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Original Article

Loss of consciousness at ictus and/or poor World Federation of Neurosurgical Societies grade on admission reflects the impact of EBI and predicts poor outcome in patients with SAH

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ABSTRACT

Background: There are many scores and markers that predict poor outcome in patients with subarachnoid hemorrhage (SAH). However, parameters that can predict outcomes in patients with SAH with high specificity and sensitivity, which can be identified in the early postictal state and utilized as a clinical marker of early brain injury (EBI) have not been identified so far.

Methods: Thirty-nine patients with SAH due to a saccular intracranial aneurysm rupture were reviewed. We retrospectively analyzed the relationships between patients' baseline characteristics and patients' outcomes to identify parameters that could predict patient outcomes in the early postictal state.

Results: In the univariate analysis, older age (>65), loss of consciousness (LOC) at ictus, poor initial World Federation of Neurosurgical Societies (WFNS) grade (3–5), and delayed cerebral ischemia (DCI) were associated with poor outcome (GOS 1–3). Statistical analyses revealed that combined LOC at ictus and/or poor initial WFNS grade (3–5) was a more powerful surrogate marker of outcome (OR 15.2 [95% CI 3.1–75.5]) than either LOC at ictus or the poor initial WFNS grade (3–5) alone. Multivariate logistic regression analyses revealed that older age, combined LOC at ictus and/or poor initial WFNS grade, and DCI were independently associated with poor outcome.

Conclusion: Combined LOC at ictus and/or poor initial WFNS grade (3–5) reflects the impact of EBI and was a useful surrogate marker of poor prognosis in SAH patients, independent of patients' age and state of DCI.

Keywords: Early brain injury, Loss of consciousness, Outcome, Subarachnoid hemorrhage, World Federation of Neurosurgical Societies grade

INTRODUCTION

Despite the development of modern neurosurgery, the morbidity and mortality of patients who have suffered from subarachnoid hemorrhage (SAH) due to a ruptured intracranial aneurysm remain high. Survival from aneurysmal SAH has increased by 17% in the past few decades; however, SAH still leads to the loss of many years of productive life.[13]

If the surgical obliteration of a ruptured aneurysm by means of clipping or coiling is performed successfully, delayed cerebral ischemia (DCI) often occurs 3–14 days after SAH onset (during the so-called “vasospasm period”), and the neurological functions of patients deteriorate.[13] In the past 60 years, cerebral vasospasm, which is the narrowing of a major cerebral artery, has been considered to be almost the only reason for DCI, and overcoming the problem of cerebral vasospasm and DCI was thought to be the critical key for improving the outcome in patients with SAH. However, in the CONSCIOUS trial, a multicenter randomized controlled trial, the endothelin antagonist clazosentan successfully decreased the extent of vasospasm but failed to decrease the morbidity and mortality of SAH.[12] These results demonstrated that cerebral vasospasm after aneurysmal SAH is not the only reason for the poor prognosis of SAH.

Recently, the concept of early brain injury (EBI) has emerged, and its relationship to DCI has attracted attention. EBI is the term used to describe the pathophysiological events between days 0 and 3 or 4 that induce immediate injury to the brain.[14] EBI includes subsequent damage to the brain. Global brain ischemia due to intracranial hypertension following aneurysmal rupture causes the activation of miscellaneous pathways, including inflammation, oxidative stress, apoptosis, and cortical spreading depolarization. Clot degeneration products located in the subarachnoid space induce cytotoxic changes that result in neuronal and endothelial cell death. In addition, microcirculation disorders and the rupture of the blood–brain barrier occur.[2,3,6,7,10,14, 23]

The above-mentioned damage resulting from EBI due to SAH seems to be difficult to directly evaluate in patients by means of objective parameters. In the present study, we retrospectively analyzed the relationships between patients’ baseline characteristics that are identifiable in the early postictal state and patients’ outcomes to identify parameters that can predict patient outcome and reflect the impact of EBI.

