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Functional Outcome Following Ultra-Early Treatment for Ruptured Aneurysms in Patients with Poor-Grade Subarachnoid Hemorrhage

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Background: Little is known regarding functional outcome following poor-grade (World Federation of Neurosurgical Societies grades IV and V) aneurysmal subarachnoid hemorrhage (aSAH), especially in individuals treated aggressively in the early phase after ictus.
Methods: We provided patients with aSAH with ultra-early definitive treatment, coiling or clipping, within 6 hours from arrival as per protocol. We classified the patients into 3 groups according to their computed tomography findings: Group 1, intraventricular hemorrhage with obstructive hydrocephalus; Group 2, massive intracerebral hemorrhage with brain herniation; and Group 3, neither Group 1 nor Group 2. We retrospectively evaluated patients with poor-grade aSAH who were admitted to our department between January 2013 and December 2016. We evaluated functional outcome at 6 months, defining modified Rankin Scale (mRS) scores of 0-2 as good and those of 3-6 as poor outcomes.
Results: A good functional outcome was observed in 39.4% (28/71) of all cases. All-cause mortality at 6 months was 15.5% (11/71). A good outcome in Group 3 was significantly higher than that in the other two groups (Group 1 and 2 vs. Group 3, 20.8% vs. 48.9%, p = 0.02), even after adjustment with a multiple logistic regression analysis (odds ratio 6.1, 95% confidence interval 1.1 to 34.8).
Conclusions: Approximately 40% of patients with poor-grade aSAH became functionally independent, and approximately half of the patients with poor-grade aSAH who had neither intraventricular hemorrhage with obstructive hydrocephalus nor with brain herniation had good functional outcomes. Although further trials are required to confirm our results, ultra-early surgery may be considered for patients with poor-grade aSAH. (J Nippon Med Sch 2019; 86: 81–90)

Key words: aneurysm, intracerebral hemorrhage, subarachnoid hemorrhage, computed tomography

Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) remains a devastating disease despite recent advances in its treatment[1–4]. Several population-based studies have reported that the overall mortality rate of aSAH is approximately 30%, and even higher mortality and morbidity rates, along with additional health care burdens, are estimated in patients with poor-grade aSAH[1,2]. Although clarifying the prognostication and treatment strategy for patients with poor grade aSAH is crucial, they remain controversial.

The grading systems of aSAH developed by Hunt and

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Hess[5], Hunt and Kosnik[6], and the World Federation of Neurosurgical Societies (WFNS)[7] are widely used for prognostication. Patients with poor-grade aSAH are often judged under withdrawal of life support (including definitive treatments to prevent re-bleeding) due to these grading systems. Although both the latest European Stroke Organization guidelines[8] and the American Heart Association/American Stroke Association guidelines[9] recommend the evaluation of patients with aSAH according to the grading system, these guidelines provide no clear recommendation for poor-grade aSAH treatments. Although the aSAH gradings may predict outcome, they are based simply on the initial neurological assessment of the patient on admission[5–7]. Moreover, the data of their original studies were accumulated approximately half a century ago[5–7].

The last 5 decades have witnessed progress in diagnostic imaging (e.g., computed tomography [CT] and CT-angiography) and treatments (e.g., clipping, coiling, and perioperative neurocritical care), which have resulted in better patient outcomes after aSAH, including in poor-grade cases[10–12]. Although several CT classifications, such as the Fisher[13], modified Fisher[14], Classen[15], Hijdra[16], and Barrow Neurological Institute scales[17] have been developed, these are scales predicting vasospasm and do not provide helpful information for decision making or predict long-term functional outcome after SAH. Thus, new CT classifications providing information that can assist the choice for the proper treatment strategy for poor-grade SAH are required. Regarding novel treatments, "ultra-early" surgeries to avoid re-bleeding were proposed with potentially promising results[18,19]. Because approximately 50% of re-bleeding occurs within 6 hours after ictus[20], ultra-early treatment may be a reasonable strategy to prevent re-bleeding with the worst outcome. However, robust evidence for this treatment is still lacking.

We therefore hypothesized that there may be some subgroups of patients who have a greater survival potential when treated with ultra-early surgeries among poor-grade aSAH. The aim of the current study was to evaluate the outcome of ultra-early treatment for patients with poor-grade aSAH who were sub-classified based on their initial CT results.

