



Prospective Analysis of Cerebral Edema Admission and Clinical Outcome in Ruptured Intracranial Aneurysm

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ABSTRACT

AIM: To evaluate the association between global cerebral edema (GCE) after subarachnoid hemorrhage (SAH) and its impact on functional outcome evaluated by the modified Rankin scale (mRS).

MATERIAL and METHODS: This is a prospective cohort study with patients who were admitted to the hospital due to SAH. During the period from January 2018 to November 2019, 107 patients with intracranial aneurysms were enrolled. Using univariate and multivariate analysis, we sought to identify predictors and evaluated the impact of GCE on outcome after 6 months using the mRS.






RESULTS: GCE was present in 54 (50.5%) patients, of which 27 (25.2%) were mild, 20 (18.7%) moderate and 7 (6.5%) were severe. Univariate analysis identified high Hunt-Hess and Glasgow coma scale on clinical admission as predictors factors of GCE ($p < 0.05$), and higher modified Fisher scale as a radiological predictor of Glasgow coma scale ($p < 0.05$). Thirty-three (30.8%) patients were deceased at 6 months. Death or severe disability were predicted by higher age, poor clinical scale on admission and severe GCE ($p < 0.05$).

CONCLUSION: GCE on admission is independently associated with poor clinical outcomes at discharge, and six months after SAH. Given its strong association with poor clinical grade on admission, GCE should be considered a straightforward and radiological important marker of early brain injury, with ominous implications.

KEYWORDS: Early brain injury, Global cerebral edema, Prediction, Prognosis, Subarachnoid hemorrhage

ABBREVIATIONS: **ACA:** Anterior cerebral artery, **AcomA:** Anterior communicating artery, **AICA:** Antero-inferior cerebral artery, **CTA:** Computed tomography angiography, **EBI:** Early brain injury, **DCI:** Delayed cerebral ischemia, **DM:** Diabetes mellitus, **GCE:** Global cerebral edema, **GCS:** Glasgow coma scale, **HH:** Hunt-Hess, **ICA:** Internal carotid artery, **MRI:** Magnetic resonance imaging, **mRS:** Modified Rankin Scale, **OR:** Odds ratios, **PCA:** Posterior cerebral artery, **PcomA:** Posterior communicating artery, **PICA:** Postero-inferior cerebellar artery, **WFNS:** World Federation of Neurosurgical Societies, **SAH:** Subarachnoid hemorrhage, **UIAs:** Unruptured intracranial aneurysms

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■ INTRODUCTION

Subarachnoid hemorrhage (SAH) caused by intracranial aneurysm rupture accounts for 5%–7% of all types of strokes (5), primarily affecting young patients during their most productive years (4). Despite improvements in neurocritical care, SAH remains a devastating neurological condition that continues to have a significant impact on morbidity and mortality (2), and has long-term consequences for functional status and quality of life (19,20).

In recent decades, most therapeutic treatments have failed to improve outcomes after SAH by preventing angiographic vasospasm and delayed cerebral ischemia (DCI). As a result, experimental and clinical research has focused on the pathophysiological mechanisms in the first 72 hours after an aneurysm rupture, referred to as “early brain injury” (EBI) (27).

Initial clinical evaluations soon after an aneurysmal rupture, such as the Hunt–Hess (HH) scale, World Federation of Neurosurgical Societies (WFNS) scale, and Glasgow Coma Scale (GCS), have been found to be clinical markers of EBI and have been regularly established as major predictors of mortality and poor functional prognosis following SAH (19,21). Similarly, the most extensively used initial radiography grading systems, Fisher scale and modified Fisher scale (mFS), have been linked to poor clinical outcomes and DCI (8), and have been identified as important biomarkers of EBI. However, the pathophysiological mechanism of EBI is thought to be a complex multifactorial process that cannot be fully explained by the volume of blood in the cisternal space alone (15,16,18).

Global cerebral edema (GCE) is commonly used as a neuroradiological marker of EBI after SAH. GCE is estimated to affect 6%–8% of the population (3,13), and has been associated as an independent risk factor for poor clinical outcomes (2,13). However, its capacity to describe EBI and, hence, poor clinical prognosis is limited due to its small proportion and lack of attention as a prognostic factor. Furthermore, there is limited information regarding the impact of GCE on functional outcomes following SAH. The major goal is to identify the characteristics that influence prognosis to better understand the disease course and improve the outcome.