MATERIALS AND METHODS

Patients populations

We retrospectively analyzed data from 39 adult patients with documented SAH due to the rupture of a saccular intracranial aneurysm, who were treated at our institution in the 3.5-year period since January 2015. Patients with SAH due to cerebral artery dissection or poor-grade SAH, who could not be surgically treated were excluded from the study. Complete medical and neurological examinations, as well as neuroimaging scans including magnetic resonance angiography or 3D computed tomography (CT) angiography, were performed on all patients. All patients included in the current study underwent clipping/coiling (stratified by site according to aneurysmal location and shape) within 72 h of onset. This study was approved by the Institutional Review Board of Keio University, School of Medicine, with the accession number 20140327. This study was performed in compliance with the Declaration of Helsinki.

Candidate parameters

Patients’ characteristics such as age, gender, clinical LOC status at ictus, Subarachnoid Hemorrhage Early Brain Edema Score (SEBES), size of aneurysm, surgical strategy (clip or coil), World Federation of Neurosurgical Societies (WFNS) grade on admission, cerebral vasospasm, and DCI were initially selected. Of these parameters, LOC at ictus, SEBES, and WFNS grade on admission were selected as possible parameters that could reflect EBI. For data assessment, a SEBES of 3 or 4 was regarded as a high SEBES according to the previous reports.[1,16] A WFNS grade of 3–5 was regarded as a poor grade. Radiological vasospasm and DCI, which are known as poor prognostic factors in patients with SAH, were also assessed for multiple regression analysis. A GOS of 1–3 at the time of discharge was considered to be a poor outcome in the present study.

Definition of vasospasm and DCI in the present study

In the present study, we found that vasospasm was present if moderate (34–66%) or severe (67–100%) vasospasm, as described previously, was present within 4–14 days from ictus.[12] DCI was defined as brain damage occurring during the vasospasm period.[19] In the present study, we restricted DCI to a newly detected cerebral infarction confirmed by either CT, magnetic resonance imaging, or both, as described previously.[21] Incidents of cerebral infarction due to surgical procedures (e.g., obliteration of perforators) were not regarded as DCI.

Statistical analysis

We statistically analyzed the relationships between the baseline characteristics of the patients and patient outcomes. Baseline characteristics were compared between the different GOS groups using the Chi-square test for nominal variables and logistic regression analysis for continuous variables (i.e., age and the diameter of the aneurysm). Multivariate logistic regression analyses were also performed to account for patient characteristics and clinical parameters that were statistically significant in univariate analysis. Model selection using an adjusted R^2, Akaike’s information criterion with a correction for small sample sizes Akaike’s information criterion (AICc), and the Bayesian information criterion (BIC) was also performed. $P = 0.05$ was considered statistically significant. For continuous variables, when statistically significant differences were identified between parameters, the cutoff points were calculated with receiver operating characteristic (ROC) curves.

RESULTS

Patient characteristics

The patient group consisted of 22 females and 17 males, and the mean age was 59.8 years (range, 24–85 years). The treatment strategies were mainly determined at the site by three on-call attending neurosurgeons (ST, TA, and TM) according to the location and shape of the ruptured aneurysm, since in Japan, the same vascular neurosurgeon does both clipping and coiling. Twenty-six aneurysms in 26 patients were clipped, and the other 13 aneurysms in 13 patients were coiled. The baseline characteristics of the patients are summarized in Table 1.

Parameters that predict patient outcome

Age

A logistic regression analysis showed that age was significantly associated with outcome. This result showed that the older patient was, the worse the patient outcome would be. Then, ROC curve analysis was used to determine the optimal cutoff point for age predicting poor outcome. The ROC curve for predicting poor outcome revealed that the area under the curve (AUC) value for age was 0.753, and the analysis identified an optimal cutoff point as 65 years old, with 66.7% sensitivity and 50.0% specificity [Figure 1]. Thus, the continuous variable of age was converted into a nominal variable with "older (≥65)" and "younger (<65)" groups for further consideration.

Diameter of aneurysm

In the present study, the diameter of the aneurysm was not significantly associated with the outcome according to logistic regression analysis.

