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# Factors Associated with Clinical Outcomes in Patients with Primary Intraventricular Hemorrhage

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**Background:** Primary intraventricular hemorrhage (PIVH) is an uncommon type of intracerebral hemorrhage. Owing to its rarity, the clinical and radiological factors affecting outcomes in patients with PIVH have not been widely studied.





**Material/Methods:** We retrospectively reviewed 112 patients (mean age 53 years) treated for PIVH at our institution from January 2004 to December 2014. Clinical and radiological parameters were analyzed 3 months after initial presentation to identify factors associated with clinical outcomes, as assessed by the Glasgow Outcome Scale (favorable  $\geq 4$ , unfavorable  $< 4$ ).

**Results:** Of the 99 patients who underwent angiography, causative vascular abnormalities were found in 46%, and included Moyamoya disease, arteriovenous malformation, and cerebral aneurysm. At 3 months after initial presentation, 64% and 36% of patients were in the favorable and unfavorable outcome groups, respectively. The mortality rate was 19%. However, most survivors had no or mild deficits. Age, initial Glasgow Coma Scale (GCS) score, simplified acute physiology score (SAPS II), modified Graeb score, and various radiological parameters reflecting ventricular dilatation were significantly different between the groups. Specifically, a GCS score of less than 13 ( $p=0.015$ ), a SAPS II score of less than 33 ( $p=0.039$ ), and a dilated fourth ventricle ( $p=0.043$ ) were demonstrated to be independent predictors of an unfavorable clinical outcome.

**Conclusions:** In this study we reveal independent predictors of poor outcome in primary intraventricular hemorrhage patients, and show that nearly half of the patients in our study had predisposing vascular abnormalities. Routine angiography is recommended in the evaluation of PIVH to identify potentially treatable etiologies, which may enhance long-term prognosis.

**MeSH Keywords:** **Cerebral Hemorrhage • Cerebral Ventricles • Intracranial Aneurysm • Intracranial Arteriovenous Malformations • Moyamoya Disease • Treatment Outcome**

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## Background

Primary intraventricular hemorrhage (PIVH) is a rare condition defined as bleeding within the ventricular system without a definite parenchymal component, and accounts for 0.31% of all stroke cases and 3.1% of intracerebral hemorrhages (ICHs) [1–6]. Intraventricular hemorrhage (IVH) occurring with ICH, subarachnoid hemorrhage (SAH), or other parenchymal hemorrhage, is referred to as secondary IVH [7,8]. PIVH commonly occurs in preterm newborns as a complication of birth, but is relatively rare in adults [9–11]. PIVH was considered fatal before the modern era of brain imaging, as it could only be diagnosed during postmortem examination. The introduction of brain imaging techniques such as computed tomography (CT) and magnetic resonance (MR) imaging has allowed for a more rapid and easier diagnosis of PIVH. However, due to its rarity, there is relatively little information regarding the clinical manifestations of PIVH, its etiology, and its prognosis. The purpose of this study was to review data from 112 patients with PIVH admitted to a single tertiary referral hospital over the last 11 years. Here, we describe their clinical characteristics, outcomes following treatment, and prognostic factors.

## Material and Methods

### Patient population and inclusion criteria

We reviewed all patients with ICH who were admitted at our institution between January 2004 and December 2014. We analyzed patients with spontaneous IVH without evidence of ICH or SAH. Exclusion criteria were: neonates (less than 1 month after birth), death within 24 hours of presentation, and life expectancy less than 6 months owing to another medical condition. We enrolled 112 patients. This study was approved by the University Hospital Ethics Committee.

### Patient management

Once PIVH was diagnosed, all patients were admitted to a neurosurgical intensive care unit (ICU). Additional radiological examinations, including CT or MR angiography, and/or transfemoral cerebral angiography (TFCA), were considered for all subjects to identify causal vascular pathologies, according to the guidelines provided by the American Heart Association and the American Stroke Association [12]. However, these studies were not performed in 13 patients (12%) due to reasons such as poor clinical status or refusal by the patient's family.

During the acute phase, systolic blood pressure was maintained below 140 mmHg, and osmotic diuretics were administered to control increased intracranial pressure (ICP). Patients with a decreased level of consciousness (Glasgow Coma Scale [GCS]

<8) were intubated to maintain the airway and to reduce the gag reflex or the chances of imminent aspiration. Mechanical ventilation was used in patients with respiratory insufficiency, as indicated by  $p\text{CO}_2 >55$  mmHg or  $p\text{O}_2 <60$  mmHg. In patients with coagulopathy, anticoagulation reversal was performed using fresh-frozen plasma or prothrombin-complex concentrate, and vitamin K. Anticoagulant or antiplatelet treatments were discontinued during the acute phase in patients who regularly took the medications. When necessary, informed consent was obtained to perform external ventricular drainage (EVD). The laterality of the EVD was chosen based on the patient's conditions and the hemorrhagic location, which was observed during the initial CT. Indications for EVD at our institution were: (1) initial GCS score of  $<12$ , (2) evidence of hydrocephalus defined as an Evans' ratio of  $>0.30$ , and (3) evidence of third or fourth ventricle obstruction with an accompanying prediction that the patient would develop hydrocephalus. Pneumatic compression stockings were used to prevent deep vein thrombosis.

### Outcomes measures

Neurological outcome at 3 months was assessed using the Glasgow Outcome Scale (GOS). Patients were divided into 2 groups according to their GOS scores: a favorable outcome group (GOS scores of 4–5) and an unfavorable outcome group (GOS scores of 1–3). Additional outcomes measures included mortality 3 months after presentation.