In this study, we intended to evaluate the association between GCE after aneurysmal SAH (aSAH) and its impact on functional outcome evaluated using the modified Rankin scale (mRS) at 6 months and determine the independent predictors of GCE and severe disability.

■ MATERIAL and METHODS

Study Design

This prospective cohort study included patients admitted to the hospital due to SAH between January 2018 and November 2019. Social and demographic data were gathered from patient charts in a database at the Hospital das Clínicas Department of Neurosurgery (HCFMUSP). A computed tomography (CT) scan and aneurysm intracranial rupture status were obtained at admission as well as the mRS score at admission, after

discharge, and at 6 months.

Population Data

During this period, 401 patients were admitted for an intracranial aneurysm diagnosis at the Hospital das Clínicas Department of Neurological Surgery. Of the 401 patients, 107 were included in this study (Figure 1).

Depending on their clinical and imaging circumstances, the patients were treated with embolization or microsurgery. The patients underwent CT upon admission and were observed for 6 months. The result following SAH was measured using the mRS at the end of the study.

Exclusion Criteria

The exclusion criteria included patients without available or poor-quality CT scan data upon admission, loss to follow-up in less than 6 months, and any pathological imaging findings other than intracranial aneurysm.

Inclusion Criteria

Patients of both sexes with ruptured intracranial aneurysm who were admitted to the Hospital das Clínicas (HCFMUSP) between January 2018 and November 2019 were included.

Ethical Standards

This research project was approved by the Ethics and Research Committee of the Hospital das Clínicas of FMUSP. Online registration CAPPesq: 15226 approved 06/20/2016. Approved on the Brazil platform CAAE number: 61719416.6.0000.0068. Patient consent was obtained for all participants.

Clinical Variables

We recorded baseline demographic data (age and sex) and social history concerning previous risk factors for aneurysmal disease, including a history of hypertension, diabetes mellitus (DM), smoking and alcohol use, and past medical history (previous SAH). On admission, we conducted neurological and general medical examinations. The GCS (24), HH scale (11), and WFNS scale were used to assess neurological status at the time of admission.

Radiographic Variables

Senior radiologist researchers independently assessed the CT scans for the existence of GCE, amount and location of blood (as measured by the mFS), and presence of hydrocephalus. We noted the aneurysm's location and size: the internal carotid artery, posterior communicating artery, choroidal artery, anterior cerebral artery, anterior communicating artery, medial cerebral artery, basilar artery, posterior cerebral artery, antero-inferior cerebral artery, and postero-inferior cerebral artery.

Radiological GCE was defined as mild, moderate, or severe. Mild edema was characterized by the absence of visible sulci caused by effacement of sulci in the cortex and absence of visible sulci with disruption of the gray–white matter junction in each hemisphere and at the level of the centrum semiovale (Figure 2A, B). Moderate edema was defined as the absence of sulci on CT at the level of the insular cortex, thalamus, basal