Materials and Methods

This retrospective clinical study included patients from the Department of Emergency and Critical Care Medicine, Nippon Medical School, Tama Nagayama Hospital, a tertiary care emergency medical and trauma center in the western part of Tokyo, Japan. Our institutional review boards approved this study (No. 2018-556).

Definitions and Treatment Protocols

In principle, we provide definitive treatment and perioperative neurocritical care to all patients with aSAH, including poor-grades cases, as per our institutional protocol. In the current study, patients with aSAH were excluded from definitive treatment if they had cardiopulmonary arrest upon arrival (CPAOA)[21,22] or no brainstem reflexes after their initial management[21,22]. In order to avoid re-bleeding, the provision of ultra-early surgery is a primary strategy in our institution. We defined ultra-early surgery as that initiated within 6 hours following arrival at the emergency department.

As soon as a patient with suspected aSAH was brought to our emergency department, we provided general anesthesia for them following an evaluation of their neurological status and initial basic management. General anesthesia involved rapid induction and total intravenous anesthesia for maintenance. Strict blood pressure (systolic blood pressure less than 120 mmHg) control was also performed[23,24]. CT and CT-angiography were performed in order to arrive at a definite diagnosis and to detect the bleeding site[25,26]. Digital subtraction angiography (DSA) was added for patients whose CT-angiography failed to detect an aneurysm[27,28], for the detection of perforating artery branches from the aneurysmal neck, and for confirming the venous system when it was necessary for open surgery. We did not wait for recovery of consciousness in patients with aSAH and provided treatment for ruptured aneurysms regardless of the aSAH grade because poor-grade aSAH is one of the important predictors of re-bleeding, which most often occurs within a few hours of the first ictus[29,30].

According to the CT findings, patients with aSAH were divided into the following 3 groups (**Fig. 1**): Group 1, intraventricular hemorrhage with obstructive hydrocephalus (IVH-hydro); Group 2, massive intracerebral hemorrhage with brain herniation (ICH-herni); and Group 3, CT findings other than those applicable to Group 1 or 2. Several studies have suggested that elevated intracranial pressure (ICP) is associated with high mortality and morbidity[31,32]; thus, we attempted to control ICP as soon as possible after the initial CT classification to avoid secondary brain injuries. For all patients in Group 1 and some of the patients in Group 3, external ventricular drainage (EVD) was inserted as soon as possible in order to control ICP[33,34]. For patients with a ICH-