Nominal variables

In the univariate analysis, older age (≥65), LOC at ictus, poor WFNS grade (3–5), and DCI were statistically significant prognostic factors in patients with SAH. Surgical complications were occurred in two out of 39 patients analyzed; however, it did not affect outcome statistically. The odds ratio (OR) and *P* values of each variable are summarized in Table 1.

Statistically significant variables that can be identified in the early stage after ictus

LOC at ictus and a poor initial WFNS grade were both statistically significant variables that could be identified in the early postictal state. These are factors that reflect initial brain damage due to ictus. Thus, to avoid confounding factors, we constructed a mosaic plot showing the relationships between WFNS grade and outcome, with overlaying LOC status (Figure 2; overlaying diagonal line indicates patients who experienced LOC at ictus). Figure 2 shows that 50% of patients (3/6) from the poor outcome group whose initial WFNS grade at ER was 1 or 2 experienced LOC at the time of ictus, and on the contrary, only 13.6% of patients (3/22) from the good outcome group whose initial WFNS grade at ER was 1 or 2 experienced LOC at the time of ictus. We considered SAH patients who experienced LOC at ictus and/or those with poor WFNS grade to be a separate subgroup in which significant brain damage at the time of ictus should be considered. The OR for the combined LOC at ictus and/or poor WFNS grade subgroup (OR 15.2 [95% CI 3.1–75.5]) was higher than that of the LOC at ictus group (OR 7.6 [95% CI 1.8–32.6]) or that of the poor WFNS grade group (OR 10.5 [95% CI 2.1–51.5]) alone [Table 1]. The adjusted coefficient of determination (adjusted R^2), Akaike's information criterion with correction for small sample sizes (AICc), and the BIC for each parameter are summarized in Table 2. According to these three parameters, combined LOC at ictus and/or poor WFNS grade was the most powerful predictor of poor prognosis based on the results of model selection. The sensitivity of LOC at ictus and/or poor WFNS grade to predict poor outcome was calculated to be 80.00%, and the specificity of that was calculated to be 79.17%. The sensitivity and specificity of the statistically significant parameters that can predict poor outcome are summarized in Table 3.

Multivariate logistic regression analysis

Multivariate logistic regression analysis was initially performed using three parameters: age, combined LOC at ictus and/or poor WFNS grade, and DCI. However, due to the small sample size, the analysis did not converge. Therefore, we adopted the model selection method and calculated the adjusted R^2, AICc, and BIC of every two or three pairs of parameters, with or without accounting for interaction [Table 2]. According to the results, the use of three statistically significant parameters in a single regression analysis without accounting for interaction was the best model for predicting poor outcome. For parameters could be identified in the early postictal state, using age and LOC at ictus and/or poor WFNS grade without interaction were also a relatively reliable predictor for prognosis, for which the adjusted R^2, AICc, and BIC values were 0.55, 30.11, and 34.41, respectively. The results of the model selection analysis showed that combined LOC at ictus and/or poor initial WFNS grade is a statistically significant marker of poor prognosis in SAH patients that is independent of patient age and state of DCI.

DISCUSSION

In the present study, we found that combined LOC at ictus and/or poor initial WFNS grade is a useful prognostic

Table 1: Baseline characteristics of the patients and results of univariate analysis.