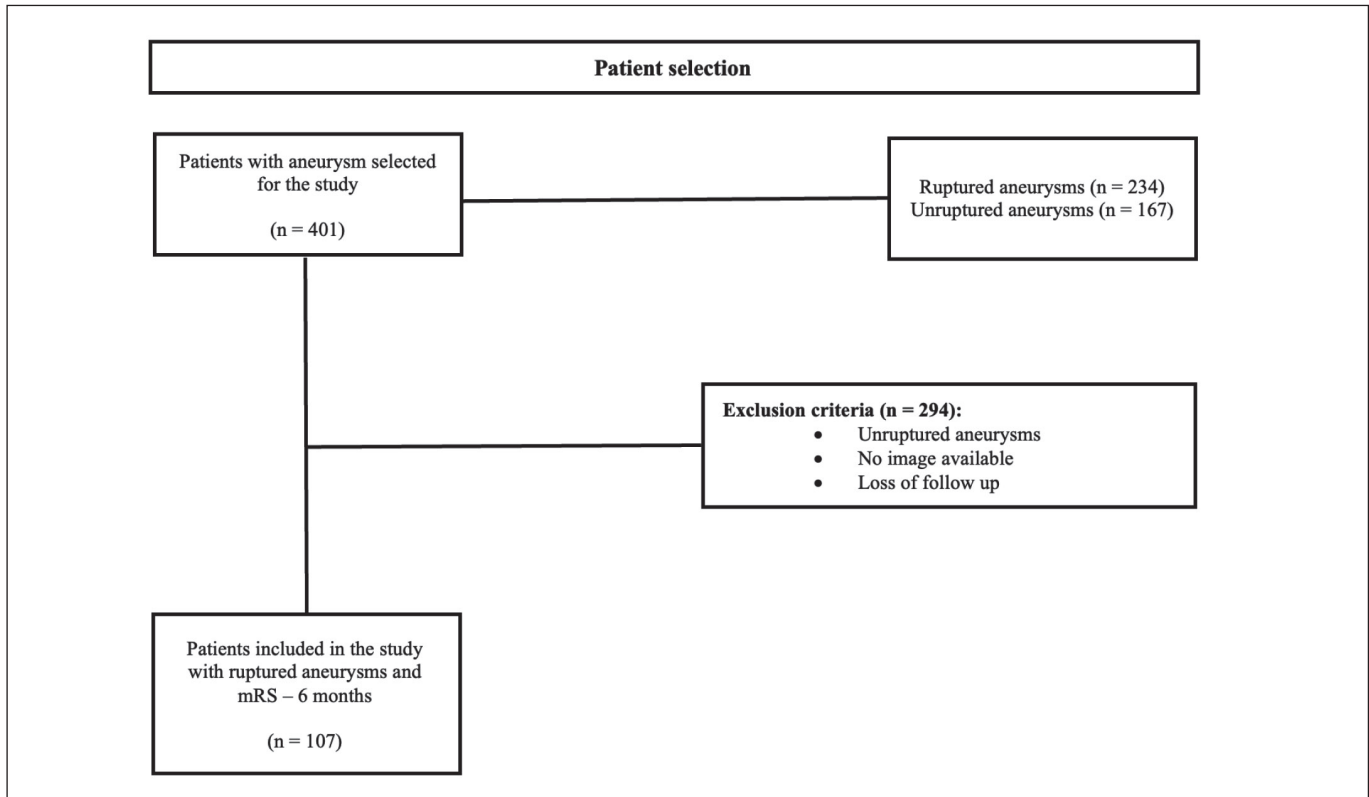


Figure 1: Flow chart. mRS: modified Rankin scale.

