Prognostic factors for adult patients with hemorrhagic moyamoya disease in the acute stage

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ABSTRACT

Objectives: Hemorrhagic moyamoya disease (MMD) is one common subtype in adult patients. However, the study about outcome of hemorrhagic MMD patients in the acute stage is still lacking. This study is aimed to explore the short-term prognostic factors for adult patients with hemorrhagic MMD in the acute stage.

Patients and Methods: Adult hemorrhagic MMD patients in the acute stage awere retrospectively analyzed. Both clinical and imaging data were collected. Unfavorable functional outcome at discharge was considered when modified Rankin Scale score ≥ 3. Multivariate logistic regression was used to investigate the prognostic factors in patients with hemorrhagic MMD in the acute stage.

Results: A total of 107 patients were included in this study. Among these patients, 17 died and 59 had unfavorable functional outcome at 9.6 ± 7.8 days. In multivariate logistic regression, admission blood glucose (odds ratio (OR) = 1.457, 95% confidence interval (CI) 1.156–1.836, P = 0.001), midline shift > 5 mm (OR = 24.268, 95%CI 4.324–136.191, P < 0.001), and subarachnoid hemorrhage (OR = 13.067, 95%CI 2.020–84.512, P = 0.007) were independently associated with death at discharge. Moreover, admission Glasgow Coma Scale (GCS) score (OR = 0.420, 95%CI 0.296–0.598, P < 0.001), midline shift > 5 mm (OR = 6.685, 95%CI 1.226–36.455, P = 0.028), and intraparenchymal hemorrhage (OR = 4.790, 95%CI 1.184–19.381, P = 0.028) were independently associated with unfavorable functional outcome at discharge.

Conclusion: This study shows that admission blood glucose, midline shift > 5 mm, and subarachnoid hemorrhage are independent predictors of short-term mortality in hemorrhagic MMD in the acute stage. In addition, admission GCS score, midline shift > 5 mm, and intraparenchymal hemorrhage are independent predictors of short-term unfavorable functional outcome in hemorrhagic MMD in the acute stage.

1. Introduction

Moyamoya disease (MMD), which is also known as spontaneous occlusion of the circle of Willis, is a rare, chronic cerebrovascular condition with a typical stenosis or obstruction of terminal of internal carotid artery (ICA) and a smoke-like collateral vascular network [1]. The reported prevalence of MMD varies in different regions, ranging from 0.09/100,000 (USA) to 16.1/100,000 (South Korea) [2]. A previous study has shown that the prevalence of MMD is 3.92/100,00 in China [3]. Hemorrhagic MMD is one common subtype (56–69%) in adult patients, especially in Asian countries [4]. The reason for intracranial hemorrhage in MMD patients is still unclear. Formation and

rupture of microaneurysms were considered as the possible cause of intracranial hemorrhage in MMD patients [5]. Hemorrhagic MMD was also found to related to A4399 T polymorphism in ring finger protein 213 gene in a Chinese population [6]. Although hemorrhagic MMD has been discussed in some previous studies, the study about outcome of hemorrhagic MMD patients in the acute stage is still lacking [7–11]. If patients with hemorrhagic MMD have good short-term outcome, they can be eligible for surgical revascularization and other treatments later. Therefore, prediction of short-term outcome is a critical issue for the management of this rare disease. Thus, this study is aimed to explore the short-term prognostic factors for adult hemorrhagic MMD patients in the acute stage.

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2. Patients and methods

2.1. Patients

Patients were retrospectively screened from hospital information system between Jan. 2010 and Sep. 2018 at West China Hospital, Sichuan University. Patients were considered as eligible if :1) Age ≥ 18; 2) Admitted to our hospital within 72 h after appearance of initial symptoms; 3) Intracranial hemorrhage, including intraparenchymal hemorrhage, intraventricular hemorrhage, and subarachnoid hemorrhage, was found on admission computed tomography (CT); 4) MMD confirmed by angiographical examination. The diagnosis of MMD in this study followed the guideline for diagnosis and treatment of MMD [12]. If medical records showed that a patient had Down syndrome, neurofibromatosis, meningitis, vasculitis, atherosclerosis, brain tumor, traumatic brain injury, or radiotherapy, this patient was excluded from this study.