### Analysis of prognostic factors affecting neurological outcomes

The potential prognostic factors discussed in previous reports of intracerebral and/or intraventricular hemorrhage were analyzed to examine their relationships with clinical outcomes [5,13–17]. The presumptive factors were either patient factors or radiologic findings, and were collected from medical records and imaging studies. Potential patient factors included: age, sex, initial GCS score, low platelet count ( $<50\,000$  mm<sup>3</sup>), prolonged prothrombin time (PT; International Normalized Ratio [INR]  $>1.4$ ), use of anticoagulants or antiplatelet agents, the presence of underlying diseases such as hypertension (determined by previous diagnosis, treatment with antihypertensive medications, or a blood pressure reading of  $>140/90$  mmHg), and diabetes mellitus (DM; determined by a fasting glucose reading of  $>7$  mmol/L or treatment with anti-diabetic medication). The severity of illness for the enrolled patients was measured using the new Simplified Acute Physiology Score (SAPS II), which is calculated based on the worst values taken during the first 24 hours after admission to the ICU. The score encompasses 15 parameters (heart rate; body temperature; white blood cell count; the ratio of partial pressure of oxygen in arterial blood to fractional inspired oxygen; bicarbonate level; systolic blood pressure; urinary output; serum urea level; serum potassium,



**Figure 1.** Calculations of ventricular system diameters. A – transverse diameter of the third ventricle. B and C – anteroposterior and transverse diameters of the fourth ventricle. D – diameter of the dominant side of the temporal horn.

sodium, and bilirubin levels; GCS score; age; type of admission; and chronic underlying disease), and has a range of 0 to 163 [18]. Additionally, parameters of the ventricular system were measured, including the transverse diameter of the third ventricle, both anterior-posterior (AP) and transverse diameters of the fourth ventricle, and temporal horn size on the dominant side. IVH volume was calculated using the modified Graeb score (mGS) system [7]. A dilated fourth ventricle was defined as one with a transverse diameter of >20 mm or an AP diameter of >12.5 mm [19], while third ventricle dilatation was defined as a transverse diameter of >10 mm [20]. Finally, dilatation of the temporal horn was determined as a size of >6 mm, and hydrocephalus was defined as an Evans' ratio of >0.30 [21]. Figure 1 summarizes the calculations for ventricular system dilatation parameters.

### Statistical analysis

Presumptive prognostic factors were compared between the favorable (GOS scores of 4–5) and unfavorable outcome (GOS scores of 1–3) groups using *t* tests for continuous variables (age, initial GCS, SAPS II score, mGS, diameters of 3<sup>rd</sup> and 4<sup>th</sup> ventricle, size of dominant side temporal horn), and either the chi-square or Fisher's exact test for categorical variables (sex, application of mechanical ventilation within 24 hours of the initial attack, prior medical comorbidities, thrombocytopenia, abnormal coagulation parameters, presence of causative vascular abnormalities, additional treatment for vascular abnormalities, and hydrocephalus). The association between presumptive factors and clinical outcomes was analyzed using a logistic regression model, and the odds ratio (OR) and 95% confidence interval (CI) were calculated. Multivariable logistic regression models were later built to control for potential confounding variables. The data are presented as mean  $\pm$  standard deviation. All of the statistical calculations were

performed using commercially available software (SPSS 11.5, IBM Corporation, Armonk, NY). *P*-values less than 0.05 were considered to be significant.

## Results

### Patient characteristics, treatment, and clinical outcomes

Table 1 summarizes the demographic and radiological data of the 112 patients included in the study. Angiography (CT or MR angiography, and/or TFCA) was performed in 99 patients (88%) and presumptive vascular pathologies for PIVH were detected in 46 patients (46%, 46/99). Among them, 28 patients (28%) were diagnosed with Moyamoya disease and 16 patients (16%) were found to have arteriovenous malformation (AVM). Two patients were revealed to have an aneurysm rupture (2%, anterior communicating artery aneurysm in one and posterior inferior cerebellar artery aneurysm in the other). Angiograms for 53 of the patients did not show any significant abnormalities that could be associated with their ventricular hemorrhage. The mean age of those patients who were identified as having underlying vascular pathologies was  $43.3 \pm 12.4$  years, which was lower than that of patients who were not diagnosed with causal vascular lesions (mean:  $60.8 \pm 20.2$  years,  $p=0.012$ ).

Based on the angiographic results, previous medical history, and laboratory findings, we identified several possible causes of PIVH, which included vascular abnormalities identified in 46 patients (41%), pre-existing hypertension reported in 31 patients (28%), and clotting disorders present in 22 patients (20%). The etiology of PIVH was not identified in 13 patients (12%). The antecedent vascular abnormalities were managed with medical or surgical interventions, including urgent