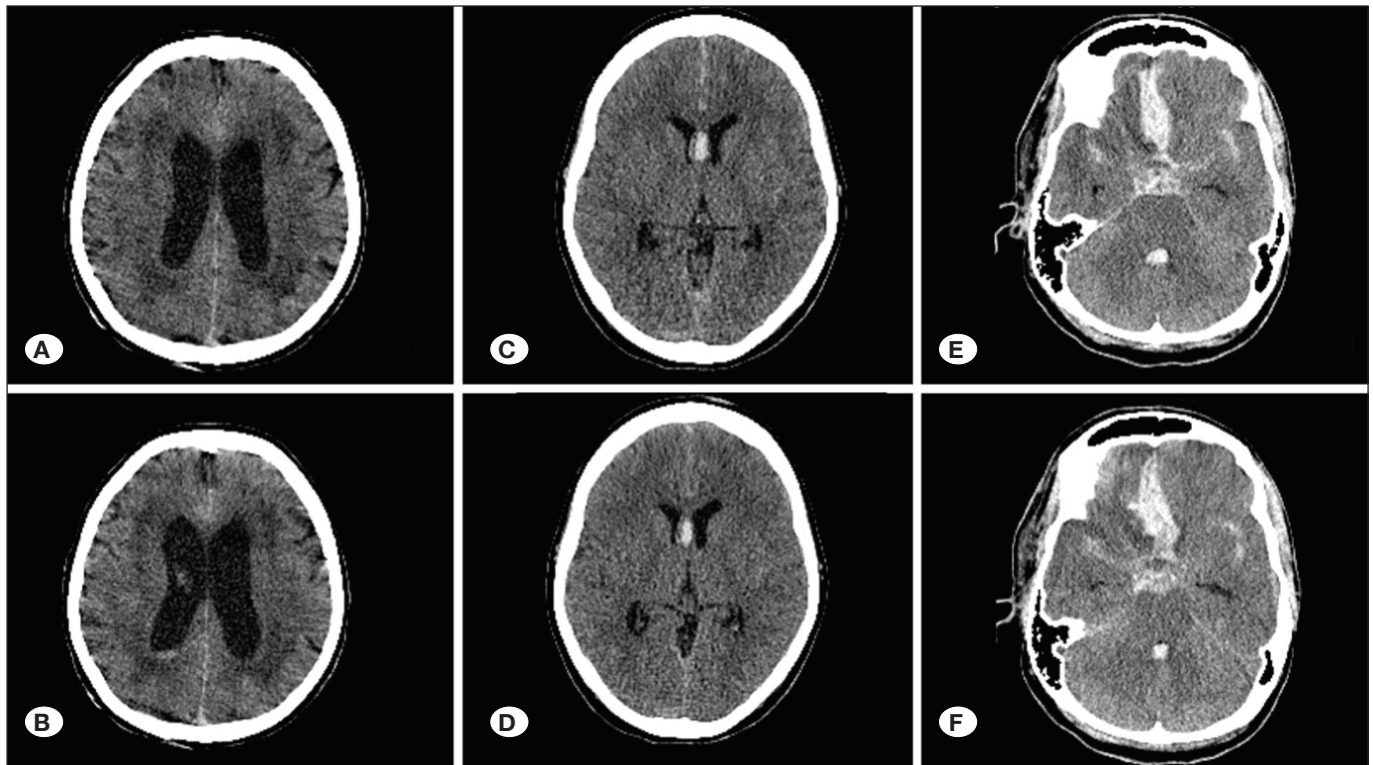


Figure 2: Classification of GCE as mild, moderate and severe. A, B) Mild edema; C, D) Moderate edema; E, F) Severe edema, based on the classification proposed.

ganglion above the lateral ventricle, and Sylvian fissure (Figure 2C, D). Severe edema was defined as all mild and moderate characteristics and basal cistern occlusion compromising the brainstem (Figure 2E, F).

Outcome Variables

Survival and functional outcomes at discharge and 6 months were assessed using the mRS. For the analysis of predictors of the 6-month outcome, death or severe disability was defined as an mRS score of 4–6.

Statistical Analysis

All analyzes were performed using the STATA Statistical Package for Macbook version 12.0. Univariate associations between predictor variables and global edema and mortality were tested with binary logistic regression analyses. To assess the validity of this approach, we performed a confirmatory univariate analysis using chi2 or Fisher exact tests for categorical variables, 2-tailed t tests for normally distributed continuous variables, and Mann-Whitney U tests for non-normally distributed continuous variables. Among similar variables that were highly intercorrelated (ie, clinical scales), only the variable with the highest odds ratio (OR) and smallest P-value in the binary logistic regression analysis was used as a candidate variable in the final multivariate model. The outcome was quantified by mRS at 6-months. Functional outcome was dichotomized as good (mRS score: 0–3; able to look after own affairs without assistance) or poor (mRS score: 4–6; moderate to severe disability or death).

Significance level was established as $p < 0.05$. For the logistic regression, an unfavorable outcome was defined as mRS greater than 2. Discrete variables are presented as numbers with percentage (%) and continuous variables as a mean with SD, or as a median with range where appropriate.

RESULTS

Between January 2018 and November 2019, 401 patients with cerebral aneurysms were included; 294 patients were excluded because they had unruptured aneurysms, the initial CT scan was not accessible, or the image quality was insufficient for evaluation. Finally, this analysis included 107 patients with ruptured aneurysms (Figure 1).

Demographic and Clinical Features

The clinical characteristics of 107 patients are summarized in Table I. The median age was 59 (50–64.5) years. Seventy-seven (74%) patients were female. The median scores (ranges) for the GCS, HH scale, and WFNS scale at admission were 14 (7–15), 2 (2–3), and 2 (1–5), respectively. Hypertension was present in 82% of the patients, 39% had previous DM, 54% were smokers, 41% had previous cardiovascular disease, 19.6% had previous SAH and multiple aneurysms, 49% showed edema on the initial CT scan, and 54% had hydrocephalus.

Radiological Analysis

Fifty-four (50.5%) patients had GCE on the initial CT scan, of

whom 27 (25.2%) were mild, 20 (18.7%) were moderate, and 7 (6.5%) were severe. Twenty patients presented with mFS grades I–II on the initial CT scan, of whom 14 (26.4%) did not present with GCE and 6 (11.11%) presented with GCE. Seventy-nine patients presented with mFS grades III–IV, of whom 33 (62.3%) did not present with GCE and 46 (85.2%) presented with GCE. There was a statistically significant difference in the mFS between patients with and without GCE ($p < 0.05$). Fifty-four (53%) patients had hydrocephalus.

