Long-Term Outcomes of Elderly Patients with Poor-Grade Aneurysmal Subarachnoid Hemorrhage

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■ OBJECTIVE: **Long-term outcomes after surgical treatment and intensive care have not been investigated in elderly patients with poor-grade aneurysmal subarachnoid hemorrhage (aSAH). This study aimed to analyze 12-month outcomes and prognostic factors of patients with poor-grade aSAH who were at least age 70 years.**

■ METHODS: **We performed a single-center, retrospective study including poor-grade (World Federation of Neurological Societies [WFNS] grades IV and V) aSAH patients who were at least age 70 years, were admitted to our stroke center, and received aneurysmal treatment between April 2012 and September 2018. The clinical outcomes were evaluated at months 3 and 12. Univariate/multivariate analyses were performed to identify the independent prognostic factors of good neurologic outcomes (modified Rankin Scale score 0–3). These factors included sex, age, WFNS grade, Fisher group, delayed cerebral ischemia, aneurysm treatment, aneurysm size, aneurysm location, and blood examination data in the 14 days post subarachnoid hemorrhage.**

■ RESULTS: **The proportion of patients with good outcomes (modified Rankin Scale score 0–3) was increased at 12 months compared with that at 3 months. No intracerebral hemorrhage was a significant predictor of good neurologic outcomes at 3 months ($P = 0.03$). The absence of delayed cerebral ischemia and small fluctuations in the average absolute daily difference from normal sodium levels were significant predictors of good neurologic outcomes at months 3 and 12 ($P = 0.04$ and $P = 0.03$, respectively).**

■ CONCLUSIONS: **The absence of delayed cerebral ischemia and small fluctuations in the average absolute daily difference from the normal sodium levels were independently associated with good neurologic outcomes at 12 months in elderly patients. Intracerebral hemorrhage did not appear to affect long-term outcomes. These findings suggest that elderly patients with severe subarachnoid hemorrhage should not be excluded from receiving surgical treatment on the basis of their age alone.**

INTRODUCTION

With the recently aging Japanese society, there is an increased frequency of elderly patients with aneurysmal subarachnoid hemorrhage (aSAH). However, it is difficult to decide on the proper treatment course for such patients.[1-3] Particularly, elderly patients with a poor neurologic grade are considered to have a poor prognosis, and thus they may not receive therapeutic interventions. Although therapeutic interventions for elderly and poor-grade aSAH patients is very challenging,[4,5] there are few prognostic reports on long-term survival and outcomes to assist clinicians in making decisions regarding therapeutic interventions in such patients.[2,3,6-8]

The aim of this study was to analyze the 12-month outcomes and the associated prognostic factors among patients aged at least 70 years with poor-grade aSAH.

METHODS

We performed a single-center, retrospective study that included all consecutive patients aged at least 70 years with poor-grade aSAH

Key words
- Elderly
- Neurologic outcomes
- Poor-grade aneurysmal subarachnoid hemorrhage

Abbreviations and Acronyms
aSAH: Aneurysmal subarachnoid hemorrhage
ICH: Intracerebral hemorrhage
mRS: Modified Rankin Scale
SAH: Subarachnoid hemorrhage
WFNS: World Federation of Neurosurgical Societies