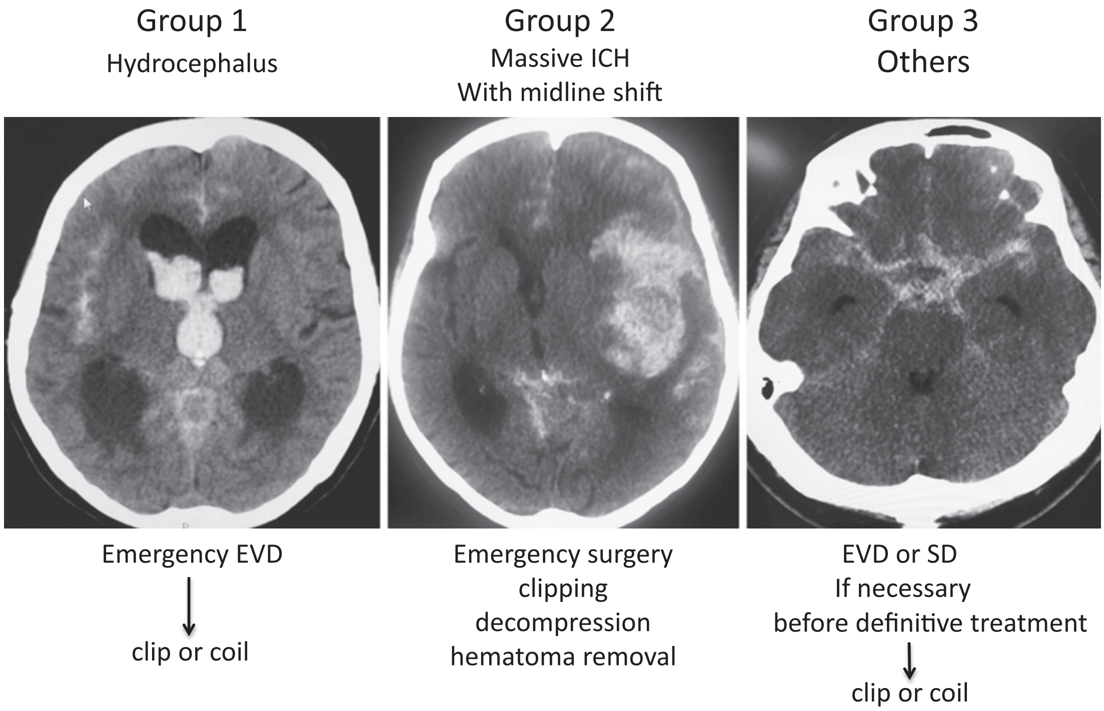

Fig. 1 Computed cosmography classification and our treatment protocol.
IVH: intraventricular hemorrhage; ICH, intracerebral hemorrhage; EVD, external ventricular drainage

herni (Group 2), hematoma evacuation, aneurysm clipping, and decompressive craniectomy were performed immediately[35–37].

We set a goal to start treatment for the ruptured aneurysms within 6 hours of admission (i.e., ultra-early treatment). For Group 1 and 3 patients, the treatment of choice for the ruptured aneurysms (i.e., surgical clipping or coil embolization) was selected based on the site, size, and shape of the aneurysm. For patients who were comparably suited to either treatment modality, endovascular coiling was selected[38,39]. The optimal treatment modality was decided through discussion among all doctors in charge at our department.

Neurocritical care, including the prevention of vasospasm and delayed cerebrovascular ischemia (DCI), was provided after the definitive treatment. Since the amount of blood in the subarachnoid space is an important predictor of vasospasm, we infused urokinase via EVD, cisternal drainage, or spinal drainage on postoperative days (PODs) 1 to 3[40]. Prophylactic treatment of vasospasm included the provision of intravenous continuous low dose nicardipine (0.5 μg/kg/min)[41,42] as oral nimodipine is not approved in Japan. Transcranial Doppler sonography measurements were routinely performed during the postoperative period[43]. Between PODs 7 and 9, DSA was performed for all patients to confirm the condition of the clip or coil and to assess the existence of vasospasm. During DSA, vasospasm was assessed and classified as none/mild (0% to 33%), moderate (34% to 66%), or severe (67% to 100%)[44] compared to the initial condition. For severe vasospasm, balloon angioplasty was performed and intrathecal administration of nicardipine via EVD or spinal drainage was performed every 12 hours until POD 14[30,45]. Vasospasm-related infarction was diagnosed based on the anatomical correlation between infarction and severe vasospasm, except in cases of surgical or other complications. On POD 14, all patients received magnetic resonance imaging (MRI)/angiography to confirm the end of the vasospasm period and check for the presence of brain damage.

Patients

We analyzed data from consecutive cases of aSAH in patients admitted between January 1, 2013 and December 31, 2016. We collected data on patient characteristics including age, sex, past medical history (hypertension, stroke, and coronary heart disease), Glasgow Coma Scale score on admission, WFNS grade (IV or V), location of the aneurysm (anterior or posterior circulation), aneurysm size, aneurysm treatment (clip or coil), time from admission to treatment, CT group, hematoma volume, decompressive craniectomy, shunt, in-hospital days, rebleeding before or after aneurysm treatment, vasospasm, DCI, mortality, and functional outcome at 6 months. We further divided Grade V into GCS 3 and GCS 4 to 6 to