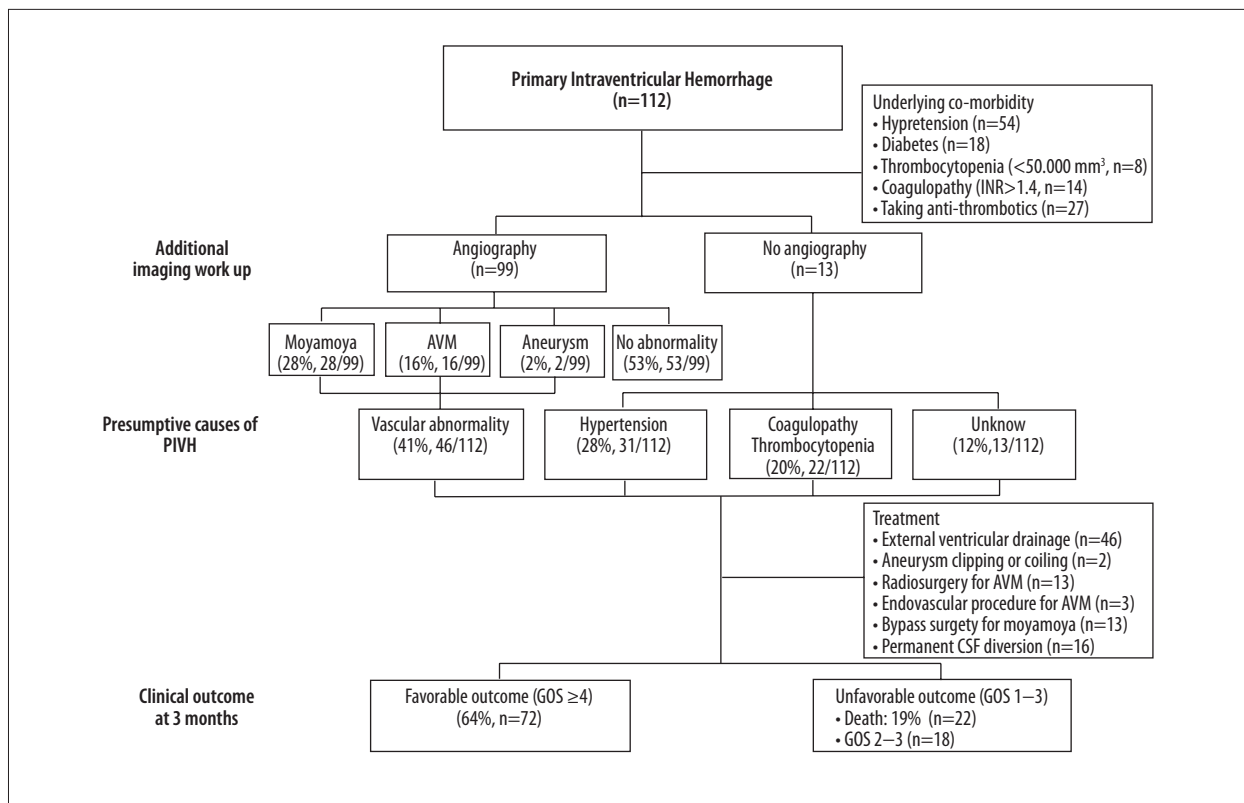
**Table 1.** Patient demographics and radiological parameters.

Variables	Patients with primary intraventricular hemorrhage (n=112)
Age (years, mean $\pm$ SD)	53.0 $\pm$ 17.8
$\geq$ 55 years	55 (49%)
<55 years	57 (51%)
Gender	
Male, n (%)	64 (57%)
Female, n (%)	48 (43%)
Initial Glasgow Coma Scale (mean $\pm$ SD)	11.2 $\pm$ 4.3
$\geq$ 13	42 (38%)
<13	70 (62%)
Simplified Acute Physiology Score (mean $\pm$ SD)	33.4 $\pm$ 20.3
$\geq$ 33	53 (47%)
<33	59 (53%)
Mechanical ventilation within 24 hours	24 (21%)
Prior medical history, n (%)	
Hypertension	54 (48%)
Diabetes	18 (16%)
Use of anticoagulant	8 (7%)
Use of antiplatelet agent	19 (16%)
Laboratory finding, n (%)	
Thrombocytopenia (<50,000 mm <sup>3</sup> )	8 (7%)
prolonged prothrombin time (INR >1.4)	14 (13%)
Positive finding in angiography, n (%)	
Moyamoya disease	28 (28%)
Arteriovenous malformation	16 (16%)
Aneurysm	2 (2%)
Modified Graeb score (mean, ranges)	15.4 $\pm$ 8.3
Transverse diameter of 3 <sup>rd</sup> ventricle (mm, mean $\pm$ SD)	10.8 $\pm$ 4.9
AP diameter of 4 <sup>th</sup> ventricle (mm, mean $\pm$ SD)	13.2 $\pm$ 6.1
Transverse diameter of 4 <sup>th</sup> ventricle (mm, mean $\pm$ SD)	18.5 $\pm$ 5.6
Dominant side temporal horn size (mm, mean $\pm$ SD)	8.4 $\pm$ 5.7
Presence of hydrocephalus (n, %)	53 (47%)
External ventricular drainage (n, %)	46 (41%)

AP – anteroposterior; INR – International Normalized Ratio; SD – standard deviation.

aneurysm clipping (1 patient) or coiling (1 patient) in the case of a ruptured aneurysm, and radiosurgery (11 patients), neuro-interventional procedure (1 patient), or a combination of the 2 (2 patients) to treat AVM, for which it had been a mean of 6 weeks (range: 5–9 weeks) since initial presentation. Either direct (8 patients) or indirect (5 patients) bypass surgery was utilized to treat patients diagnosed with Moyamoya disease, for which it had been an average of 9 weeks since the initial

IVH attack (range: 5–12 weeks). Two patients with AVM did not undergo treatment for their AVM because of refusal by their family members. Fifteen Moyamoya patients without deranged cerebral hemodynamics were maintained using medical treatment. EVD was performed in 46 patients within 3 weeks of the initial attack (range: 0–19 days). Sixteen patients underwent a permanent cerebral spinal fluid diversion procedure within 3 months (range: 35–88 days) of their initial presentation.