2.2. Clinical data

Clinical data were collected via reviewing medical records in hospital information system. The following clinical data were collected: age, sex, admission Glasgow Coma Scale (GCS) score, admission blood pressure, medical histories (hypertension, diabetes mellitus, previous stroke, smoking and alcohol abuse), and results of admission laboratory examinations (red blood cell, white blood cell, platelet count, blood glucose, prothrombin time, activated partial thromboplastin time, and international normalized ratio). The information about short-term outcome, defined as death and modified Rankin Scale (mRS) score at discharge, were also obtained.

2.3. Imaging analysis

We obtained and analyzed the admission CT scans of included patients for following characteristics: midline shift, hydrocephalus, subarachnoid hemorrhage, intraparenchymal hemorrhage, and intraventricular hemorrhage. Midline shift was measured at the level of septum pellucidum on CT scan and was considered as obvious if > 5 mm [13]. Hydrocephalus was considered if lateral ventricles extended without enlarged cisterns and sulci on CT scan [14]. Subarachnoid hemorrhage, intraparenchymal hemorrhage, and intraventricular hemorrhage were determined based on CT scan. Based on angiographical examinations, Suzuki stage, bilateral or unilateral MMD, and presence of intracranial aneurysm were determined. The definition of Suzuki stage followed the previous study, which categorized MMD patients to six stages based on the angiographic results [15].

2.4. Statistical analysis

Mean ± standard deviations or median (interquartile ranges) were used to describe continuous variables. Frequency was used to describe categorical variables. Unfavorable functional outcome was considered when mRS score ≥ 3. All variables were analyzed using t-test, rank sum test, or chi-square test if appropriate. Multivariate logistic regression was used to investigate the association between potential prognostic factors and outcome in patients with hemorrhagic MMD in the acute stage. All statistical analyses were completed with SPSS Statistics (Version 22.0, IBM). If P < 0.05, it was considered that the statistical significance existed.

3. Results

Between Jan. 2010 and Sep. 2018, a total of 151 patients with hemorrhagic MMD were identified in our hospital. Among these patients, 42 were excluded because the interval between onset of intracranial hemorrhage and admission was longer than 72 h. Another two patients

Table 1

Characteristics of patients dead or alive at discharge.

	Dead (n = 17)	Alive (n = 90)	P
Age, year	47.4 ± 14.1	44.3 ± 12.7	0.377
Male	6	38	0.594
GCS score	8 (6, 11)	13 (9, 15)	< 0.001
SBP, mmHg	145.9 ± 34.0	137.4 ± 25.0	0.341
DBP, mmHg	83.3 ± 17.4	81.4 ± 18.6	0.681
RBC, 10^{12}/l	4.23 ± 0.64	4.45 ± 0.56	0.158
WBC, 10^9/l	15.90 ± 4.73	12.68 ± 4.99	0.016
PLT, 10^9/l	209.47 ± 75.08	179.63 ± 60.73	0.077
BG, mmol/l	9.72 ± 3.53	7.32 ± 2.14	0.014
PT, s	11.87 ± 1.18	11.79 ± 1.05	0.773
APTT, s	25.66 ± 6.12	26.56 ± 5.55	0.546
INR	1.04 ± 0.11	1.03 ± 0.10	0.600
Hypertension	7	21	0.125
Diabetes mellitus	2	1	0.065
Previous stroke	5	14	0.170
Smoking	4	15	0.498
Alcohol abuse	2	21	0.355
MS > 5 mm	12	20	< 0.001
Hydrocephalus	5	12	0.096
SAH	7	28	0.417
IPH	12	44	0.100
IVH	14	70	> 0.999
Suzuki stage > 3	1	18	0.297
Bilateral MMD	12	62	0.889
Aneurysm	3	20	> 0.999