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(World Federation of Neurological Societies [WFNS] grade IV, V) who were admitted to our stroke center between April 2012 and September 2018. We included 4 patients with a cerebral dissecting aneurysm. We excluded the patients who did not undergo vascular evaluation (n = 25) and who did not receive aneurysm treatment (Figure 1). We planned to proceed with aneurysm repair if the neurologic and general conditions of the elderly patients indicated that aggressive treatment should be administered. Aneurysm treatment is selected by the vascular team according to the characteristics of the ruptured aneurysm and the patient's condition. In principle, surgical clipping is mainly selected for patients with intracerebral hemorrhage (ICH) and middle cerebral artery or distal anterior cerebral artery aneurysm. Conversely, endovascular coiling is selected for patients who are aged at least 80 years or for those with posterior circulation aneurysms. Microsurgical or endovascular treatment was performed in the acute phase of the ictus. We principally placed external ventricular drainage intraoperatively and performed decompressive hemicraniectomy only in cases in the microsurgical groups in which there was a large amount of brain swelling. Instead, we placed lumbar cerebrospinal drainage postoperatively in the endovascular groups. All patients were followed up in the hospital or via telephone interviews at months 3 and 12. The clinical outcomes were evaluated with the modified Rankin Scale (mRS); mRS 0–3 was defined as a good neurologic outcome. Data on the following clinical characteristics were collected: age, sex, blood examinations including daily serum sodium and plasma D-dimer levels checked on admission and every 3 days, WFNS grade on admission, Fisher group, ICH, and delayed cerebral ischemia. Delayed cerebral ischemia was defined as the presence of cerebral infarction on computed tomography or magnetic resonance scan of the brain within 14 days after subarachnoid hemorrhage (SAH) that was not present on the computed tomography or magnetic resonance scan between 24 and 48 hours after early aneurysm occlusion and was not attributable to other causes, such as surgical clipping or endovascular treatment.[9] We also calculated the average daily difference from the normal sodium level (140 mmol/L). To investigate the fluctuation in the daily serum sodium levels, the absolute value of the difference from the normal sodium level was also calculated. Data on the aneurysmal size, location, treatment methods, intraoperative rebleeding, and shunt dependence were also collected. This study was approved by our institutional review board (18–097), and individual patient consent was not required as this was a retrospective study.

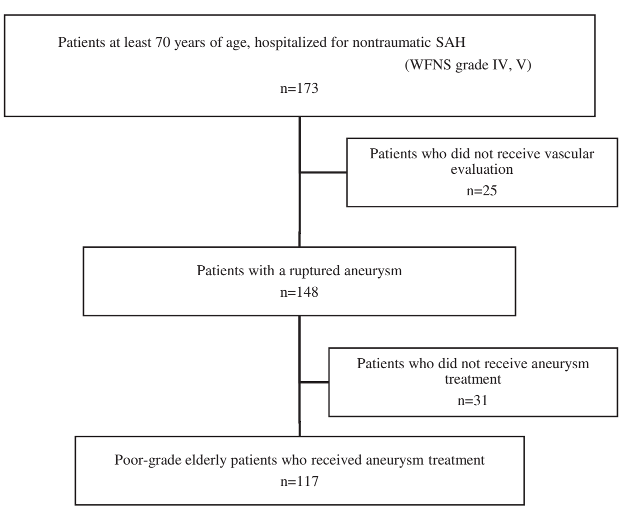

Figure 1. Flow diagram displaying patient selection to analyze 12-month outcomes and prognostic factors in our stroke center. SAH, subarachnoid hemorrhage; WFNS, World Federation of Neurosurgical Societies.

All statistical analyses were performed with the commercially available software SPSS version 24 (IBM Corporation, Armonk, New York, USA). Categorical variables were examined using the Fisher exact or the Pearson χ^2 tests as appropriate. Normal variables were evaluated using the Student *t*-tests. Nonnormal variables were compared using the Mann-Whitney U test. Quantitative variables were expressed as the median (interquartile range) or number and proportion (%) of patients, as appropriate. Variables that were significant in the univariate analysis were included in the multiple logistic regression analysis to evaluate mRS outcomes. Probability values <0.05 were considered statistically significant.

RESULTS

Overall, 117 poor-grade SAH patients were included in the study; clinical and demographic characteristics of the patients based on age are shown in Table 1. Overall 108 (92.3%) and 9 (7.7%) patients had baseline mRS scores of 0–2 and 3, respectively. Thirty-eight (32.5%), 28 (23.9%), 36 (30.8%), and 15 (12.8%) patients were 70–74, 75–79, 80–84, and aged at least 85 years, respectively. In most age groups, WFNS grade V patients tended to be more common than grade VI patients; 24 (63.2%), 18 (64.3%), 20 (55.6%), and 4 (26.7%) patients who were 70–74, 75–79, 80–84, and aged at least 85 years, respectively, were WFNS grade V. Aneurysmal repair was performed on days 0–1, 2, and 3 or later in 111 (94.9%), 3 (2.6%), and 5 (4.3%) patients, respectively.