**Figure 2.** Flow chart showing the patient population and treatment outcomes in patients with primary ventricular hemorrhage. AVM – arteriovenous malformation; GOS – Glasgow Outcome Scale; INR – International Normalized Ratio; PIVH – primary intraventricular hemorrhage.

All 112 patients were evaluated 3 months after initial presentation, at which point 72 (64%) presented with favorable outcomes as determined by GOS scores of 4–5, while the other 40 patients (36%) presented with poor outcomes as indicated by GOS scores of 1–3. A total of 22 patients (19%) were dead. Eighteen patients (16%) died of intractable intracranial pressure, thought to be a direct consequence of PIVH, within a week after ictus. Four patients died due to other causes, including a sudden onset of ventricular tachycardia and respiratory arrest, pneumonia, and sepsis of unknown origin. The majority of the survivors (72/90, 80%) presented with no deficits or mild deficits (GOS  $\geq 4$ ) 3 months after initial presentation. Brief demographic data and treatment outcomes are shown in Figure 2.

### Patient and hemorrhagic factors

The patient and hemorrhage factors were compared between the favorable and unfavorable groups (Table 2). The mean age of the patients in the unfavorable outcome group was significantly higher than that of the favorable group ( $p=0.001$ ). The initial GCS score was  $13.3 \pm 2.7$  in the favorable outcome group, which was significantly higher than the score of  $7.2 \pm 4.1$  measured in the unfavorable group ( $p < 0.001$ ). The mean SAPS II

score was significantly lower in the favorable group ( $27.8 \pm 16.8$  vs.  $43.5 \pm 22.2$ ,  $p < 0.001$ ). The prevalence of pre-existing hypertension was higher in the unfavorable outcome group (57% vs. 43%). However, the difference between the 2 outcome groups did not reach statistical significance ( $p=0.143$ ). A total of 27 patients were taking anticoagulants (8 patients) or antiplatelet agents (19 patients). However, there was no significant difference between the 2 groups ( $p=0.382$  for anticoagulant,  $p=0.245$  for antiplatelet). The outcomes of patients who presented with abnormal bleeding profiles, including low platelet counts ( $<50\,000\text{ mm}^3$ ) and prolonged PTs (INR  $>1.4$ ), were also not significantly different from those of patients with normal bleeding profiles ( $p=0.155$  and  $0.551$ , respectively). The presence of causative vascular lesions was found not to be likely to affect neurological outcome ( $p=0.330$ ). Additionally, treatment for underlying vascular pathologies, such as neck clipping or coiling for aneurysms, radiosurgery or neuro-intervention for AVM, or direct or indirect bypass surgery for Moyamoya disease, did not influence short-term clinical outcomes ( $p=0.583$ ).

Radiologic factors, determined from the initial CT scan, included mGS, the transverse diameter of the third ventricle, the AP and transverse diameters of the fourth ventricle, the size of the temporal horn on the dominant side, the presence of



**Table 2.** A comparison of clinical characteristics and radiological parameters between the favorable and unfavorable outcome groups.

Variables	Favorable outcome (GOS $\geq$ 4, n=72)	Unfavorable outcome (GOS <4, n=40)	p-value
Age (years, mean $\pm$ SD)	49.6 $\pm$ 18.4	59.5 $\pm$ 14.7	0.001*
Initial Glasgow Coma Scale (mean $\pm$ SD)	13.3 $\pm$ 2.7	7.3 $\pm$ 4.1	<0.001*
Simplified Acute Physiology Score (mean $\pm$ SD)	27.8 $\pm$ 16.8	43.5 $\pm$ 22.2	<0.001*
Male gender	41 (57%)	23 (58%)	0.955
Mechanical ventilation within 24 hours	12 (17%)	12 (30%)	0.099
Prior medical history, n (%)			
Hypertension	31 (43%)	23 (57%)	0.143
Diabetes	9 (13%)	9 (23%)	0.167
Use of anticoagulant	4 (5.6%)	4 (10%)	0.382
Use of antiplatelet agent	10 (14%)	9 (23%)	0.245
Laboratory finding, n (%)			
Thrombocytopenia (<50,000 mm <sup>3</sup> )	7 (10%)	1 (2.5%)	0.155
Prolonged prothrombin time (INR >1.4)	8 (11%)	6 (15%)	0.551
Presence of causative vascular abnormality, n (%)	32 (44%)	14 (35%)	0.330
Additional treatment for causative vascular abnormality, n (%)	21 (29%)	8 (20%)	0.583
Modified Graeb score (mean, ranges)	12.3 $\pm$ 7.4	21.1 $\pm$ 6.9	<0.001*
Transverse diameter of 3 <sup>rd</sup> ventricle (mm, mean $\pm$ SD)	8.8 $\pm$ 3.6	14.4 $\pm$ 5.0	<0.001*
AP diameter of 4 <sup>th</sup> ventricle (mm, mean $\pm$ SD)	10.9 $\pm$ 4.1	17.5 $\pm$ 7.0	<0.001*
Transverse diameter of 4 <sup>th</sup> ventricle (mm, mean $\pm$ SD)	16.7 $\pm$ 4.9	21.7 $\pm$ 5.3	<0.001*
Dominant side temporal horn size (mm, mean $\pm$ SD)	6.5 $\pm$ 3.3	11.9 $\pm$ 7.4	0.001*
Presence of hydrocephalus (n, %)	24 (33%)	29 (73%)	<0.001*
External ventricular drainage (n, %)	15 (21%)	31 (78%)	<0.001*

AP – anteroposterior; INR – International Normalized Ratio; SD – standard deviation. \* Indicates statistically significant difference of  $p < 0.05$ .

hydrocephalus, and whether there was a need to perform EVD in the patient. Ventricular hematoma volume (as assessed by mGS), the size of the third and fourth ventricles, and the size of the temporal horn of the dominant lateral ventricle were significantly larger in the unfavorable outcome group than in the favorable group ( $p < 0.05$  for all factors).