Data are mean ± standard deviation, median & interquartile range, or number of patients. GCS = Glasgow coma scale; SBP = systolic blood pressure; DBP = diastolic blood pressure; RBC = red blood cell; WBC = white blood cell; PLT = platelet count; BG = blood glucose; PT = prothrombin time; APTT = activated partial thromboplastin time; INR = international normalized ratio; MS = midline shift; SAH = subarachnoid hemorrhage; IPH = intraparenchymal hemorrhage; IVH = intraventricular hemorrhage; MMD = moyamoya disease.

were excluded because their angiographical examinations were unavailable. Finally, a total of 107 patients were included in this study. The mean duration of hospitalization was 9.62 ± 7.82 days. A total of 17 patients died and 59 patients had unfavorable functional outcome at discharge.

3.1. Predictors of death at discharge

We compared both the clinical and imaging characteristics in hemorrhagic MMD patients dead and alive at discharge. Patients dead at discharge had significantly lower admission GCS score (P < 0.001), higher admission leukocyte count (P = 0.016), higher admission blood glucose (P = 0.014) than those alive at discharge. Moreover, comparing to survivors at discharge, non-survivors had a significantly more frequent presence of midline shift > 5 mm (P < 0.001) (Table 1). In multivariate logistic regression, admission blood glucose (odds ratio (OR) = 1.457, 95% confidence interval (CI) 1.156–1.836, P = 0.001), midline shift > 5 mm (OR = 24.268, 95%CI 4.324–136.191, P < 0.001), and subarachnoid hemorrhage (OR = 13.067, 95%CI 2.020–84.512, P = 0.007) were independently associated with death at discharge in MMD patients with intracranial hemorrhage (Table 2).

3.2. Predictors of unfavorable functional outcome at discharge

Clinical and imaging characteristics in patients with favorable and unfavorable functional outcome were compared. Patients with unfavorable functional outcome had significantly lower admission GCS score (P < 0.001) and admission leukocyte count (P = 0.001) than those with favorable functional outcome. In imaging characteristics, Midline shift > 5 mm (P < 0.001), hydrocephalus (P = 0.017), and intraparenchymal hemorrhage (P = 0.002) were significantly different between patients with favorable and unfavorable functional outcome

Table 2

Multivariate logistic regression for death at discharge.

Variables	Death		
	OR	95% CI	P
Age	1.005	0.949–1.065	0.855
GCS score	0.860	0.692–1.070	0.177
WBC	1.019	0.874–1.189	0.808
PLT	1.003	0.993–1.013	0.581
BG	1.457	1.156–1.836	0.001
MS > 5 mm	24.268	4.324–136.191	< 0.001
Hydrocephalus	1.720	0.281–10.509	0.557
SAH	13.067	2.020–84.512	0.007
IPH	2.089	0.491–8.887	0.318
IVH	4.493	0.656–30.748	0.126
Suzuki stage > 3	0.381	0.034–4.213	0.431

GCS = Glasgow coma scale; WBC = white blood cell; PLT = platelet count; BG = blood glucose; MS = midline shift; SAH = subarachnoid hemorrhage; IPH = intraparenchymal hemorrhage; IVH = intraventricular hemorrhage.

Table 3

Characteristics of patients with favorable and unfavorable functional outcome at discharge.

	mRS (3-6) (n = 59)	mRS (0-2) (n = 48)	P
Age, year	46.2 ± 11.9	43.1 ± 13.9	0.232
Male	28	16	0.140
GCS score	9 (7, 11)	15 (13, 15)	< 0.001
SBP, mmHg	139.3 ± 28.4	138.1 ± 24.6	0.818
DBP, mmHg	83.4 ± 15.6	79.5 ± 21.3	0.269
RBC, 10^{12}/l	4.41 ± 0.60	4.41 ± 0.56	0.981
WBC, 10^9/l	14.59 ± 5.17	11.48 ± 4.43	0.001
PLT, 10^9/l	194.93 ± 65.40	171.40 ± 59.85	0.057
BG, mmol/l	7.94 ± 2.70	7.40 ± 2.35	0.277
PT, s	11.68 ± 1.01	11.95 ± 1.12	0.201
APTT, s	25.90 ± 4.95	27.05 ± 6.35	0.296
INR	1.03 ± 0.09	1.04 ± 0.11	0.410
Hypertension	18	10	0.257
Diabetes mellitus	2	1	> 0.999
Previous stroke	12	7	0.438
Smoking	12	7	0.438
Alcohol abuse	15	8	0.273
MS > 5 mm	27	5	< 0.001
Hydrocephalus	14	3	0.017
SAH	18	17	0.680
IPH	39	17	0.002
IVH	48	36	0.426
Suzuki stage > 3	7	12	0.077
Bilateral MMD	42	32	0.615
Aneurysm	12	11	0.747