Predictor of Admission GCE

Four clinical and radiographic variables were associated with GCE on admission CT scan (Table I). The univariate analysis identified high HH scale, WFNS scale, and GCS scores as clinical predictors of GCE ($p < 0.05$) and higher mFS score as a radiological predictor of GCS ($p < 0.5$).

Predictors of Mortality

Thirty-three (30.8%) patients died 6 months after SAH. The mortality rate was 35.2% in patients with GCE on the initial CT scans, compared with 26.4% in those without GCE. Only three variables were associated with death at 6 months (Table II). The univariate analysis identified higher age, poor HH grade, and GCS score as predictors of mortality ($p < 0.05$). Treatment was not evaluated as a variable in the present study.

Predictor of Death or Severe Disability

Of the 74 patients who survived, 67 were not severely disabled [mRS 0 to 3], and 7 were severely disabled [mRS 4 to 5]. Four variables were associated with death and severe disability at 6-months (Table III). The univariate analysis identified older age, poor HH grade, GCS, and severe GCE as predictors of mortality ($p < 0.05$). Multivariate logistic regression identified aneurysm size (OR, 1.14; 95% CI, 0.99–1.39) and severe GCS (OR, 7.23; 95% CI, 1.85–28.25) as independent predictors of death or severe disability (Table IV). Despite not presenting a statistically significant difference in the univariate analysis, we believe that the aneurysm size variable has a strong implication for prognosis. GCE was not associated with worse mRS score at 6 months; however, when we stratified this variable between mild, moderate, and severe, the last variable was strongly associated with poor clinical outcomes in the multivariate analysis.

DISCUSSION

Clinical scores, such as the HH scale, GCS, and WFNS scale scores, have traditionally been employed as indicators of clinical severity and prognosis. Radiological prognostic indicators have also been demonstrated to influence mortality in patients with SAH; however, GCE is frequently overlooked (4,7). GCE after SAH has been shown to be a significant predictor of poor long-term clinical outcomes (6,14). The fact that a poor clinical scale on admission (GCS, HH scale, or WFNS scale) was associated with GCE suggests that this is a radiological marker of EBI and may indicate microvascular injury induced by cerebral circulatory arrest (7).

Currently, a significant amount of research on aSAH has shift-

Table I: Patients Baseline Characteristics

Baseline characteristic of the patients (n=107)	No Edema (n=53)	Edema (n=54)	p-value
Age years, median (range)	59 (47 - 65)	59 (50 - 64)	0.5
Female sex, n (%)	36 (70.5)	41 (77.36)	0.43
Hypertension, n (%)	33 (84.62)	25 (71.43)	0.16
Smoking, n (%)	20 (51.28)	23 (65.71)	0.2
Diabetes, n (%)	18 (46.15)	11 (31.43)	0.19
Alcoholism, n (%)	8 (20.51)	8 (22.86)	0.8
Previous SAH, n (%)	9 (23.08)	4 (11.43)	0.18
Multiple aneurysm, n (%)	9 (19.57)	7 (13.46)	0.41
Aneurysm size (mean \pm SD)	6.12 \pm 3.76	7.47 \pm 5.55	0.14
Radiological cerebral edema features, n (%)			
Mild, n (%)	-	27 (50)	-
Moderate, n (%)	-	20 (37)	-
Intense, n (%)	-	7 (13)	-
Modified Fisher scale, median (range)	3 (3-4)	3 (3-4)	0.01*
Hydrocephalus, n (%)	20 (51.28)	24 (54.55)	0.76
Clinical scale on admission			
GCS, median (range)	14 (13 - 15)	13.5 (6 - 15)	0.02*
WFNS, median (range)	2 (1 - 3)	2 (1 - 5)	0.01*
Hunt-Hess, median (range)	2 (1 - 3)	2 (2 - 4)	0.008*
Location of aneurysm			
Anterior circulation, n (%)	47 (94)	46 (90.2)	
Posterior circulation, n (%)	3 (6)	5 (9.8)	0.47
Outcome			
mRS at discharge	1 (1-3)	1 (1-3)	0.64
mRS at 6 months	3 (1-6)	3 (1-6)	0.5

Data are presented as mean (SD) for continuous variables, median (range) for ordinal variables and count (valid percentage) for categorical variables. **SAH:** Subarachnoid hemorrhage; **GCE:** Global cerebral edema; **GCS:** Admission Glasgow Coma Scale; **mRS:** Modified Rankin scale; **WFNS:** World Federation of Neurosurgical Societies Scale; statistically significant.