### Evaluation of prognostic factors

Table 3 summarizes the results of the logistic regression analysis performed on the clinical/radiological characteristics and clinical outcomes. The results of the univariate analysis indicate that older age ( $\geq 55$  years), low initial GCS score (GCS <13),

high SAPS II (SAPS II  $\geq 33$ ), high mGS score, increased transverse diameter (>10 mm) of the third ventricle, increased AP (>12.5 mm) or transverse (>20 mm) diameter of the fourth ventricle, an increase in both the AP (>12.5 mm) and transverse (>20 mm) diameters of the fourth ventricle, a dominant-side temporal horn size of over 6 mm, the presence of hydrocephalus, and performance of EVD are all significantly associated with poor outcomes in patients with PIVH. Results of the multivariate analysis indicate that low GCS scores during initial presentation (GCS <13), severe illness within 24 hours of admission (SAPS II  $\geq 33$ ), and dilatation of the fourth ventricle in both the AP and transverse directions are independent factors associated with clinical outcomes.

**Table 3.** Results of univariate and multivariate analysis for outcome in patients with primary intraventricular hemorrhage.

Variables	Univariate			Multivariate		
	OR	95% CI	p value	OR	95% CI	p value
Age ≥55 years	2.8	1.2–10.1	0.002*	1.1	0.6–2.2	0.354
Initial GCS score <13	4.5	1.3–15.7	<0.001*	3.5	1.2–5.8	0.015*
SAPS II ≥33	4.4	1.9–10.1	<0.001*	2.9	1.1–4.8	0.039*
Modified Graeb score	1.4	1.1–2.0	<0.001*	1.0	0.6–2.0	0.478
Dilated 3 <sup>rd</sup> ventricle(>10 mm)	10.0	3.9–26.1	<0.001*	1.8	0.9–2.8	0.161
Dilated AP diameter of 4 <sup>th</sup> ventricle (>12.5 mm)	4.7	2.0–10.8	<0.001*	0.8	0.5–1.3	0.452
Dilated transversediameter of 4 <sup>th</sup> ventricle (>20 mm)	3.6	1.5–8.7	0.004*	1.2	0.5–1.6	0.222
Dilated AP (>12.5 mm) and transverse diameter(>20 mm) of 4 <sup>th</sup> ventricle	8.4	3.4–21.0	<0.001*	2.6	1.1–4.6	0.043*
Dilated dominant sidetemporal horn (>6 mm)	4.7	1.8–12.0	0.001*	1.3	0.4–2.0	0.403
Hydrocephalus	5.3	2.3–12.3	<0.001*	0.9	0.3–2.9	0.643
External ventricular drainage	13.1	5.1–33.3	<0.001*	1.1	0.3–1.8	0.325

AP – anteroposterior; CI – confidence interval; GCS – Glasgow Coma Scale; OR – odds ratio; SAPS II – Simplified Acute Physiology Score. \* Indicates statistically significant difference of  $p < 0.05$ .

### Case illustrations

#### Case 1 (Figure 3)

A 50-year-old man with hypertension presented with sudden onset of headache, followed by altered mental status (GCS 9). Brain CT demonstrated a massive pure IVH. The patient's mGS was 22. Although hydrocephalus was not observed (Evans ratio=0.27), the patient presented with fourth ventricle obstruction. EVD was performed through the left Kocher's point and his GCS score recovered to 15. TFCA did not identify the predisposing vascular pathology. With conservative care and EVD management, the patient was discharged 3 weeks later without any neurologic deficits.