Table 2 shows the factors associated with prognosis at 3 and 12 months after SAH. Twenty-seven (23%) and 34 (29%) patients had mRS scores ≤3 at months 3 and 12, respectively. Fisher groups 1–2 (P = 0.03), ICH (P = 0.02), delayed cerebral ischemia (P = 0.03), the average absolute daily difference from the normal sodium level (P = 0.01), and the maximum plasma D-dimer level within 14 days (P = 0.03) were significantly associated with mRS scores at 3 months after SAH. Additionally, delayed cerebral ischemia (P = 0.04), the absolute daily difference from the normal sodium level (P = 0.02), and the maximum plasma D-dimer level (P = 0.02) were significantly associated with mRS scores at 12 months after SAH.

Table 3 shows the multivariate logistic regression analysis of predictors of good neurologic outcomes (mRS score 0–3) at 3 and 12 months after SAH. SAH without ICH (odds ratio [OR], 3.30; 95% confidence interval [CI], 1.16–16.13; P = 0.03), absence of delayed cerebral ischemia (OR, 4.17; 95% CI, 1.08–16.13; P = 0.04), and the average absolute daily difference from the normal sodium level (140 mmol/L)

Table 1. Baseline Characteristics of 117 Poor-Grade Subarachnoid Hemorrhage Patients

Variable	70–74 years, n (%)	75–79 years, n (%)	80–84 years, n (%)	85+ years, n (%)
All patients	38 (32.5)	28 (23.9)	36 (30.8)	15 (12.8)
Female sex	21 (55.3)	24 (85.7)	32 (88.9)	12 (80)
Mean age, years (SD)	72.3 (1.1)	76.6 (1.4)	82.1 (1.7)	87.2 (1.9)
WFNS				
Grade IV	14 (36.8)	10 (35.7)	16 (44.4)	11 (73.3)
Grade V	24 (63.2)	18 (64.3)	20 (55.6)	4 (26.7)
Mean duration of hospitalization, days (SD)	52.9 (15.9)	48.1 (20.1)	42.3 (26.4)	45.8 (27.8)
Aneurysm treatment				
Clipping	27 (71.1)	18 (64.3)	16 (44.4)	3 (20)
Coiling	11 (28.9)	11 (39.3)	20 (55.6)	12 (80)
Discharge				
Home	1 (2.6)	0 (0)	1 (2.8)	0 (0)
Rehabilitation	24 (63.2)	16 (57.1)	16 (44.4)	2 (13.3)
Hospital	7 (18.4)	7 (25)	12 (33.3)	11 (73.3)
Died	6 (15.8)	5 (17.9)	7 (19.4)	2 (13.3)

SD, standard deviation; WFNS, World Federation of Neurosurgical Societies grade.

(OR, 1.36; 95% CI, 1.03–1.79; $P = 0.03$) remained significant 3 months after SAH. Absence of delayed cerebral ischemia (OR, 3.28; 95% CI, 1.01–10.75; $P = 0.04$) and the average absolute daily difference from the normal sodium level (140 mmol/L) (OR, 1.33; 95% CI, 1.04–1.71; $P = 0.03$) remained significant 12 months after SAH.

Figure 2 shows the distribution of mRS at 3 and 12 months after SAH. In most age categories, the proportion of good neurologic outcomes increased at month 12 compared with that at month 3. Although there was a higher frequency of patients with an mRS score of 6 among those who were aged at least 80 years, the frequency of patients with an mRS score of 6 did not differ between months 3 and 12 among patients in their 70s.

DISCUSSION

Many studies have suggested that aneurysmal treatment should be very carefully considered for elderly or poor-grade SAH patients owing to their poor prognosis[2,5,10-12]; however, some studies show the effectiveness of surgical treatment and neurointensive care for such patients.[3,4,13-15] It has been reported that the long-term outcomes of patients with SAH tend to improve, even among the elderly, when compared with the outcomes at discharge.[3,7] Especially in the elderly, there are few reports of long-term prognosis over 3 months, and in this report we demonstrated that in the real-world of the aging Japanese society, the 12-month prognosis could be improved from the 3-month outcome.

