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【 ORIGINAL ARTICLE 】

Correlation between a Bedridden Status and the Long-term Outcome in Hemodialysis Patients after Intracerebral Hemorrhaging

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Abstract:

Objective The quality of life and activities of daily living (ADL) are generally poor among dialysis patients after intracerebral hemorrhaging, and their precise clinical course remains unclear. In addition, the association between the severity of cerebral hemorrhaging and the long-term prognosis in these patients has not been fully elucidated. This study aimed to evaluate the subsequent prognosis of hemodialysis patients who survived the acute phase of intracerebral hemorrhaging.

Methods We included hemodialysis patients who were admitted to Nagasaki University Hospital between 2007 and 2015 for intracerebral hemorrhaging treatment. After excluding cases of in-hospital death, survivors were classified using the 5-point modified Rankin Scale (mRS), which specifically measures the ADL in patients with cerebrovascular diseases. The patients were followed up at the medical facilities to which they were transferred in the same medical zone until 2017.

Results Out of 91 patients with cerebral hemorrhaging (65±11 years old, 66% men, hemodialysis duration 108±91 months), 62 survived until discharge. Twenty-one patients died during observation, largely due to infectious diseases, such as sepsis and pneumonia (n=16, 76%). Compared to patients with mRS 0-4 (n=31), those with mRS 5 (n=31) showed a significantly poorer prognosis. The hazard ratio adjusted for age and antiplatelets was 13.7 (95% confidence interval: 3.88-63.7, p<0.001).

Conclusion Hemodialysis patients with intracerebral hemorrhaging who were bedridden showed poor outcomes. The major causes of death were infections. Therefore, these patients should be carefully monitored for infections in order to improve their prognosis.

Key words: intracerebral hemorrhaging, hemodialysis, prognosis, functional outcome, modified Rankin Scale, quality of life

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Introduction

Patients with end-stage renal failure are known to have an increased risk of cardiovascular events (1), with cerebral hemorrhaging being the most critical complication because hemodialysis patients easily bleed and develop large hematomas (2, 3). In fact, patients on hemodialysis can have a

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3.8-fold higher risk of cerebral hemorrhaging than non-dialysis patients (4). Furthermore, cerebral hemorrhaging likely carries a higher risk of death than cerebral infarction among dialysis patients (4).

In addition to mortality, the negative impact of cerebral hemorrhaging on activities of daily living (ADL) must also be understood (5), as even though hemodialysis patients might survive the acute phase of cerebral hemorrhaging, their residual life prognosis might deteriorate. For example, some patients who survive cerebral hemorrhaging may suffer from paralysis, which significantly reduces their quality of life. Previous general population studies have shown that patients with a poor ADL after stroke tend to die earlier than those with a normal ADL (5-7). However, the prognosis of hemodialysis patients who survive cerebral hemorrhaging has not yet been clarified.

We previously conducted cross-sectional studies of hemodialysis in patients with cerebral hemorrhaging in the acute phase, during surgery, and in intensive care (8, 9). However, it might also be important to assess the chronic phase in these patients. In the present study, we conducted a long-term follow-up of hemodialysis patients with acute cerebral hemorrhaging treated at our hospital and compared their life prognosis based on their ADL at discharge.

Materials and Methods

Study population and data collection

This was an observational study conducted among facilities in the same medical zone, which consisted of Nagasaki City and two other towns (see Supplementary material 1 and 2 for details regarding the Nagasaki City medical zone). We included hemodialysis patients who were treated for acute intracerebral hemorrhaging at Nagasaki University Hospital between January 2007 and January 2015. These patients were diagnosed with acute intracerebral hemorrhaging based on neuroimaging [computed tomography (CT)] at Nagasaki University Hospital within three days of experiencing neurological symptoms. Patients with the following conditions were excluded: those with subarachnoid hemorrhaging, traumatic cerebral hemorrhaging, and hemorrhaging after ischemic stroke. Patients were followed up until December 31, 2017, at four facilities in the same medical zone eligible to treat in-hospital hemodialysis patients, where almost all patients transferred from our hospital are treated.