#### Case 2 (Figure 4)

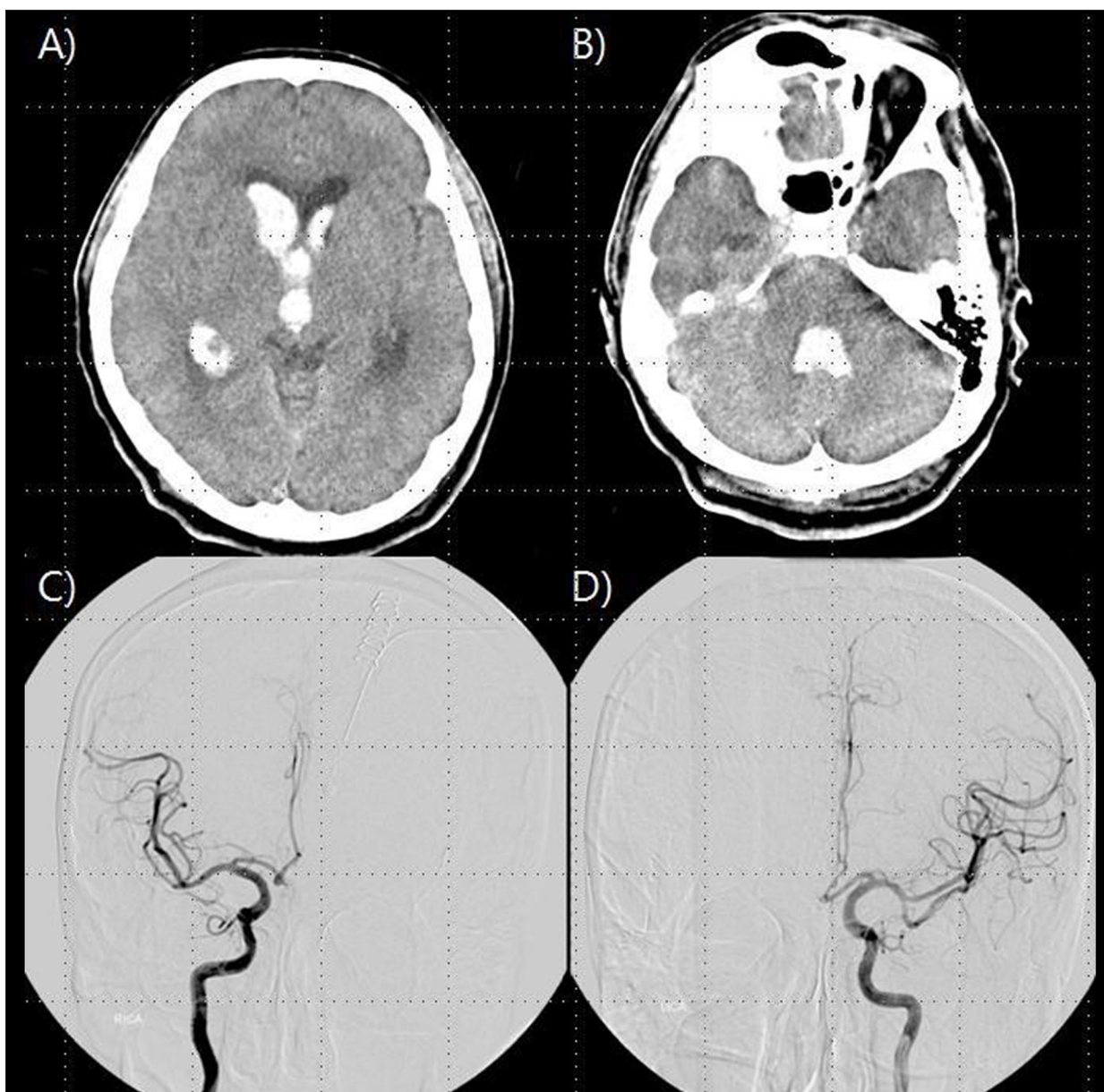
A 78-year-old woman with a history of hypertension presented with sudden onset of altered mental status (GCS 3). She had been taking an antihypertensive agent and an antiplatelet agent. Initial brain CT demonstrated a massive pure IVH. The patient's mGS was 27 and hydrocephalus was observed. EVD was performed through the right Kocher's point. Despite administration of osmotic diuretics and EVD management, the patient's ICP remained high. CT angiography showed no

vascular abnormalities. The patient died on the sixth in-patient day due to intractable increased ICP.

### Discussion

In the present study, we investigated the prognostic factors that contribute to clinical outcomes in patients with PIVH. Importantly, we found that low GCS at ictus and an increase in the diameter of the fourth ventricle in both the AP and transverse directions were independent factors that predicted poor outcome.

PIVH is associated with several possible causative factors, including hypertension, arteriovenous malformation, cerebral aneurysm, tumor, coagulopathy, vasculitis, and choroid plexus cysts [1,4,21–28]. A history of hypertension has been consistently reported as a major risk factor for spontaneous intracranial hemorrhage, and is responsible for 38–80% of PIVH cases [1,5,13,27,29]. In the current study, while many patients had a history of hypertension, pre-existing hypertension itself was not found to affect patient outcome. Although the prognostic value of premorbid hypertension for outcome determination has not yet been fully investigated, intensive antihypertensive treatment during the acute phase has been noted

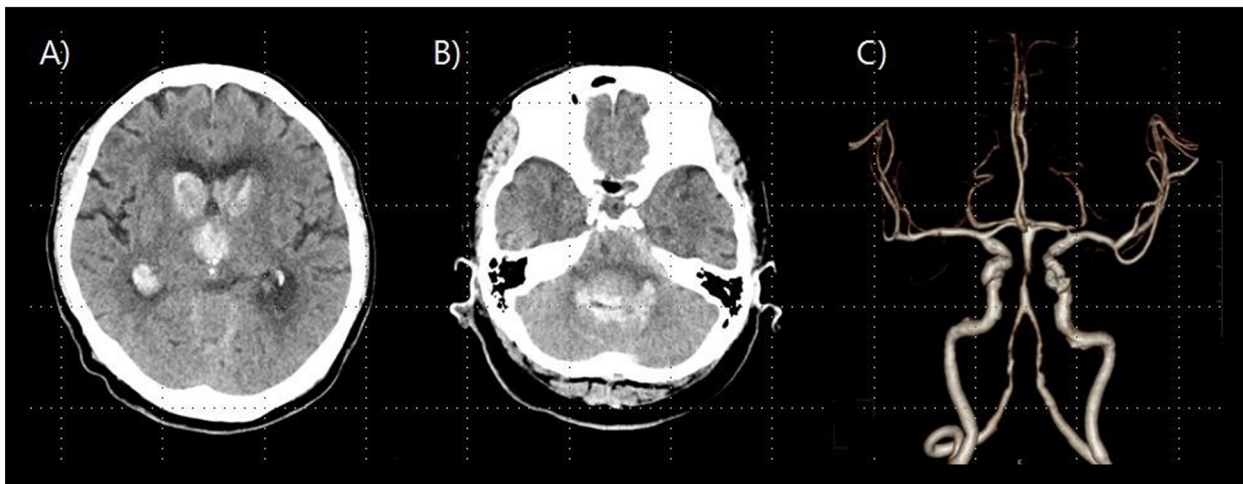


**Figure 3.** Case Illustration 1. A 50-year-old man presented with altered mental status of acute onset. Initial brain CT indicated primary intraventricular hemorrhage – A and B. Transfemoral cerebral angiography showed no vascular anomalies accounting for the primary intraventricular hemorrhage – C and D.

