus (RBCI >1.0), DIND occurrence, and rMTT-CTX and rMTT-BG prolongation. However, in the subsequent multivariate analyses, the Spearman's correlation coefficient between rCBF-CTX and rCBF-BG and that between rMTT-CTX and rMTT-BG was >0.70 (Table 3). Therefore, to avoid multicollinearity, we adopted rCBF-CTX and rMTT-BG with larger AUC values than the others in the analyses. According to the results of the multivariate logistic regression analysis, a higher WFNS grade (odds ratio [OR]=2.063 ; p=0.018 ; 95% confidence interval [CI], 1.131-3.763), DIND occurrence (OR=8.048 ; p=0.019 ; 95% CI, 1.411-45.890), and rM-

Table 2. Analysis results for the area under the receiver operating characteristic (ROC) curve, cutoff point (CP) based on Youden's index, sensitivity, specificity, positive and negative likelihood ratio (LR+, LR−), and diagnostic odds ratio (DOR) to discriminate unfavorable outcome of aneurysmal subarachnoid hemorrhage

Variable	AUC	Optimal CP	Sensitivity	Specificity	LR+	LR−	DOR
rCBF-CTX (ml/100 g_brain/min)	0.622	16.6	0.353	0.868	2.674	0.745	3.588
rCBF-BG (ml/100 g_brain/min)	0.590	26.1	0.765	0.605	1.937	0.388	4.986
rMTT-CTX (s)	0.718	6.2	0.412	0.974	15.846	0.604	26.249
rMTT-BG (s)	0.771	4.9	0.882	0.579	2.095	0.204	10.280

Abbreviations : rCBF : regional cerebral blood flow, CTX : cortex, BG : basal ganglia, rMTT : regional mean transit time, AUC : area under the curve, CP : cutoff point, LR+ : positive likelihood ratio, LR− : negative likelihood ratio, DOR : diagnostic odds ratio

Table 3. Spearman's correlation coefficient for each CTP-derived parameter

CTP-derived parameters	rCBF-CTX	rCBF-BG	rMTT-CTX	rMTT-BG
rCBF-CTX	1.0	-	-	-
rCBF-BG	0.797	1.0	-	-
rMTT-CTX	−0.536	−0.465	1.0	-
rMTT-BG	−0.542	−0.539	0.920	1.0

Abbreviations : CTP : computed tomography perfusion, rCBF : regional cerebral blood flow, CTX : cortex, BG : basal ganglia, rMTT : regional mean transit time

TT-BG (OR=3.476 ; p=0.013 ; 95% CI, 1.301-9.285) were the independent risk factors for unfavorable outcomes. Table 4 summarizes these results.

Discussion

Considering its severity, aSAH requires urgent treatment, and surgical clipping or endovascular coil embolization is the only acceptable radical treatment, which is essential to prevent acute worsening[2]. However, these treatments are invasive and expensive ; therefore, surgical indications should be identified according to the accurate estimates of the outcome as various factors are associated with a poor outcome. The severity of aSAH is generally determined by several grading systems, such as the Hunt and Hess grade[27], the Hunt and Kosnik grade[28], the WFNS grade[22], and the recently advocated modified WFNS grade[29]. The WFNS grade is strongly related to the patient outcome and is used as an indicator in treatment decisions[16-22]. It is mainly assessed according to the Glasgow Coma Scale score, which measures the level of consciousness. Although it is easy to use and reasonably correlates with the clinical outcomes, the precise evaluation of consciousness is often challenging. Suwatcharangkoon *et al*. reported that the disturbance in consciousness after the onset of aSAH is primarily due to cerebral hypoperfusion[30]. Furthermore, they claimed that pathological conditions such as epileptic seizures, acute hydrocephalus, cerebral edema aggravation, rebleeding, and neurogenic cardiopulmonary dysfunction can contribute toward disturbed consciousness[30]. From our experience, some patients spontaneously recover from a coma caused by the strong impact of an aneurysm rupture. Several pathological conditions may be simultaneously related to the generation of consciousness disorder in the acute phase of aSAH ; thus, the level of consciousness may fluctuate, and sometimes the WFNS grade alone may be insufficient to decide on a treatment strategy, especially when the patient has a poor WFNS grade. Therefore, apart from the clinical findings, objective indicators derived from the evaluation of cerebral circulation are considered necessary.

This study evaluated the diagnostic accuracy and usefulness of CTP-derived parameters in the acute phase of aSAH in predicting poor outcomes. In the ROC analysis, the AUC values of rMTT-CTX and rMTT-BG were >0.70, suggesting that rMTT had a moderate diagnostic value[31]. Moreover, we analyzed CTP-derived parame-

Table 4. Results of the univariate and multivariate logistic regression analyses of the risk factors related to the unfavorable outcomes in patients with aneurysmal subarachnoid hemorrhage