Data are mean ± standard deviation, median & interquartile range, or number of patients. mRS = modified Rankin scale; GCS = Glasgow coma scale; SBP = systolic blood pressure; DBP = diastolic blood pressure; RBC = red blood cell; WBC = white blood cell; PLT = platelet count; BG = blood glucose; PT = prothrombin time; APTT = activated partial thromboplastin time; INR = international normalized ratio; MS = midline shift; SAH = subarachnoid hemorrhage; IPH = intraparenchymal hemorrhage; IVH = intraventricular hemorrhage; MMD = moyamoya disease.

(Table 3). In multivariate logistic regression, admission GCS score (OR = 0.420, 95%CI 0.296–0.598, P < 0.001), midline shift > 5 mm (OR = 6.685, 95%CI 1.226–36.455, P = 0.028), and intraparenchymal hemorrhage (OR = 4.790, 95%CI 1.184–19.381, P = 0.028) were independently associated with unfavorable functional outcome at discharge in patients with hemorrhagic MMD in the acute stage (Table 4).

4. Discussion

Based on a retrospective cohort including 107 patients, this study explored the short-term prognostic factors in a rare cerebrovascular condition, hemorrhagic MMD in the acute stage. In this study, higher

Table 4

Multivariate logistic regression for unfavorable functional outcome at discharge.

Variables	mRS (3-6)		
	OR	95% CI	P
Age	1.058	0.997–1.026	0.061
GCS score	0.420	0.296–0.598	< 0.001
WBC	0.947	0.756–1.186	0.638
PLT	1.012	0.999–1.026	0.076
BG	0.684	0.467–1.001	0.051
MS > 5 mm	6.685	1.226–36.455	0.028
Hydrocephalus	2.409	0.232–25.077	0.462
SAH	0.828	0.161–4.261	0.821
IPH	4.790	1.184–19.381	0.028
IVH	2.203	0.349–13.929	0.401
Suzuki stage > 3	0.444	0.066–3.004	0.405

GCS = Glasgow coma scale; WBC = white blood cell; PLT = platelet count; BG = blood glucose; MS = midline shift; SAH = subarachnoid hemorrhage; IPH = intraparenchymal hemorrhage; IVH = intraventricular hemorrhage.

admission blood glucose, midline shift > 5 mm, and subarachnoid hemorrhage were found to be independent predictors for death at discharge in patients with hemorrhagic MMD in the acute stage. Moreover, we found lower admission GCS score, midline shift > 5 mm, and intraparenchymal hemorrhage were independent predictors of unfavorable functional outcome in patients with hemorrhagic MMD in the acute stage. These findings can help us predict short-term outcome in patients with hemorrhagic MMD in the acute stage.