to improve clinical outcomes [30]. A recent randomized controlled trial in 2839 patients with ICH demonstrated that early intensive interventions to lower blood pressure toward a target systolic level of <140 mmHg improved functional outcomes, although the mortality rate was not affected [31,32]. Therefore, strict blood pressure control during the acute phase of PIVH may be critical to improving clinical outcome. In this study, we evaluated the presence of predisposing vascular abnormalities using conventional cerebral angiography and/or CT/MR angiography, and found that nearly half of the angiographically examined patients had presumptive pathologies

for their IVH, which included Moyamoya disease, AVM, and a ruptured cerebral aneurysm. A previous review study including 339 PIVH patients in 14 case series reported the rates of AVM, aneurysms, and Moyamoya disease as 31%, 22%, and 3%, respectively [14]. We found a relatively higher incidence of Moyamoya disease than was found in previous series. This might be explained by the fact that this disease is more prevalent among East Asian populations [33,34]. The present study also indicates that patients with underlying vascular pathologies leading to PIVH are younger than those with normal angiographic results. This indicates that additional diagnostic





**Figure 4.** Case Illustration 2. A 78-year-old woman presented with altered mental status of acute onset. Initial brain CT showed a primary intraventricular hemorrhage – A and B. CT angiography indicated no vascular anomalies accounting for the primary intraventricular hemorrhage – C.

imaging should be performed in cases of PIVH to detect underlying pathologies, especially in young patients. Neither the presence of causative vascular abnormalities nor the treatment of the underlying lesions affected the short-term clinical outcome of PIVH in our study. The comparable outcomes observed between patients with causative predisposing vascular lesions and those without obvious vascular pathologies may be attributed to the absence of re-hemorrhage during early period regardless of treatment for underlying vascular etiologies. Although the efficacies of the treatments for aneurysms, AVM, and Moyamoya disease were not defined by measurements of short-term outcomes in the present study, we believe that treatment of the vascular causal factors may enhance long-term outcomes by reducing the risk of re-bleeding in the group of PIVH patients who had vascular predisposing factors. How many of the 13 patients who did not have angiographic studies had possible vascular causes for PIVH is not known, and this might have affected the outcome results. Thus, the lack of difference in neurological outcomes between patients with and without possible vascular etiology of PIVH must be interpreted with caution. Further studies and additional follow-up are warranted to document the influence of vascular etiologies on the prognosis of PIVH.

There is considerable variability in the results of previous studies that have attempted to determine factors associated with outcome in cases of PIVH [1,15,25,27,35].

McCallum et al. [16] reported the clinical outcomes of 23 patients with intraventricular hemorrhage, showing that 13 patients were dead within a mean of 2.3 days, and the consciousness level during the initial attack was considered to be a major factor affecting neurological outcome. Similarly, in a study of 15 patients with pure intraventricular hemorrhage,

Jayakumar et al. [15] reported 0% mortality in patients with normal or mildly disturbed mental status at presentation, whereas 100% of initially decerebrating patients died. Interestingly, the outcomes for the patients were either good or death, indicating that none of the surviving patients had any significant neurological deficits. The lack of parenchymal damage in PIVH was considered to be the cause of this extremely different outcome. In addition to initial consciousness level, the authors noted that the amount of hematoma in the ventricle, the occurrence of hematoma in the cistern, hydrocephalus, and brain atrophy are all prognostic factors. Flint et al. [14] reported their experience with 15 cases of PIVH. In their series, the majority (80%) of patients presented with altered mental status at ictus, and EVD was performed in 11 patients (73%). One patient (7%) died while hospitalized and 8 patients (53%) recovered to an independent neurological status. Based on systematic review, the authors noted that patient age and the amount of IVH independently predicted in-hospital mortality. A recent study of 12 patients with PIVH indicated a 41.7% mortality rate during a median of 18.5 days of hospital stay [13]. In this study, very old age ( $\geq 85$  years) was associated with patient death. In the series, 1 patient (8.3%) underwent surgical intervention (EVD), and 6 of the 7 survivors had moderate or severe disability at discharge (modified Rankin scale grade 3 or more). By comparing 133 subcortical hemorrhages, the authors noted that very old age ( $\geq 85$  years), atrial fibrillation, headache, and altered consciousness at onset are independent predictors of PIVH. The relatively high mortality and poor neurological outcomes in this series are likely to be associated with the old age of the study population (mean age: 79 years). In another recent analysis of 24 patients with PIVH, a low initial GCS score ( $\leq 8$ ), low full outline of unresponsiveness score ( $\leq 10$ ), and development of early hydrocephalus were thought to be independent predictors of mortality [5]. Lee et al. [36]

found that IVH itself is not a direct cause of death, but rather acts in conjunction with altered cerebrospinal fluid circulation following ventricular hemorrhage, cerebral edema, or increased intracranial pressure. Furthermore, the authors state that the level of consciousness during the initial presentation, the cause of ventricular hemorrhage, amount of ventricular dilation, shifting of the midline structure, and hemorrhagic patterns are all key aspects influencing prognosis in patients with PIVH. In an analysis of 50 patients with CT-documented fourth IVH, Shapiro et al. [19] suggested that the hemorrhagic dilation of the fourth ventricle is an ominous finding, as all patients with this symptom died despite aggressive therapy. Autopsies of these patients revealed medullopontine softening on gross examination, and multiple pontine microinfarcts upon histological assessment. Consistent with these results, our data indicate that dilation of the fourth ventricle to diameters of over 20 and 12.5 mm in the transverse and AP directions, respectively, is an independent unfavorable prognostic factor, as well as a lower GCS score at ictus. Taken together, it seems that hemorrhagic dilation of the fourth ventricle, followed by a sudden increase in intraventricular pressure, places pressure on the brain stem and impairs perforator perfusion. This may promote irreversible ischemic injury to the brain stem, which is the major control center for consciousness and respiration.