ed to understanding the pathophysiological mechanism and prevention of EBI. GCE is thought to be caused by rebound hyperemia associated with blood-brain-barrier disruption in the setting of abnormal autoregulation after an initial increase in intracranial pressure followed by intracranial circulatory arrest, which may trigger early GCE through cytotoxic edema. In addition, there are several neuroinflammatory energy dysfunctions secondary to cortical spreading depolarization and microglial activation as the initiation of the proinflammatory response. Searching for new therapies focusing on pathophysiological mechanisms causing EBI may help to treat aSAH complications and, thus, reduce poor clinical outcomes (22).

Autoregulation malfunction, hemorrhage products (e.g., thrombin), and ischemic injury are all capable of producing inflammation and vasogenic edema in experimental intracerebral hemorrhage models (9,30). Cerebral edema may also be caused by hypo-osmolality and hyponatremia after SAH; however, there is no strong evidence to support this association (23,28). Critical care treatment methods, such as rigorous blood pressure, salt, and intracranial pressure control, can help reduce edema and improve outcomes after SAH.

According to MRI investigations of aSAH, edema is a progressive condition, with radiographic evidence of increased

Table II: Predictor of Mortality

Variable	Dead		p-value
	Yes (n=33)	No (n=74)	
Age (mean ± SD)	62.36 ± 12	55.28 ± 12.65	0.008
Female sex, n (%)	23 (76.6)	54 (72.97)	0.69
Hypertension, n (%)	-	58 (78.3)	-
Smoking, n (%)	-	43 (58.1)	-
Aneurysm size (mean ± SD)	7.9 ± 6.6	6.31 ± 3.6	0.11
Multiple aneurysms, n (%)	2 (6.45)	14 (20.9)	0.07
Radiographic features, n (%)			
No edema, n (%)	14 (42.4)	39 (52.7)	0.33
GCE Mild, n (%)	10 (30.3)	17 (22.97)	0.4
GCE Moderate, n (%)	5 (15.15)	15 (20.27)	0.5
GCE Severe, n (%)	4 (12.12)	3 (4.05)	0.11
Fisher III - IV, n (%)	27 (81.8)	57 (77)	0.5
Hydrocephalus, n (%)	9 (60)	35 (51.47)	0.55
Clinical scales, n (%)			
GCS, median (range)	13 (6 - 15)	15 (10.5 - 15)	0.009
Hunt-Hess grade	2 (2 - 4)	2 (1 - 3)	0.004

Data are presented as mean (SD) for continuous variables, median (range) for ordinal variables and count (valid percentage) for categorical variables. **GCE:** Global cerebral edema; **GCS:** Admission Glasgow Coma Scale.

Table III: Predictor of Severe Disability

Variable	Death or Severe Disability (n=40)	Mild disability (n=67)	p-value
Age (mean ± SD)	62.10 ± 11	54.68 ± 13.07	0.004
Female sex, n (%)	28 (75.68)	49 (73.13)	0.77
Hypertension, n (%)	7 (100)	51 (76.12)	0.14
Smoking, n (%)	4 (57.14)	39 (58.21)	0.95
Aneurysm size (mean ± SD)	7.6 ± 6.22	6.29 ± 3.61	0.15
Multiple aneurysms	4 (10.53)	12 (20)	0.21
Radiographic features, n (%)			
No edema	18 (45)	35 (52.24)	0.46
GCE Mild	12 (30)	15 (22.39)	0.38
GCE Moderate	5 (12.5)	15 (22.39)	0.2
GCE Severe	5 (12.5)	2 (2.9)	0.05
Fisher III - IV, n (%)	33 (82.5)	51 (76.12)	0.43
Hydrocephalus	15 (71.43)	29 (46.77)	0.05
Clinical scales, n (%)			
GCS, median (range)	14 (6 - 15)	14.5 (10.5 - 15)	0.01
Hunt-Hess grade	2 (2 - 4)	2 (1 - 3)	0.042

Data are presented as mean (SD) for continuous variables, median (range) for ordinal variables and count (valid percentage) for categorical variables. **GCE:** Global cerebral edema; **GCS:** Admission Glasgow Coma Scale.