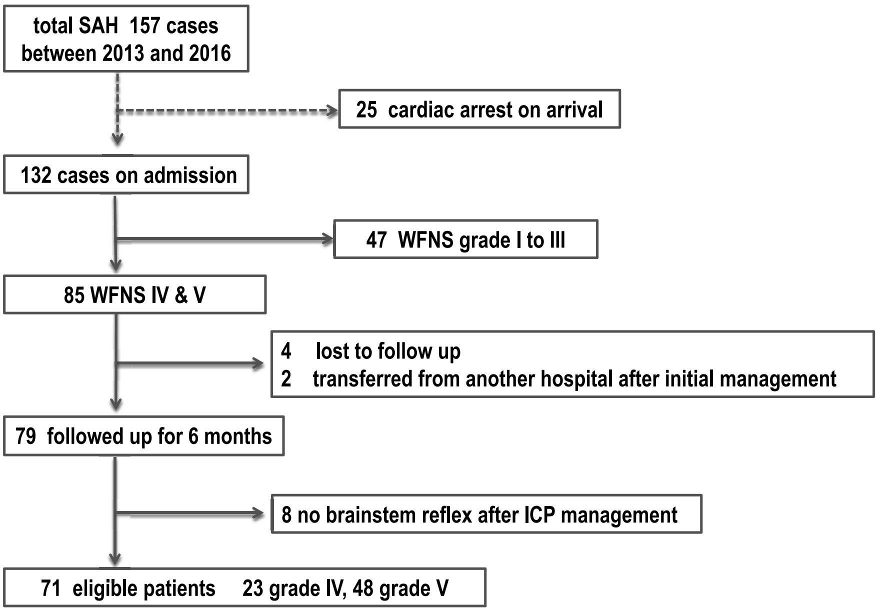

Fig. 2 Patient selection
ICP: intracranial pressure; SAH: subarachnoid hemorrhage; WFNS: World Federation of Neurosurgical Societies

present the data more clearly.

Endpoints

The primary outcomes for the current study were functional outcome and all-cause mortality at 6 months. The functional outcome was assessed based on the modified Rankin Scale (mRS) data collected on outpatient basis or via telephone questionnaires conducted by 2 independent neurosurgeons at our institution. Scores were classified as good (mRS scores 0 to 2) or poor functional outcomes (mRS scores 3 to 6)[46].

Statistical Analysis

We compared the background characteristics and treatments between the good and poor functional outcome groups. Continuous variables were compared between the groups using a t-test or Mann-Whitney's *U* test and categorical variables were analyzed using chi-square or Fisher's exact tests, as appropriate. We further performed a stratified analysis according to the results of the initial CT. We performed a logistic regression analysis in which CT classification was associated with the primary outcome, and adjusted for the following factors: age, sex, treatment methods, and time from onset to definitive treatment. Odds ratios (OR) with 95% confidence intervals (CI) were calculated. All data were analyzed using SPSS 23.0 for Windows (IBM Corp., Armonk, NY, USA); $p < 0.05$ was considered statistically significant.

Results

Patient Selection and Baseline Characteristics

During the study period, a total of 3,625 patients were admitted to our department; one quarter of whom were admitted due to stroke. A total of 157 patients with aSAH were admitted to our hospital. We excluded 25 CPAOA cases that were diagnosed by lumbar puncture or autopsy imaging. Among the 132 remaining patients with aSAH, 85 were patients with a poor-grade (64.4%). Eight of those patients had no brainstem reflex after ICP management (respiratory management, mannitol infusion, and EVD) and supportive care was commenced without providing a definitive treatment. Two patients were transferred from another hospital after initial management and 4 patients were lost to follow up. In total, 71 patients, 23 with WFNS grade IV and 48 with grade V, were included in the current study (**Fig. 2**). **Table 1** presents the baseline characteristics of the study patients. Average time from admission to emergent EVD insertion and emergent surgery in Group 2 was 105 and 127 minutes, respectively.

Outcomes

A good functional outcome (mRS scores of 0 to 2) was observed in 39.4% (28/71) of patients (**Table 2**). We found that 47.9% (34/71) of patients had an mRS score of 3 or less (i.e., mRS scores of 0 to 3). All-cause mortality at 6 months was 15.5% (11/71). There was a significantly higher number of patients with good outcomes in Group 3 than in the other 2 groups (Group 1 and 2 vs. Group 3,