Data on patients' demographic characteristics were collected from their medical records at Nagasaki University Hospital. Data on the hemodialysis condition, ADL (walking independently), medical history, medications, and laboratory data before the onset were collected from medical referral letters. In addition, the patients' place of death (inside or outside Nagasaki University Hospital) and functional prognoses at discharge were evaluated. To evaluate the post-discharge prognosis in the patients, a follow-up survey was conducted at the medical facilities to which they were transferred.

The functional status was evaluated using the modified Rankin Scale (mRS) as follows: 0, no symptoms at all; 1, no significant disability despite symptoms; 2, slight disability (unable to carry out all previous activities but able to look after own affairs without assistance); 3, moderate disability (requiring some help but able to walk without assistance); 4, moderately severe disability (unable to walk without assistance and unable to attend to own bodily needs without assistance); 5, severe disability (bedridden, incontinent, and requiring constant nursing care and attention); and 6, death (10). The mRS is commonly used to evaluate functional outcomes after stroke. The mRS was determined by neurosurgeons at discharge.

The demographic data of patients on hemodialysis in the Nagasaki City medical zone were based on the data annually published by the Nagasaki Regional Council for Renal Failure (11).

The Institutional Review Board of Nagasaki University Hospital, the principal research institute coordinating this study, approved the study protocol (1602221-6). In addition, the Institutional Review Board or Ethics Committee of the individual participating institutes approved this study, which was conducted in accordance with the Declaration of Helsinki. Due to the retrospective design of this study, the respective Ethics Committees waived the need for obtaining informed consent, and the patients were informed by the respective centers that they could opt out of the study.

Statistical analyses

The patients were divided into a bedridden group (mRS 5) and a non-bedridden group (mRS 0-4) according to the mRS score at discharge. Categorical variables were assessed using the chi-squared test, and continuous variables were evaluated using Wilcoxon's rank-sum test to study the association between variables and categories. A survival curve was plotted using the Kaplan-Meier method and assessed using the log-rank test. Cox hazard proportional models were applied to estimate hazard ratios for the survival curve for mRS 0-4 vs. mRS 5.

All tests were two-sided, and a p value less than 0.05 was considered statistically significant. All statistical analyses were performed using the JMP® Pro 15 software program (SAS Institute, Cary, USA).

Results

Gross outcome at the acute phase

Of the 91 patients who received treatment for acute cerebral hemorrhaging at Nagasaki University Hospital during the study period, 29 died before discharge, and 62 survived. The patients' characteristics are presented in Supplementary material 3. The patients who died of cerebral hemorrhaging tended to have lower Glasgow Coma Scale scores (6.6±3.3 vs. 12±3.5, $p<0.0001$) and higher National Institute of

Table 1. Patient Characteristics (Bedridden Vs. Non-bedridden).

	Bedridden (mRS 5) n=31	Non-bedridden (mRS 0-4) n=31	p value
Age (year)	69±11	61±11	<0.001
Male, n (%)	46	54	0.42
Duration of hemodialysis, (month)	121±92	94±82	0.29
Medical history			
Ischemic heart disease, n (%)	13	6.5	0.39
Cerebral infarction, n (%)	39	32	0.60
Intracranial hemorrhage, n (%)	25	19	0.13
Prosthetic valve replacement, n (%)	0	3.3	0.23
Comorbidities			
Diabetes mellitus, n (%)	43	30	0.28
Atrial fibrillation, n (%)	19	6.7	0.13
Dyslipidemia, n (%)	17	20	0.79
Baseline medications			
Number of antihypertensive agents	1.6±1.3	2.0±1.2	0.18
Antiplatelet, n (%)	71	19	0.02
Warfarin, n (%)	3.2	13	0.15
mRS ≤3, n (%)	74	100	<0.001
Ultrafiltration volume per dry weight (%)	3.6±1.6	3.7±1.9	0.99
Pre dialysis systolic BP (mmHg)	161±18	166±18	0.40
Pre dialysis diastolic BP (mmHg)	60±9.9	63±11	0.27
Laboratory data			
Hemoglobin (g/dL)	11±1.5	10±1.5	0.21
Blood urea nitrogen (mg/dL)	59±14	61±16	0.45
Creatinine (mg/dL)	8.7±2.8	11±2.8	0.003
Serum calcium (mg/dL)	8.7±1.0	8.9±0.83	0.40
Corrected calcium (mg/dL)	9.2±1.0	9.2±0.71	0.97
Phosphate (mg/dL)	4.8±1.5	4.9±1.4	0.88
iPTH (pg/mL)	130±163	164±142	0.22
Albumin (g/dL)	3.5±0.54	3.7±0.48	0.22