Table IV: Multivariable Logistic Regression Analysis Identifying Predictors of Severe Disability and Death at 6-Months

Variable	Severe Disability and death	p-value
Age (mean ± SD)	1.06 (0.99 - 1.12)	0.09
Aneurysm size (mean ± SD)	1.14 (0.99 - 1.39)	0.05
GCE moderate/severe	1.08 (0.12 - 3.11)	0.5
Fisher III - IV, n (%)	1.15 (0.13 - 6.23)	0.9
Hydrocephalus	1.15 (0.22 - 3.63)	0.8
Severe GCS (GCS <9)	7.23 (1.85 - 28.25)	0.007

CI: Confidence interval; **GCS:** Glasgow coma scale; **SD:** Standard deviation.

edema on days 2 and 7 following hemorrhage (3,29), with progressive improvement in some patients. Westermaier et al. used a rat model to investigate the progression of cerebral edema in the first hours after SAH (26). They discovered a link between increased brain water content and the severity of perfusion deficit, implying that the progression of brain edema is linked to the severity of ischemia and acute vasoconstriction, which is consistent with the pathophysiological cascade of Mocco et al. (17). However, the pathophysiology associated with vasospasm, rather than EBI due to aneurysm rupture, is a limitation in patients with increasing edema (25).

Ahn et al. in a previous study tried to establish an SEBS score to determine the edema in SAH; however, this score did not consider a crucial feature that is obliteration of the basal cisterns and brainstem compression (1). Nonetheless, the score may cause bias in the analysis by overestimating and underestimating the information in specific circumstances. As a result, in this study, we decided to take a different approach to GCE classification and split it into three categories: mild, moderate, and severe, considering cistern patency and brainstem compression.

Our prospective data showed that severe GCE was an independent predictive factor of poor functional outcome following SAH, as measured by the mRS at 6 months in a CT scan on admission. GCE, which is regarded as an important marker of EBI, was strongly associated with patients with extensive SAH (as measured by the mFS) and worse clinical scores on admission.

Admission GCE was present in 54 (50.5%) of our patients, which was similar to the findings of Helbok et al. (10); however, previous reports have found a lower frequency (3,12). In the univariate analysis, GCE was predicted by a poor clinical scale on admission and high grade on the mFS, which was in accordance with previous reports (1,3,21). However, age, hypertension, smoking, diabetes, previous SAH, hydrocephalus, and multiple aneurysms were not associated with GCE. One explanation for the lack of a statistical difference between age and cerebral edema could be age-related atrophy. Claassen et al. observed an association

between a large aneurysm size and GCE (3). Although we observed a tendency of larger aneurysm size in GCE, it was not statistically significant in the univariate analysis.

GCE was not associated with a poorer mRS score at 6 months; however, when this variable was classified as mild, moderate, or severe, the latter was highly associated with a worse clinical outcome. Because of the link between severe GCE and low clinical grade at presentation, these individuals should be treated and monitored more closely.

Limitations of the Study

The results of this study must be considered within the context of certain limitations. A moderate number of patients were lost to follow-up. Although the GCE was examined by an expert, observer bias could have affected the diagnosis and degree of edema. In conclusion, larger cohorts with additional confounding variables and demographics are required. Sentinel headaches were not assessed because obtaining complete information from patients in poor clinical settings makes the accurate diagnosis of previous warning headaches challenging, especially in patients with low GCS scores. The presence or absence of GCE may be relevant in the future for risk classification and therapy targeting to reduce the effects of EBI after SAH. To learn more, further prospective studies are needed.

CONCLUSION

This prospective study indicates that severe GCE on the initial CT scan on admission is independently associated with poor outcomes at discharge and 6 months after SAH. Given its strong association with poor admission clinical grade, severe edema, and poor clinical outcome, GCE should be considered a straightforward and important radiological marker of EBI after SAH, with ominous implications.

AUTHORSHIP CONTRIBUTION

Study conception and design: NNR, DZO, LZP, JPMT, MHY, MJT, EGF

Data collection: MJT, EGF

Analysis and interpretation of results: NNR, DZO, LZP, JPMT, MJT, EGF

Draft manuscript preparation: NNR, DZO, LZP, EGF

Critical revision of the article: NNR, DZO, LZP, EGF

Other (study supervision, fundings, materials, etc...): NNR, DZO, MJT, EGF, JPMT, NCB, GBB

All authors (DZO, NNR, LZP, JPMT, NCB, ACSSC, MHY, GBB, MJT, EGF) reviewed the results and approved the final version of the manuscript.

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