SAPS II is widely used in the general ICU for grading derangements in the physiologic homeostasis of individual patients, as well as for prognostic calculations [18,37]. In the present study, SAPS II score, obtained within 24 hours of admission, was significantly associated with neurological outcomes in patients with PIVH, which is consistent with the results of other types of stroke [38–40]. This is partly explained by the fact that both GCS and age, which are well known potential prognostic factors of stroke, are major components of the scoring system. To verify how the severity of systemic illness and extracerebral organ dysfunction play important roles in the prognoses of patients with PIVH, further studies analyzing the relationships between individual variables that contribute to the overall SAPS II and patients' outcomes will be necessary.

The overall mortality rate in the present study was 19%. Sixteen percent of the patients likely died as a direct consequence of PIVH within a week of their initial presentation. Three months later, nearly two-thirds (64%) of all patients presented with favorable outcomes. The majority of the survivors (80%) had no deficits or mild deficits ( $GOS \geq 4$ ). The reported rate of poor outcome following a large series of intracerebral hemorrhages ranges from 49% to 78%. Therefore, the neurological prognosis of PIVH is likely superior to that of intracerebral hemorrhage [41,42]. This relatively favorable neurological course for PIVH might be associated with comparatively little brain parenchymal damage.

Coagulopathy, including anticoagulant or antiplatelet agent therapy, is a proven risk factor for hemorrhagic stroke [5,13,27,29,30,43]. The number of patients who had coagulopathy or thrombocytopenia in our study was congruent with the results of previous studies [15,22,25,27,35,44]. Anticoagulant-associated hemorrhagic stroke is associated with an increased risk of hematoma expansion and a higher mortality rate [45–47]. However, we found that a medical history of anticoagulant or antiplatelet agent use, or coagulopathy did not affect clinical outcome. This discrepancy may partly be explained by the aggressive reversal of anticoagulation during the hyper-acute phase in the subjects, which can prevent hematoma expansion or re-bleeding. There are many reports demonstrating that clinical improvement can be achieved through the reversal of thrombocytopenia and coagulopathy [30,48–50]. Recently, patients with severe coagulation factor deficiency or severe thrombocytopenia have been recommended to receive appropriate factor replacement therapy or platelets, respectively [30]. Therefore, adequate use of hemostatic agents and transfusion of blood should be considered when managing patients with PIVH. Although the optimal time to resume anticoagulants or antiplatelet agents after ICH or IVH is uncertain, current guidelines recommend the avoidance of oral anticoagulation medication for at least 4 weeks to lower the risk of recurrence [30,49,51].

A standard treatment plan for PIVH has not yet been established. Although various treatment protocols including supportive medical treatments, steroids, antihypertensive agents, and EVD methods are in use, there is still controversy surrounding the effects of these methods. In the present study, many of the patients received EVD, of whom the majority displayed unfavorable outcomes ( $GOS < 4$ ). Considering that EVD was conducted primarily in those who had poor consciousness levels with significant hydrocephalus, which might be associated with a poor prognosis, it is difficult to judge the effects of the treatment modality by itself. Recently, several small studies of intraventricular thrombolysis in combination with EVD have shown promising results in patients with IVH [52–54]. These studies suggest that thrombolytic treatment hastens the clearance of ventricular hematomas and normalizes ICP. In a review of 7 independent studies using intraventricular thrombolytic agents in patients with IVH, good neurologic outcomes were observed in 50 of the 74 patients [55]. However, the procedure was associated with serious complications, including bacterial meningitis ( $n=5$ ), increased hematoma volume ( $n=1$ ), and extradural hematomas ( $n=2$ ). Although there is anecdotal evidence for the safety of this treatment and its possible therapeutic value, there is insufficient evidence to support its clinical efficacy. Therefore, a large, randomized, prospective study of thrombolytic treatment in PIVH is needed.

There are several limitations to this study. First, this was a retrospective study. As a result, there was potential for significant

selection bias. Second, the number of patients enrolled in this study was relatively small, especially for the group of unfavorable-outcome patients. This limited our ability to subdivide the patient groups into co-affecting area and systemic complication groups. Additionally, different surgeons with different treatment preferences undertook the patients' care, adding to between-patient variability. Other unmeasurable underlying differences between the groups may have confounded our results. A further study in a larger number of patients and a scrupulous prospective set of clinical data is required to gain more accurate knowledge of predictive factors for patients with spontaneous primary intraventricular hemorrhage.

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## Conclusions

The overall mortality of PIVH in our study was 19%. Most deaths occurred within 1 week of initial presentation and were a direct consequence of PIVH. Most survivors had relatively satisfactory neurological outcomes. Initial GCS score, severity of illness as indicated by SAPS II, and dilatation of the fourth ventricle in both the AP and transverse directions were identified as major independent prognostic factors. Predisposing vascular abnormalities such as Moyamoya disease, AVM, or cerebral aneurysm were identified in nearly half of the PIVH patients. Routine angiography should be included in the examination and diagnosis of patients with PIVH to identify potentially treatable causes of the hemorrhage.

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