	Total, *n*=39	GOS=4, 5, *n*=24	GOS=1–3, *n*=15	*P*-value	OR[a] (95%CI[b])
Age, mean±SD (range)	59.8±13.6 (24–85)	55.1±11.7 (24–75)	67.3±13.3 (45–66)	0.0034***	
Age, *n*(%)				0.0024***	10.0 (2.2–45.6)
≧65	14	4 (16.7)	10 (66.7)		
<65	25	20 (83.3)	5 (23.3)		
Sex, *n* (%)				1	
Female	22	14 (58.3)	8 (53.3)		
Male	17	10 (41.7)	7 (46.7)		
LOC at the time of ictus, *n* (%)				0.0069**	7.6 (1.8–32.6)
+	15	5 (20.8)	10 (66.7)		
−	24	19 (79.2)	5 (33.3)		
SEBES score				1	
High (3, 4)	10	6 (25.0)	4 (26.7)		
Low (1, 2)	29	18 (75.0)	11 (73.3)		
Size of AN, mean±SD (range)	5.1±2.1 (1.4–11.4)	4.7±2.0 (1.4–11)	5.7±2.3 (2.5–11.4)	0.198	
Surgical strategy, *n* (%)				0.73	
Clipping	26	15 (62.5)	11 (73.3)		
Coiling	13	9 (37.5)	4 (26.7)		
Surgical complication*, *n* (%)				0.1417	
Yes	2	0 (0)	2 (13.3)		
None	36	24 (100.0)	13 (86.7)		
WFNS grade, *n* (%)				0.0035***	10.5 (2.1–51.5)
Poor (3–5)	12	3 (12.5)	9 (60.0)		
Good (1, 2)	27	21 (87.5)	6 (40.0)		
Radiological vasospasm, *n* (%)				0.079	
Yes	13	5 (20.4)	8 (53.3)		
No	26	19 (79.6)	7 (46.7)		
DCI, *n* (%)					
Yes	6	1 (4.2)	5 (33.3)	0.0236**	11.5 (1.6–235.8)
No	33	23 (95.8)	10 (66.7)		
LOC/WFNS grade, *n* (%)					
LOC+ or poor grade	17	5 (20.4)	12 (80.0)	0.0006***	15.2 (3.4–89.5)
Other	22	19 (79.6)	3 (20.0)		

SEBES: Subarachnoid Hemorrhage Early Brain Edema Score. *Only surgical complications that could ultimately affect outcome were counted, **$P \leq 0.01$, ***$P \leq 0.001$, [a]Odds ratio, [b]95% confidence interval

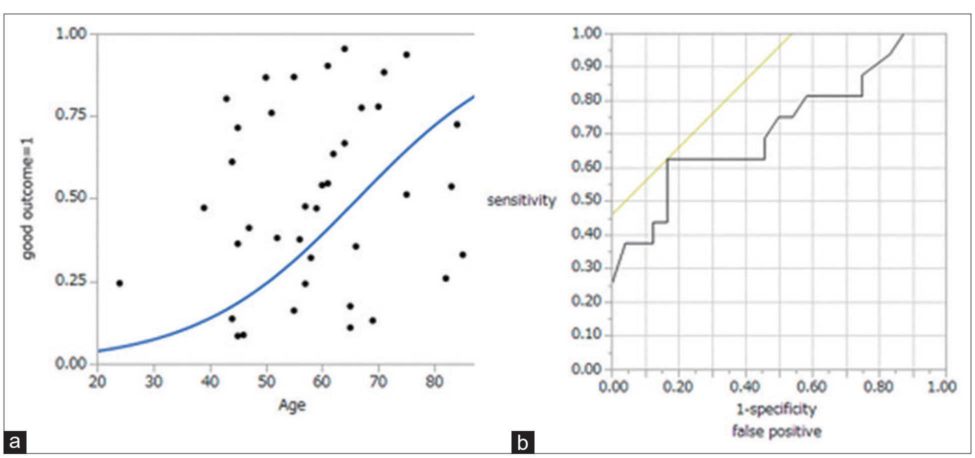

Figure 1: (a) Logistic regression analysis showed that age was significantly associated with outcome. The result showed that the older patient was, the worse the outcome would be. (b) The receiver operating characteristic curve for predicting poor outcome revealed that the area under the curve value for age was 0.753, and the analysis identified an optimal cutoff point of 65 years old.

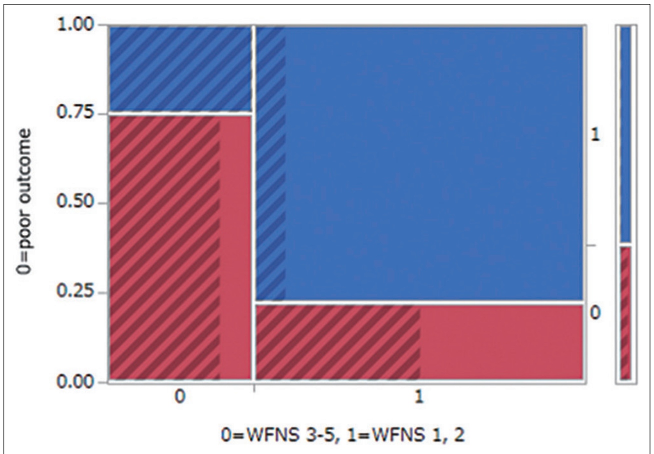

Figure 2: A mosaic plot showing the relationships between the World Federation of Neurosurgical Societies grade and outcome with loss of consciousness (LOC) status overlaid (diagonal line indicates patients who experienced LOC at ictus).