Predictor	Univariate analysis			Multivariate analysis		
	Odds ratio	Lower-Upper 95% CI	p value	Odds ratio	Lower-Upper 95% CI	p value
Age	1.104	1.033-1.181	0.004			
WFNS grade	1.949	1.228-3.093	0.005	2.063	1.131-3.763	0.018
Modified Fisher CT group (3, 4)	3.613	0.408-31.974	0.248			
Intraventricular hematoma (present)	3.333	0.973-11.415	0.055			
RBCI (>1.0)	4.620	1.200-17.789	0.026			
Aneurysm size (mm)	1.172	0.984-1.397	0.076			
DIND (present)	7.556	1.850-30.862	0.005	8.048	1.411-45.890	0.019
rCBF-CTX (ml/100 g_brain/min)	0.875	0.744-1.029	0.107			
rCBF-BG (ml/100 g_brain/min)	0.946	0.847-1.057	0.326			
rMTT-CTX (s)	2.223	1.173-4.214	0.014			
rMTT-BG (s)	3.323	1.490-7.412	0.003	3.476	1.301-9.285	0.013

Abbreviations : CI : confidence interval, WFNS : World Federation of Neurosurgical Societies, CT : computed tomography, RBCI : relative bicaudate index, DIND : delayed ischemic neurologic deficits, rCBF : regional cerebral blood flow, CTX : Cortex, BG : basal ganglia, rMTT : regional mean transit time

ters using multiple logistic regression analysis with the forward-stepwise method and found three significant and independent risk factors, namely a high WFNS grade, DIND occurrence, and rMTT-BG prolongation, for predicting poor outcomes. The results of the multivariate analysis revealed that rMTT-BG was a significant risk factor with an OR of 3.48 for predicting unfavorable outcomes. Although rMTT-CTX was not included in the multivariate analysis model to avoid multicollinearity, the result of the AUC of rMTT-CTX and DOR at 6.2 s, the optimal cutoff value based on Youden's index, indicated that rMTT-CTX was also particularly useful for detecting unfavorable results[32,33]. The prolongation of MTT, assessed early after aSAH onset, is reported to be a useful index for predicting poor outcomes, which is consistent with our results[34-38]. Similar results have been reported in an experimental study using rabbits[39]. In addition, evaluation of rCBF may also be useful in detecting the occurrence of DIND or unfavorable outcomes, although the estimation of rMTT is suggested to be superior to that of rCBF[34,35,37-39]. This may be explained by the extended penumbra model, proposed by Østergaard *et al*., which reflects the capillary blood flow impairment. According to this model, capillary transit time becomes heterogeneous in the penumbra region, while the amount of capillary blood flow could be preserved in the early stages of aSAH[40,41]. In addition, MTT is reportedly the most sensitive parameter for depicting ischemic lesions, even in an early stage, compared with the other parameters[42,43]. In agreement with the previous reports, the multivariate analysis in this study revealed a high grade of WFNS, along with the prolongation of MTT, to be an independent risk factor for unfavorable outcomes. Hence, refereeing to both the WFNS grade and MTT may help to improve the distinction of patients who were previously considered to have paradoxical clinical features, such as poor consciousness on admission but favorable outcomes at discharge and vice versa. To date, the patients with a WFNS grade of 4 or 5 have been considered to be severe cases with a poor prognosis, and surgery has been discouraged in many of these cases. However, based on the results of the present study, a more aggressive approach is required when determining the need for surgery in patients presenting with no obvious impairment of the cerebral circulation. We believe that CTP is the most suitable modality for the assessment of cerebral perfusion in cases of acute aSAH, and we recommend its use in clinical practice.

We carefully investigated the available studies on CTP; however, we found only a few studies focusing on the difference in cerebral perfusion between the CTX and the BG. Compared to the BG, cerebral perfusion in the CTX can be more easily complicated by several factors, such as hypoperfusion caused by ICP elevation, cortical spreading depolarization, and epileptic discharge[44,45]. A study by van Asch *et al*. suggested that in patients with acute hydrocephalus, the deep brain (such as the BG or periventricular white matter) is the dominant location of cerebral circulation disorders[46]. Hence, analyses that consider both rMTT-BG and rMTT-CTX values may allow for more precise decisions, including various pathological factors associated with cerebral circulatory disturbances.

This study has several limitations. First, the patient conditions at the time of CT evaluation were not always precisely uniform. Although we performed echocardiography in all patients to exclude severe cardiac hypofunctions, such as Takotsubo cardiomyopathy, and kept vital signs as constant as possible, the cardiac output still changed because of the blood pressure fluctuation, and the heart rate might have affected the CTP measurements in some patients. Sufficient sedation, analgesia, and blood pressure control were provided during the preoperative examination to reduce the inaccuracy of the examinations caused by pain or restlessness and to avoid rerupture of the aneurysm. However, the magnitude of effect of the sedative and antihypertensive therapy on the dynamics of cerebral perfusion remains unclear. Second, this study did not consider the possibility of other perioperative complications or comorbidities of aSAH that might have affected the outcome at discharge. Third, we could not exclude the possibility of random errors because of our small sample size. Further, the sizes of the favorable and unfavorable groups were unbalanced. As the incidence of aSAH is reportedly 10 in 100,000 patients[47], enrolling an appropriate number of patients from a single institution may be overambitious.

Further investigation and data accumulation by means of a multicenter study is therefore warranted to establish the validity of the CTP examination.

Conclusions

This study revealed that patient characteristics, such as high WFNS grade, DIND occurrence, and rMTT prolongation among CTP-derived perfusion parameters upon admission, are useful factors to predict unfavorable outcomes in patients with aSAH. However, further investigations are necessary to establish how the disturbed cerebral perfusion during the early stage of aSAH leads to poor patient outcomes.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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