Table 1 Demographic and clinical characteristics of patients

Variables	Good outcome (n = 28)	Poor outcome (n = 43)	p
Age	54.5 (46.3-67.3)	71 (60.0-77.0)	<0.01
Sex, male	12 (42.9)	19 (44.2)	0.91
Past medical history			
Hypertension	6 (21.4)	15 (34.9)	0.23
Stroke	0	3 (7.0)	0.15
Heart disease	0	4 (9.3)	0.10
GCS	6.5 (3-10)	4 (3-6)	0.02
WFNS grade			0.01
grade IV	14 (50)	9 (20.9)	
grade V	14 (50)	34 (79.1)	
WFNS grade V (n = 48)			0.37
GCS 3	9 (64.3)	17 (50)	
GCS 4-6	5 (35.7)	17 (50)	
Aneurysm location			0.51
Anterior	25 (89.3)	36 (83.7)	
Posterior	3 (10.7)	7 (16.3)	
Aneurysm size, mm	6.0 (4.5-8)	6.0 (4.0-11)	0.10
Aneurysm treatment			0.39
Clip	18 (64.3)	31 (73.8)	
Coil	10 (35.7)	11 (26.2)	
Admission to definitive treatment, min	332 (209-529)	292 (167-538)	0.67
Hematoma	5 (17.9)	12 (27.9)	0.33
Hematoma volume, mL	30.0 (18.5-66.0)	69.0 (20.8-94.5)	0.23
Decompressive craniectomy	5 (17.9)	9 (20.9)	0.75
Shunt	2 (7.1)	9 (20.9)	0.12
In-hospital days	31 (24-40)	48 (35-72)	<0.01

Data were presented as n (%) or median (interquartile). GCS, Glasgow Coma Scale; WFNS, World Federation of Neurosurgical Societies; EVD, external ventricular drainage

Table 2 Functional outcome after 6 months based on computed tomography (CT) classification

	CT classification			
	Group 1	Group 2	Group 3	Total
Good outcome	2 (15.4)	3 (27.3)	23 (48.9)	28 (39.4)
Poor outcome	11 (84.6)	8 (72.7)	24 (51.1)	43 (60.6)

All data were presented with n (%)
Group 1, intraventricular hemorrhage with obstructive hydrocephalus; Group 2, massive intracerebral hemorrhage with brain herniation; and Group 3, CT findings other than those applicable to Group 1 or 2.

20.8% vs. 48.9%, p = 0.02). Group 3 was significantly associated with a good functional outcome even after adjustment with a logistic regression analysis (OR 6.1, 95% CI 1.1 to 34.8). Regarding severity, the functional outcome of patients with WFNS grade IV was better than that of patients with grade V (grade IV vs. grade V, 60.9% vs. 29.2%, p =0.01). Among 48 patients with grade V in this study, 26 patients had GCS 3 (54.2%). There was no significant difference in functional outcome for patients with GCS 3 compared with patients with GCS 4 to 6 (GCS 3 vs. GCS 4-6, 34.6% vs. 22.7%, p =0.37).

In this study, re-bleeding before definitive treatment occurred in 5 cases (7.0%) (**Table 3**). In 2 of 5 cases, re-bleeding occurred throughout the induction of general anesthesia. In the remaining 3 cases, re-bleeding occurred while the patients were waiting for their operations and all cases were due to a dissecting aneurysm (a dissection of posterior inferior cerebellar artery, an internal carotid

Table 3 Complications during perioperative period

Complications		Good outcome (n = 28)	Poor outcome (n = 43)	p value
Re-bleeding	Before aneurysm treatment	1 (3.6)	4 (9.3)	0.36
	After aneurysm treatment	0	0	
Vasospasm	None/mild	24 (85.8)	30 (70.0)	0.72
	Moderate	2 (7.1)	5 (11.6)	
	Severe	2 (7.1)	3 (7.0)	
Delayed cerebrovascular ischemia	Vasospasm related	0	3 (7.0)	0.19
	Any other cause	3 (10.7)	7 (16.3)	

All data were presented with n (%)

artery anterior wall blister-like aneurysm and a dissection of A1 segment of anterior cerebral artery). Regarding the patient of a dissection of posterior inferior cerebellar artery, the brainstem reflex disappeared after re-bleeding and definitive treatment could not be performed (mRS 6). Regarding the patient of an internal carotid artery anterior wall blister-like aneurysm, we could perform clipping directly for the lesion without any bypass in the acute phase (mRS 5). Regarding the patient of a dissection of A1 segment of anterior cerebral artery, internal trapping of the lesion was immediately performed but the patient was lost because of brain swelling in acute phase (mRS 6). Thus, 4 of 5 cases were classified into the poor-outcome group.

DCI occurred in 18.3% (13/71) of cases, and severe vasospasm was observed in 7.0% (5/71) of cases. Vasospasm-related infarction occurred in 4.2% (3/71) of cases.