Table 2: Results of model selection analysis using adjusted coefficient of determination (adjusted R2), AIC with a correction for small sample sizes (AICc), and BIC.

	Adjusted R^2	AICc	BIC
Single regression analysis			
Age over 65	0.20	46.11	49.10
DCI	0.12	50.23	53.22
LOC+ and/or poor WFNS gr	0.27	42.46	45.45
Multiple regression analysis			
Age, LOC/WFNS	0.55	30.11	34.41
With interaction	0.55	32.60	38.08
Age, DCI	0.31	42.69	46.99
With interaction	0.31	44.94	50.42
DCI, LOC/WFNS	0.36	40.20	44.51
With interaction	0.36	42.28	47.75
Age, DCI, and LOC/WFNS	0.65	27.40	32.88
With interaction	0.65	35.83	43.87

BIC: Bayesian information criterion, DCI: Delayed cerebral ischemia, WFNS: World Federation of Neurosurgical Societies, AIC: Akaike's information criterion

Table 3: Sensitivity and specificity for parameters identified in the univariate analysis.

	Sensitivity (%)	Specificity (%)
LOC/WFNS	80.00	79.17
Age	66.67	83.33
DCI	33.33	95.83

LOC: Loss of consciousness, DCI: Delayed cerebral ischemia, WFNS: World Federation of Neurosurgical Societies

marker that can be identified in the early postictal state with 80.00% sensitivity and 79.17% specificity. Multiple regression analysis with model selection methods revealed that combined LOC at ictus and/or poor initial WFNS grade is a prognostic marker that is independent of patient age and the state of DCI. This fact showed that the prognoses of SAH patients have already been determined, to some extent, as early as the time of admission. We will thus interpret the result that combined LOC at ictus and/or poor initial WFNS grade reflects the impact of EBI.

EBI causes subsequent damage to the brain. Global brain ischemia due to intracranial hypertension following aneurysmal rupture causes the activation of miscellaneous pathways, including inflammatory, oxidative stress, apoptotic, and cortical spreading depolarization pathways, among others.[16] LOC at ictus has been reported to result from transient global ischemia due to the elevation in intracranial pressure (ICP).[18] Zoerle *et al*. reported an interesting finding regarding ICP in patients with SAH. In the study, the authors found that the mean ICP is associated with the severity of EBI and mortality.[24] According to their results, patients with the highest mean ICP, i.e., an ICP greater than 20 mmHg, had significantly higher mortality.[24] According to this result, LOC at ictus reflects high ICP in the patient and, thus, means the existence of EBI. For the WFNS grading system, a previous report stated that SAH-induced brain injury may be substantially more severe in patients with Glasgow Coma Scale (GCS) 13 than in those with GCS 14, and the grading system may not be able to distinguish patients with heterogeneous backgrounds of EBI.[15] At present, LOC at ictus can distinguish patients suffering from EBI from its counterparts considerably well. Combining both LOC at ictus and/or poor WFNS grade could overcome the above shortcomings of WFNS grading for predicting the impact of EBI and could serve as a more reliable predictor of EBI.