Data is expressed in mean±standard deviation. mRS: modified Rankin Scale, BP: blood pressure, iPTH: intact parathyroid hormone

Health Stroke Scale scores (23±10 vs. 11±9, p<0.0001) on admission and showed a higher prevalence of intracerebroventricular hemorrhaging (97% vs. 47%, p<0.0001) than survivors. The baseline clinical features of survivors in the bedridden and non-bedridden groups are shown in Table 1.

Bedridden and non-bedridden groups

The mRS scores of the 62 patients who survived until discharge were as follows: mRS 5 (n=31), mRS 4 (n=15), mRS 3 (n=8), mRS 2 (n=4), mRS 1 (n=3), and mRS 0 (n=1). The survivors were divided into two groups based on their mRS scores (bedridden, mRS 5; non-bedridden, mRS 0-4), as shown in Table 1. The mean age of the bedridden group was significantly higher than that of the non-bedridden group (69±11 years vs. 61±11 years, p=0.0054). The bedridden group was more likely to be prescribed antiplatelet drugs than the non-bedridden group (71% vs. 19%, p=0.015). The proportion of patients in the bedridden group who could walk independently (mRS ≤3) before onset was significantly lower than that in the non-bedridden group (74% vs. 100%, p=0.0005).

The mean observation period was 631 days. On comparing the survival curves of both groups, the survival rate in the bedridden group was found to be significantly lower than that in the non-bedridden group (Figure). The age-adjusted hazard ratio of the bedridden group compared to that of the non-bedridden group was 8.72 [95% confidence interval (CI) 2.82-33.9, p<0.0001], and despite adjusting for age and antiplatelet drug use, the hazard ratio remained significantly higher at 13.7 (95% CI: 3.88-63.7, p<0.001). Furthermore, the hazard ratio was significantly higher than that of the non-bedridden group at 17.3 (95% CI: 4.24-101, p=0.0001) after adjusting for age and independent walking (Table 2). Five patients died in the non-bedridden group, and 16 patients died in the bedridden group during the study period. One patient in the non-bedridden group and three in the bedridden group died of cerebral hemorrhaging. However, many patients died of infections, such as sepsis and pneumonia. The causes of death are listed in Table 3. There was no significant difference in terms of the cause of death between the two groups.