Several studies have shown that clipping for elderly patients has a worse prognosis than coil embolization[1,12,16]; however, in this study, there was no significant difference between these treatment methods at months 3 and 12. This could be due to our treatment strategy of selected microsurgical clippings or endovascular coiling according to the characteristics of the ruptured aneurysm and the patient's condition.

Patients with Fisher group 1–2 or ICH on admission had significant differences in clinical outcomes at 3 months, but by 12 months this difference was no longer significant. In the multivariate analysis, there were significant differences only among patients with ICH at 3 months. A previous study showed that patients with ICH on admission had poor outcomes[10]; however, few studies have reported on the long-term outcomes. The bleeding caused by ICH on admission might only be prominent in the early stages. Over time, the onset of cerebral hemorrhage may not relate to prognosis. Conversely, among patients with delayed cerebral ischemia, significant differences were observed at months 3 and 12; this was confirmed in the multivariate analysis. These findings suggest that delayed cerebral ischemia was the strongest prognostic factor for poor long-term outcomes in these patients. These results indicate the importance of treatment to avoid delayed cerebral ischemia and to ensure good long-term outcomes.[17]

Some studies have shown that the maximum D-dimer level is related to the early clinical status,[18,19] but the relationship with long-term outcomes is not clear. Our study revealed no relationship between D-dimer levels and long-term outcomes in the multivariate analysis. As was found for ICH, these parameters might not be relevant for long-term outcomes.

Recently, Eagles et al.[20] reported that serum sodium level fluctuations were associated with clinical prognosis and delayed

Table 2. Factors Associated with Outcomes 3 and 12 Months After Subarachnoid Hemorrhage

	3 Months after Subarachnoid Hemorrhage			12 Months after Subarachnoid Hemorrhage		
	mRS Score ≦3	mRS Score >3		mRS Score ≦3	mRS Score >3	
Variable	**(n = 27)**	**(n = 90)**	***P* Value**	**(n = 34)**	**(n = 83)**	***P* Value**
Female sex, n (%)	22 (81)	67 (74)	0.45	26 (76)	63 (76)	0.95
Age category						
Over 75, n (%)	16 (59)	63 (70)	0.30	20 (59)	59 (81)	0.20
Over 80, n (%)	9 (33)	42 (47)	0.22	12 (35)	39 (47)	0.25
WFNS			0.59			0.19
Grade IV, n (%)	13 (48)	38 (42)		18 (53)	33 (40)	
Grade V, n (%)	14 (52)	52 (58)		16 (47)	50 (60)	
Fisher group 1—2	5 (19)	4 (4)	**0.03**	4 (12)	5 (6)	0.24
ICH, n (%)	8 (30)	49 (54)	**0.02**	13 (38)	44 (53)	0.14
Delayed cerebral ischemia, n (%)	3 (11)	29 (32)	**0.03**	5 (15)	27 (33)	**0.04**
Aneurysm treatment			0.84			0.87
Endovascular, n (%)	12 (44)	42 (47)		15 (44)	39 (47)	
Microsurgical clipping, n (%)	15 (56)	49 (54)		19 (56)	45 (54)	
Aneurysm location			0.34			0.63
Anterior circulation, n (%)	21 (78)	75 (83)		27 (79)	69 (83)	
Posterior circulation, n (%)	6 (22)	15 (17)		7 (21)	14 (17)	
Shunt dependence, n (%)	6 (22)	28 (31)	0.37	9 (26)	25 (30)	0.69
Intraoperative rebleeding, n (%)	1 (4)	5 (6)	0.57	2 (6)	4 (5)	0.56
Maximum aneurysm size, (mm) (IQR)	6.2 (3.2)	7.3 (4.3)	0.49	5.8 (3.4)	7.7 (3.7)	0.83
L/D (for 14 days post SAH)						
Minimum sodium level, (mmol/L) (SD)	136.1 (3.7)	135.7 (3.7)	0.06	137.1 (2.6)	135.3 (4.0)	0.11
Average daily difference from normal (140) sodium level, (mmol/L) (IQR)	1.3 (4.5)	2.1 (5.3)	0.42	1.5 (4.1)	2.1 (5.6)	0.56
Average absolute daily difference from normal (140) sodium levels, (mmol/L) (IQR)	3.4 (1.1)	4.9 (2.8)	**0.01**	3.6 (1.7)	5.0 (2.9)	**0.02**
Maximum plasma D-dimer Level, (μg/mL) (IQR)	8.4 (5.1)	22.0 (17.9)	**0.03**	8.7 (5.0)	22.3 (17.1)	**0.02**
Plasma D-dimer level at admission, (μg/mL) (IQR)	5.8 (5.1)	13.5 (6.9)	0.27	5.5 (5.4)	14.0 (9.8)	0.10