The previous studies have already reported LOC at ictus as a predictor of clinical outcome. Suwatcharangkoon *et al*. analyzed the data of 1460 consecutively treated patients with SAH and reported that 40.4% of them experienced LOC at the onset of SAH.[18] The percentage of patients who experienced LOC at ictus in that study (40.4%) is very similar to that found in the present study (39.5%). The authors found that LOC was associated with poor clinical grade, more subarachnoid and intraventricular blood, a higher frequency of global cerebral edema, and poor outcome. In addition, they concluded that LOC at ictus is an important manifestation of EBI after SAH.[18] The results of the current study are in line with these results, and we would additionally insist on the usefulness of poor initial WFNS grade in combination with LOC at ictus to identify patients who are considerably impacted by EBI with less omission. The concept of accounting for both LOC at ictus and poor initial WFNS grade that are adopted in the present study is also supported by a report by SAHIT collaborators in 2017. In the study, they used a propensity score matching algorithm to show that LOC at ictus is associated with functional outcomes in good-grade patients.[22]

SAHIT is a tool that was developed for the reliable estimation of SAH outcomes.[9] In the study, a core model including patient age, premorbid hypertension, and neurological grade on admission was used to predict risk of functional outcome and had good discrimination, with an area under the receiver operator characteristics curve (AUC) of 0.80 when the core model was extended to a "neuroimaging model," with the inclusion of clot volume, aneurysm size, and location, the AUC slightly improved to 0.81.[9] This result is also in line with the result of our present study in that age and neurological grade on admission considerably affected the outcome. Our present method has an advantage in that we can score the impact of EBI very easily using only LOC status and the initial WFNS grade.

Many other useful outcome predictors have also been confirmed in patients with SAH. Faust *et al*. reported that a mean arterial blood pressure elevated >25% within the 1st week after SAH was associated with an unfavorable outcome.[4] Another group reported that early alterations in routine blood tests, such as white blood cell, sodium level, or C-reactive protein level, have also been reported as prognostic factors in patients with SAH.[17] Radiological assessment, such as volumetric measurement of bleeding volume or analysis diffusion tensor imaging, is another approach for predicting the outcome of patients with SAH.[5,11] In one study, a volume of more than 20 mL of blood in the initial CT was reported to be related to poor outcome.[11] Of these methods, our current approach is one of the easiest ways to assess outcome; it also has the advantage of being able to be assessed immediately after admission, and it is also useful for estimating the impact of EBI in the patient.

To screen, the patients who are considerably impacted by EBI are important so we can provide more prudent care to these patients. However, even if we could screen for these kinds of patients, improvement in the clinical outcome of these patients could not be achieved without first elucidating the mechanism of EBI and developing a new medical approach for EBI. To achieve this goal, our group is now working on basic research to elucidate the molecular mechanism of EBI. In particular, we are now trying to identify microRNAs that are specifically overexpressed or downregulated by EBI that can be separated from exosomes within the patients' peripheral blood samples to serve as a clinical marker of EBI (data not shown). After the initial rupture of the aneurysm, abnormalities such as dysfunction in autoregulation, clot degeneration products, neuroinflammation, and hyponatremia/endocrine dysfunction occur.[8] At the molecular level, it has been reported that the expression levels of molecules such as aquaporin-4, matrix metalloproteinase-9, SUR1-TRPM4 cation channels, vascular endothelial growth factor, bradykinin, and others occur.[8] We believe that finding microRNA that is altered by the rupture of aneurysms could more simply explain the complex mechanism of EBI because each miRNA has many potential mRNA targets; thus, a broad spectrum of gene expression could be affected by the presence or absence of an individual miRNA.[20]

The current study also has certain limitations. The number of patients included in the current study was relatively small. The small study sample prevented us from conducting multivariate analysis with three parameters at 1 time; however, model selection suggested that combined LOC at ictus and/or poor WFNS grade was a useful predictor of the prognoses of patients with SAH, independent of age or DCI.

CONCLUSION

Combined LOC at ictus and/or poor initial WFNS grade is a useful surrogate marker of poor prognosis in SAH patients that is independent of patient age and the state of DCI. The results revealed that the prognoses of patients with SAH are largely affected by brain damage in the early postictal state (i.e., EBI). The influence of EBI on outcome in patients with SAH has emerged along with the development of modern treatment strategies that prevent vasospasm. Understanding the pathology of EBI, as well as developing new therapeutic and diagnostic strategies to prevent EBI, will be important in future.

Declaration of patient consent

Institutional Review Board (IRB) permission obtained for the study.

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Conflicts of interest

There are no conflicts of interest

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