Discussion

In the current study, we found that 39.4% of patients with aSAH with WFNS grades VI or V experienced good functional outcomes (mRS scores of 0 to 2) 6 months after receiving ultra-early surgery and subsequent neurocritical care. All-cause mortality at 6 months was 15.5% among these patients. Importantly, approximately half of the patients with poor-grade aSAH without CT-confirmed IVH-hydro or ICH-herni experienced good functional outcomes at 6 months.

In the latest European Stroke Organization guidelines[8] and American Heart Association/American Stroke Association guidelines[9], although use of the grading systems is recommended for the prediction of outcome, there are no guidelines indicating whether treatment should vary according to grade. In the current study, we provided ultra-early treatment with perioperative neurocritical care to all patients with aSAH (except for patients after CPAOA or with no brainstem reflex), including poor-grades cases, as per our institutional protocol. Although most studies define early treatment as initiating treatment within 72 hours, we aimed to initiate definitive treatment within 6 hours. In our study, the re-bleeding rate of ruptured aneurysms was much lower (7.0%) than that reported in previous studies[19].

In the original papers by Hunt, which were published in 1968[5] and in 1974[6], patients with grade III or worse were not treated in the early stage, resulting in mortality rates of 100% for patients with grade V and 93% for grade IV, respectively. Moreover, in a large international study that was used for WFNS grading[47], two thirds of comatose patients did not receive any definitive treatment for ruptured aneurysms, which resulted in a good outcome in only 13% of patients. One of the reasons for this catastrophic finding may be due to re-bleeding in the early phases after SAH. The risk of re-bleeding is highest in the acute phase, with a re-bleeding rate of approximately 9-17% within the first 24 hours[48]. Nearly 30% of all re-bleeding occurs within 3 hours, and nearly 50% occurs within 6 hours of symptom onset[20]. Early re-bleeding is associated with worse outcomes[20]. Patients with poor-grade tend to be at a higher risk of re-bleeding[19,49]. Ideally, aneurysm obliteration should be performed as early as possible to prevent re-bleeding[8,9]. However, the benefits of early definitive treatment remain controversial for patients with aSAH[50], especially for those with poor-grade aSAH. One study showed early definitive treatment to be associated with less re-bleeding and a higher proportion of favorable outcomes[18], while another did not[51].

Regarding severity, the functional outcome of patients with grade IV was better than that of patients with grade V. GCS on admission was also significantly related to functional outcome. However, there was no significant difference in functional outcome for patients with GCS 3 compared with patients with GCS 4 to 6. Of all treated patients, one recent report concerning only patients with grade V suggested that there was no difference in functional outcome between the GCS 3 and GCS 4 to 6 subgroups[52]. There is a possibility that GCS 3 is not necessarily the severest in terms of functional outcome among patients with grade V who undergo definitive treatment.