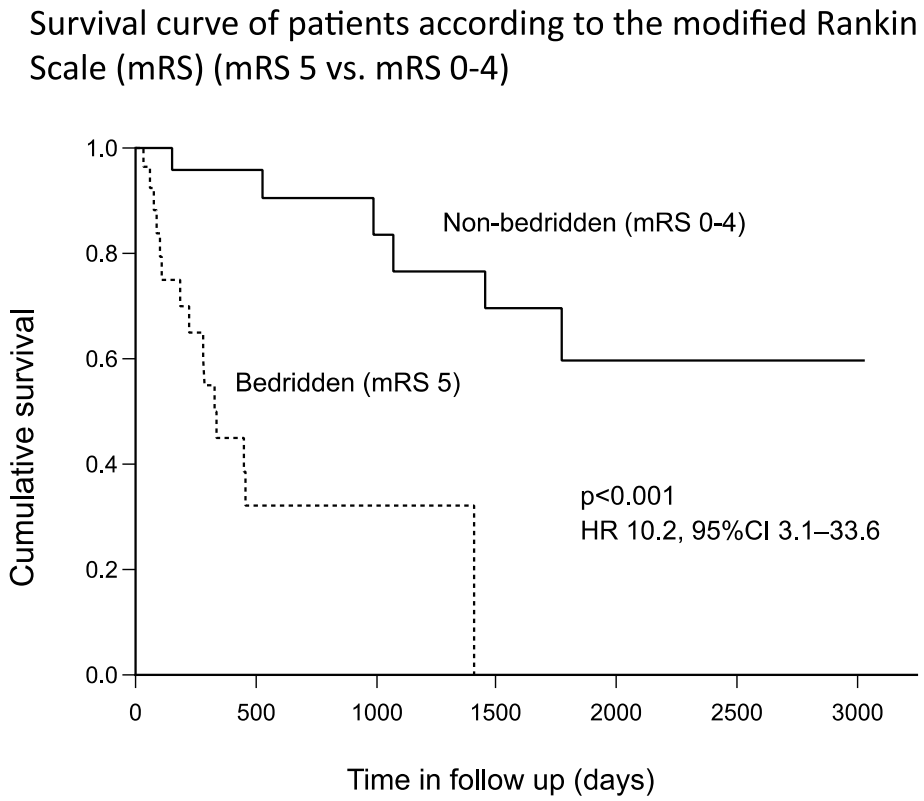

Figure. **Survival curve of patients according to the modified Rankin Scale (mRS) (mRS 0-4 vs. mRS 5); p<0.001. HR: hazard ratio, CI: confidence interval**

Table 2. **Hazard Ratios of All-mortality Based on Multivariate Cox Hazard Proportional Models.**

	Model 1		Model 2		Model 3	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Bedridden vs. non-bedridden (mRS 5 vs. mRS 0-4)	8.72 (2.82-33.9)	<0.001	13.7 (3.88-63.7)	0.001	17.3 (4.24-101)	<0.001
Age (year)	1.06 (1.02-1.10)	0.009	1.05 (1.01-1.10)	0.009	1.06 (1.02-1.11)	0.009
Antiplatelet			2.64 (0.96-8.7)	0.062		
Initial mRS≤3					0.59 (0.17-1.76)	0.062

Model 1: just adjusting age (considering aging). Model 2: Model 1+antiplatelet (known to poor prognosis factor in the general population). Model 3; Model 1+initial mRS (excluding the effects of ADL before onset). mRS: modified Rankin Scale, CI: confidential interval

Table 3. **Causes of Death among the Hemodialysis Patients with Acute Cerebral Hemorrhage Who Were Transferred to Other Facilities.**

	Bedridden (mRS 5)	Non-bedridden (mRS 0-4)
Pneumonia	5	2
Other infectious diseases	7	2
Cerebral hemorrhage	3	1
Other	1	

mRS: modified Rankin Scale

Discussion

In this retrospective study, we evaluated the prognosis of hemodialysis patients who survived the acute phase of intracerebral hemorrhaging. We found that the deterioration of the ADL in hemodialysis patients after acute cerebral hemorrhaging was directly proportional to worsening of their prognosis. In addition, infections, such as sepsis and pneumonia, were responsible for a significant number of deaths

when compared to cerebral hemorrhaging.

Several factors have been reported to be associated with the prognosis of patients with cerebral hemorrhaging. In the general population, the mRS can be used to predict not only the prognosis of patients with stroke but also the functional outcomes, such as ADL (12). The mRS scores among hemodialysis patients with cerebral hemorrhaging were well-correlated with patients' prognoses as previously described. Age has been reported as a negative functional prognostic factor after stroke (5). In the present study, the average age of patients in the bedridden group was higher than that of patients in the non-bedridden group.

The involvement of antiplatelet drugs in causing cerebral hemorrhaging in dialysis patients is controversial. Some studies have reported that antiplatelet drugs do not affect the patient prognosis (13, 14), while others have reported that they increase the risk of a poor prognosis among hemodialysis patients with cerebral hemorrhaging (8-15). Antiplatelet drugs are thought to increase the volume of hematomas, as they are hemorrhagic in nature, and a growing hematoma can irreversibly damage the brain. Our results suggest that antiplatelet drugs might have affected patients' ADL at discharge. We recommend that the risk of cerebral hemorrhaging be considered when prescribing antiplatelet drugs to patients with ischemic diseases, such as cerebral infarction and angina.