Hyperglycemia, low GCS and midline shift have been previously shown to be associated with poor short-term outcome [16–21]. In this study, we found admission blood glucose was independently related to mortality at discharge, GCS score was an independent predictor of unfavorable functional outcome at discharge, and obvious midline shift was independently correlated with both mortality and unfavorable functional outcome at discharge in hemorrhagic MMD in the acute stage. In a retrospective study including 212 patients with hemorrhagic MMD, Li et al. found that hemorrhagic type could be related to outcome [22]. However, this finding was not confirmed by multivariate analysis [22]. This study found subarachnoid hemorrhage as an independent predictor of mortality and intraparenchymal hemorrhage as an independent predictor of unfavorable outcome. Our study also found that some radiological factors, such as Suzuki stage and bilateral stenosis, were not significantly associated with short-term outcome in these patients. The possible explanation is that these radiological factors mainly reflect the long-term pathological process of MMD, but short-term outcome is mainly influenced by the factors related to the acute stage after hemorrhage. Another important factor, age, was also not significantly associated with short-term outcome in this study, which may be caused by the relatively young age in this cohort. All these findings should be confirmed by further studies with larger sample size.

Previous studies mainly focused on the long-term prognosis in patients with hemorrhagic MMD. In Su et al.'s study, 26 adult patients with hemorrhagic MMD were included for long-term follow-up and cognitive impairment was found in patients receiving conservative treatment [23]. In another study, high mental burden was found in adult patients with hemorrhagic MMD [24]. In a retrospective study by Jiang et al., Suzuki stage progression was identified as a predictor of rebleeding after surgical revascularization in adult patients with hemorrhagic MMD [25]. In another retrospective study with 52 patients, reduced basal perfusion was found to be related to rebleeding in hemorrhagic MMD [26]. Morioka et al. suggested the rebleeding in hemorrhagic MMD could be related to age of patients [27]. Including 212 patients with hemorrhagic MMD, Li et al.'s study reported that 65.6% patients had a Glasgow Outcome Scale score of 5, which suggested these patients could had a relatively good outcome after appropriate

treatment [22]. However, in their study, the onset-to-admission time and follow-up time were unclear [22]. Although long-term outcome is crucial for adult patients with hemorrhagic MMD, prediction of short-term outcome is also important so that patients can get opportunities to receive further treatments. The results of this study have suggested that although the short-term mortality is relatively low, more than a half of these patients have unfavorable short-term functional outcome. However, the related literature is still insufficient, and these findings should be confirmed by further studies.

The best treatment of hemorrhagic MMD is still unclear. Medical treatment, such as antiplatelet drug, has been widely used in MMD patients, but its efficacy is still controversial [4,28]. The role of surgical revascularization in patients with hemorrhagic MMD is also a controversial issue [11]. Jiang et al. investigated the role of bypass surgery in outcome of hemorrhagic MMD patients and found surgical revascularization could improve the prognosis in these patients [7]. Miyamoto et al. reported that significant difference of rebleeding was found between direct bypass group and medical group in Japan Adult Moyamoya Trial [8]. Jang et al. showed that bypass surgery could decrease recurrent stroke in hemorrhagic MMD [29]. Choi et al. found that direct or combined bypass surgery could be more effective than indirect surgery to decrease rebleeding in adult patients with hemorrhagic MMD [30]. Recently, Ding et al. conducted a network meta-analysis and found a direct bypass surgery can be the optimal therapy for patients with hemorrhagic MMD [31]. Surgical revascularization is important for improving outcome in patients with hemorrhagic MMD. However, management in acute stage after intracranial hemorrhage is also vital. This study has showed several prognostic factors in patients with hemorrhagic MMD in the acute stage, which may be helpful to improve management in hemorrhagic MMD and select eligible patients for surgical revascularization treatment.

There are still some limitations in this study. This was a retrospective study in a single center and the sample size was small, which could affect the accuracy of final results. Moreover, we were only able to obtain the follow-up data at discharge, so long-term prognostic factors could not be explored in this study. Furthermore, some important factors, such as condition of heart and lung, ASA grade, and brain perfusion, were not discussed in this study due to insufficient data. More prospective studies with large sample size are needed to confirm the current findings in this study.

In conclusion, this study shows that admission blood glucose, midline shift > 5 mm, and subarachnoid hemorrhage are independent predictors of short-term mortality in hemorrhagic MMD in the acute stage. In addition, admission GCS score, midline shift > 5 mm, and intraparenchymal hemorrhage are independent predictors of short-term unfavorable functional outcome in hemorrhagic MMD the acute stage.

Funding

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