Originally, conventional CT sub-classifications were established for the prediction of vasospasm[13–17]. Although DCI due to vasospasm is one of the main causes of poor outcome, it is not the only one. Despite the higher rate of vasospasm in patients with a poor-grade[14,53], our results show that severe vasospasm and DCI due to severe vasospasm occurred in only 7% and 4.2% of patients, respectively. In addition, almost all patients with a poor-grade are ordinarily categorized in a limited group, such as Fisher group 3 or 4, because of the large volume of the hemorrhage. In the current study, we used a standardized approach for patients with a poor-grade where we used the CT results to categorize the treatment plan and considered both ICP and definitive aneurysmal treatment. For patients in Group 1 in our protocol, i.e., those with IVH-hydro, the immediate insertion of EVD to control ICP was essential for life-saving purposes[33,34]. The average time from admission to emergent EVD insertion was 105 minutes. In Group 2, i.e., cases with massive ICH-herni, immediate evacuation of the hematoma by craniotomy was required for urgent decompression. The average time from admission to emergent surgery in Group 2 was 127 minutes. In such cases, subsequent aneurysm clipping should be performed during the same operation[35–37]. We defined ultra-early surgery as that taking place within 6 hours of the patient's arrival at the hospital. Our results indicate that approximately 40% of patients with poor-grade aSAH, in whom treatment is sometimes withheld at certain institutions, experienced a good functional outcome at 6 months. Approximately half of the patients achieved a mRS score of 3 or less. Furthermore, approximately half of the patients in Group 3 experienced good outcomes, a rate significantly higher than that in the other two groups. For patients in Groups 1 and 2, the functional outcome was poorer than that of patients in Group 3 regardless of immediate intervention. For patients with obstructive hydrocephalus (e.g., packed IVH), immediate ICP control with EVD alone might be insufficient. A previous study suggested that extensive periventricular brain damage in MRI was found in patients with poor-grade aSAH with packed IVH, which was related to a poor outcome[54]. Another study suggested that not only ICP control, but also immediate clot evacuation from the ventricle using neuroendoscopic procedures was associated with a better functional outcome[55]. For patients with aSAH accompanied by massive ICH with brain herniation, initial brain damage may be inevitable. Although it highly depends on the site of the ICH, hemiparesis, visual field deficits, cognitive disturbance, and epilepsy are the most frequent disabilities[56]. If initial brain damage is not severe (WFNS grade IV) and immediate intervention is achieved, some patients may have good outcomes[57,58]. Conversely, in our study, in patients with poor-grade aSAH without IVH with obstructive hydrocephalus or massive ICH with brain herniation, a good functional outcome was accomplished in approximately 50% by all means of continuous efforts, from ultra-early surgery to intensive care management, in a tertiary care emergency hospital. We speculate that the reasons why some Group 3 patients had a poor outcome were hypoperfusion due to initial intracranial pressure elevation, hypoxia and hypoventilation due to respiratory causes (e.g. neurogenic stunned myocardium), and seizure (e.g. non-convulsive status epilepticus). Medical complications in the neurocritical care period, such as fever, hyperglycemia, anemia, hyponatremia, and infection may be associated with a poor outcome[59,60]. However, some patients may have had neither initial organic brain damage nor irreversible global brain damage. We hypothesize that these patients may have contributed to the better functional outcome in Group 3 compared to Group 1 or 2. Although further multi-center studies are required to validate our findings, the current results suggest that our protocol may be rational and feasible.

There were some limitations to the current study. First, this was a single center observational study performed at a tertiary care emergency hospital in Japan without a control group. Therefore, we cannot generalize the results of the current study to other institutions or different emergency system areas. Second, although we evaluated the 6-month functional outcome in the current study, longer follow-up periods (e.g., 1 year or more) may be preferable for the evaluation of long-term functional outcomes. However, we selected a 6-month follow-up period because of its feasibility in the current study, which focused on the results of routine clinical practice. Third, comparisons with the results of similar studies need to be conducted carefully. One of the issues with comparing studies is patient selection. In most studies involving patients with poor-grade aSAH, the outcome is calculated based on all patients who are alive upon arrival. Patients without recovery of the brainstem reflex after initial ICP management are generally included. These patients may not become functionally independent; therefore, outcomes evaluated under the exclusion of these patients may be more accurate. Fourth, a more precise scale, such as the Medical Outcomes Study 36-Item Short-Form Health Survey, may be more accurate for evaluating detailed functional outcomes. Thus, our results cannot be generalized. Further large-scale, multi-center, interventional studies are required to confirm our findings.

Conclusions

Our results suggest that approximately 40% of patients with aSAH with WFNS grades VI or V experienced good functional outcomes 6 months after receiving ultra-early surgery and subsequent neurocritical care. Moreover, approximately half of the patients with poor-grade aSAH without CT-confirmed intraventricular hemorrhage with obstructive hydrocephalus or massive intracerebral hemorrhage with brain herniation had good functional outcomes at 6 months. Although further trials are required to confirm our results, ultra-early surgery and subsequent neurocritical care after CT sub-classification may be considered for treatment in patients with poor-grade aSAH.

Abbreviations

aSAH: aneurysmal subarachnoid hemorrhage
CPAOA: cardiopulmonary arrest upon arrival
DCI: delayed cerebrovascular ischemia
DSA: digital subtraction angiography
EVD: external ventricular drainage
ICH-herni: intracerebral hemorrhage with brain herniation
ICP: intracranial pressure
IVH-hydro: intraventricular hemorrhage with obstructive hydrocephalus
mRS: modified Rankin Scale
POD: postoperative day
WFNS: World Federation of Neurosurgical Societies

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Conflict of Interest: None declared.

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