In our study, infectious diseases accounted for most deaths in the bedridden group. Regarding the cause of death after cerebral hemorrhaging in the general population, infections accounted for about 34% of deaths, of which 66% were due to sepsis, 14% due to aspiration pneumonia, and 11% due to viral or bacterial pneumonia (16). Of these, aspiration pneumonia is thought to have been caused by dysphagia after stroke (17, 18). Dysphagia after stroke develops within hours to days after the onset, and patients sometimes recover spontaneously. However, there are reports of nearly 50% of patients developing dysphagia after 6 months (19). Although patients with higher mRS scores were more likely to suffer from dysphagia than those with lower scores (20), there was no significant difference between the two groups in terms of pneumonia.

The majority of dialysis patients in Japan die from heart failure, infectious diseases, and cerebrovascular diseases (21). Among these, cerebrovascular diseases are thought to be involved in aspiration pneumonia. Treatment options for swallowing disorders after stroke include acupuncture, behavioral therapy, drug therapy (angiotensin-converting enzyme inhibitors), and various types of stimulations, such as neuromuscular electrical stimulation (22). It should be emphasized that oral care is another option for preventing aspiration pneumonia. A growing body of evidence has shown that periodontal diseases and renal failure are closely related (23), and poor oral health might increase the risk of pneumonia due to colonization by microorganisms (24). Post-stroke patients are known to have poor oral health conditions, so maintaining good oral hygiene is recommended for these patients (25).

Recent studies have suggested that post-stroke infectious diseases are associated with central nervous system (CNS) injury (26, 27). CNS impairment can lead to the release of cytokines, which can alter both the central and peripheral physiology. It can also lead to stimulation of the hypothalamic-pituitary-adrenal axis, resulting in the secretion of cortisol and catecholamines from the adrenal glands (28). These hormones suppress the immune function. Further research concerning the prevention of infection after stroke is needed.

The strength of the present study was that we were able to assess the long-term prognosis of the study participants. Generally, patients are transferred from one hospital to another after receiving treatment for the acute phase of cerebral hemorrhaging. However, only Nagasaki University Hospital treated hemodialysis patients with acute cerebral hemorrhaging until March 2015 in the Nagasaki City medical zone. Furthermore, there are few facilities suitable for the hospitalization of hemodialysis patients in the same area. Therefore, hemodialysis patients with cerebral hemorrhaging were able to be followed up starting from the acute phase.

However, several limitations associated with the present study also warrant mention. First, this was a retrospective study with a small sample size, and the results may not be generalizable because all of the patients were Japanese, and the Nagasaki City medical zone is a very small area. Furthermore, we were unable to assess hemodialysis patients with cerebral hemorrhaging who were not transferred to our hospital or whose cause of death could not be determined. Second, although we discussed dysphagia above, dysphagia was not always evaluated throughout the observation period. Since the ADL of patients was evaluated at the time of discharge, the timing of the evaluation varied for each case.

Studies concerning interventions, such as physical therapy, to improve the prognosis of patients after cerebral hemorrhaging will be needed in the future.

Conclusion

Acute cerebral hemorrhaging can be lethal in dialysis patients. In the present study, one-third of dialysis patients with cerebral hemorrhaging died in the acute phase, and another one-third became bedridden after the acute phase of cerebral hemorrhaging. Even after surviving, the prognosis of bedridden patients was poor, and they tended to die of infectious diseases, including pneumonia. To prevent aspiration pneumonia after stroke, the early evaluation of the swallowing function as well as dietary modification and swallowing therapy, such as behavioral therapy, are required, especially in bedridden patients. Keeping the oral environment clean also helps prevent aspiration pneumonia. Clinicians should be careful when administering antiplatelet drugs after cerebral hemorrhaging, as these can worsen the functional status or cause death in the acute phase.

The authors state that they have no Conflict of Interest (COI).

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