Boldface font indicates statistical significance.
mRS, modified Rankin Scale; WFNS, World Federation of Neurosurgical Societies; ICH, intracerebral hemorrhage; IQR, interquartile range; L/D, laboratory data; SAH, subarachnoid hemorrhage; SD, standard deviation.

Table 3. Multivariate Logistic Regression Analysis of Predictors for Modified Rankin Scale (0—3) Scores Among Elderly Patients

Variable	OR (95% CI)	*P* Value
3 months after subarachnoid hemorrhage		
Fisher group 1—2	2.94 (0.44—20.00)	0.27
Without ICH	3.30 (1.16—16.13)	**0.03**
Absence of delayed cerebral ischemia	4.17 (1.08—16.13)	**0.04**
Average absolute daily difference from normal sodium levels (140 mmol/L)	1.36 (1.03—1.79)	**0.03**
Maximum plasma D-dimer level	1.06 (0.98—1.14)	0.13
12 months after subarachnoid hemorrhage		
Absence of delayed cerebral ischemia	3.28 (1.01—10.75)	**0.04**
Average absolute daily difference from normal sodium levels (140 mmol/L)	1.33 (1.04—1.71)	**0.03**
Maximum plasma D-dimer level	1.04 (0.97—1.10)	0.21

Boldface font indicates statistically significant ORs.
OR, odds ratio; CI, confidence interval; ICH, intracerebral hemorrhage.

cerebral ischemia. Moreover, it has been suggested that electrolyte management, focused on sodium levels in conjunction with water balance management, is important for poor-grade SAH.[21-27] This is supported by the findings from this study that there was a significant difference in the prognosis based on sodium levels at months 3 and 12 in the multivariate analysis. The confounding

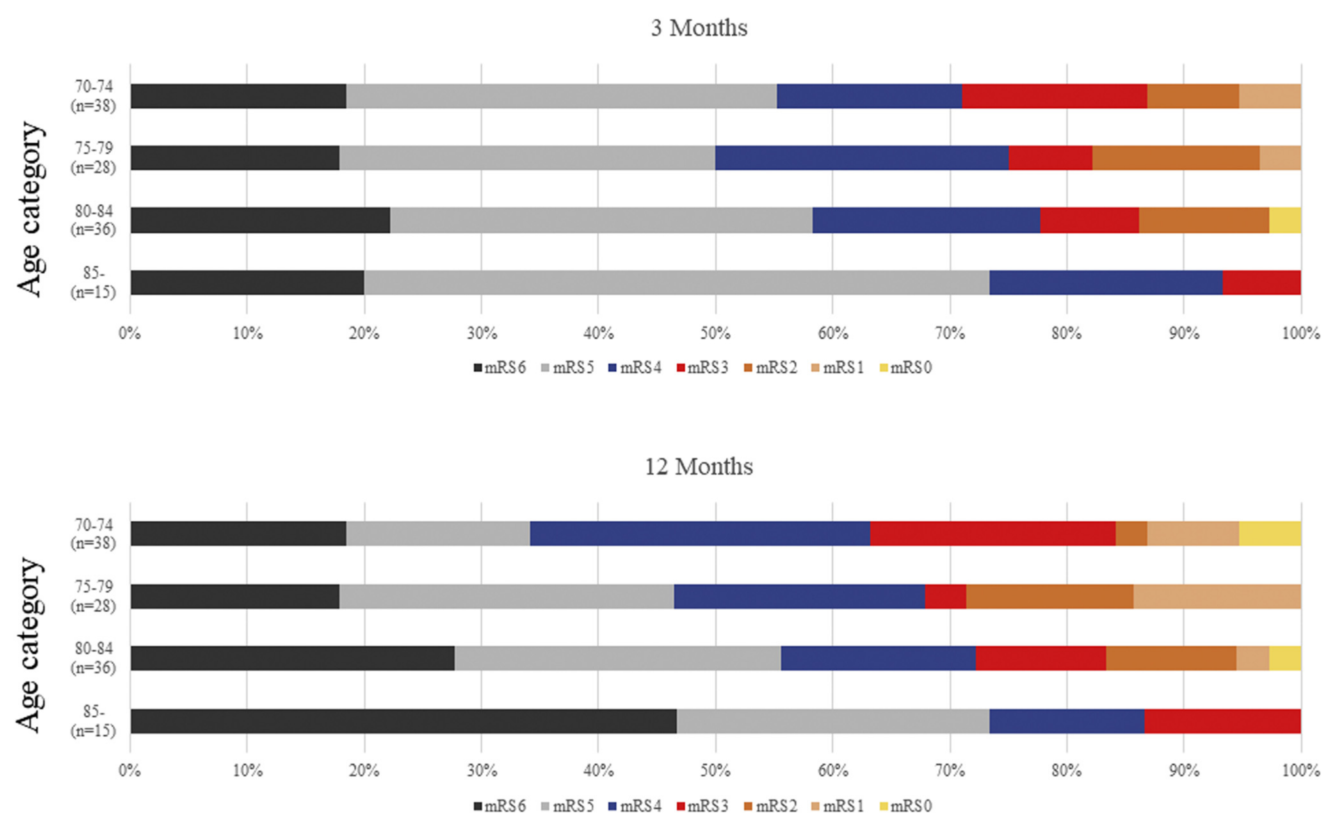

Figure 2. Distribution of the modified Rankin Scale (mRS) scores at 3 and 12 months after subarachnoid hemorrhage in poor-grade elderly patients receiving aneurysm treatment.

relationship with delayed cerebral ischemia must be considered but may be particularly important for elderly individuals who are considered to have less reserve capacity of water homeostasis. For this reason, it is important that elderly patients receive intensive postoperative management, including monitoring of serum sodium levels, to obtain a good long-term prognosis. With regard to the fluctuating serum sodium levels, the relationship between the measurement of the antidiuretic hormone and the treatment site for cerebral aneurysms remains unclear. Further studies are required to determine whether aggressive monitoring and treatment of sodium levels among elderly patients can favorably influence outcomes.

There are several limitations that merit mentioning in this study. Our study was retrospective and conducted at a single institution; therefore it is subject to methodological limitations. The treatment strategy was selected by the stroke center vascular teams, thus compromising randomization and increasing the potential for selection bias. WFNS grade was evaluated based on the level of consciousness at the time of admission; at this time, there might be a temporary poor level of consciousness due to SAH. Additionally, no definitive conclusions can be made given the small number of severe patients; future studies should investigate larger cohorts of patients from different locations.

CONCLUSIONS

We report the long-term prognosis of elderly patients with severe SAH. This study demonstrated that the long-term prognosis improved gradually, even among severe SAH elderly patients, if they received aneurysmal repair and the best postoperative treatment. Regarding factors associated with good long-term prognosis, management of delayed cerebral ischemia and fluctuations in serum sodium levels might be important. Although a challenging treatment group was evaluated in this study, several cases had a good prognosis. Thus elderly patients with severe SAH should not be excluded from receiving surgical treatment on the basis of their age alone.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Shinichiro Yoshikawa: Investigation, Formal analysis, Writing - original draft. **Tomoya Kamide:** Conceptualization, Formal analysis, Writing - review & editing. **Yuichiro Kikkawa:** Supervision, Writing - review & editing. **Kaima Suzuki:** Investigation, Writing - review & editing. **Toshiki Ikeda:** Supervision, Writing - review & editing. **Shinya Kohyama:** Supervision, Writing - review & editing. **Hiroki Kurita:** Supervision, Writing - review & editing.

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