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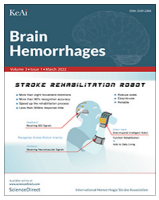

Research Article

Evolving approaches in the management of patients with subarachnoid hemorrhage from 2002 to 2022: The impact of clazosentan and treatment modalities on outcomes

Hajime Maeda [a,b], Tsuyoshi Izumo [a,*], Kazuaki Okamura [a], Susumu Yamaguchi [c], Yoichi Morofuji [a], Takayuki Matsuo [a]

[a] Department of Neurosurgery, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki 852-8501, Japan
[b] Department of Neurosurgery, Nagasaki Rosai Hospital, Nagasaki 857-0134, Japan
[c] Department of Neurosurgery, Sasebo City General Hospital, Nagasaki 857-8511, Japan

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ABSTRACT

Objective: This study aimed to assess the changes in patient demographics, aneurysm characteristics, and treatment modalities for subarachnoid hemorrhage (SAH) over the past two decades.
Methods: We analyzed SAH 6,446 patients between 2002 and 2022, which was divided into three periods: 2002–2011 (FP), 2012–2021 (SP), and post-clazosentan 2022 (PC). The final cohort included 2878, 2016, and 152 patients in FP, SP, and PC groups, respectively. We examined patient demographics, surgical procedures, spasm prevention therapy, and delayed ischemic neurological deficits (DIND).
Results: The mean age of the patients increased over the study period (64, 66, and 68 years in FP, SP, and PC groups, respectively). Clipping was the predominant method during FP (79 %); however, coiling surpassed clipping in 2022 (coiling vs. clipping, 47 % vs. 46.3 %). Before clazosentan introduction, fasudil was the primary spasm prevention treatment (>80 %); however, its use decreased (63.9 %) after clazosentan introduction. DIND varied across FP, SP, and PC groups (37.4 %, 24.2 %, and 16.7 % respectively). Age and generation were significantly associated with DIND and irreversibility.
Conclusion: Regarding the management of patients with SAH, shift from clipping to coiling, and the introduction of new spasm prevention treatments such as clazosentan were observed, led to a decrease in DIND.

1. Introduction

Subarachnoid hemorrhage (SAH) is a life-threatening intractable condition. Most SAHs are caused by ruptured intracranial aneurysms; however, arterial dissection, cerebral arteriovenous malformation, dural arteriovenous fistula, other trauma, or an unknown source of bleeding are also known to cause SAH.[1–3] The sequelae caused by cerebral vasospasm, which can occur between a few days and 2 weeks after the onset of hemorrhage, are important factors in disease prognosis. Clot hemolysis and the release of vasoconstricting agents may contribute to cerebral vasospasm, which typically begins approximately 3 days after SAH onset, peaks in severity on days 8–11, and resolves by day 21.[4] Cerebral vasospasm leads to delayed ischemic neurological deficits (DIND) in 17–40 % of patients with aneurysmal SAH.[5] If the degree of vasospasm is mild or if spasm treatment is successful, the symptoms may be transient (reversible DIND), but approximately half of the patients will have irreversible vasospasm resulting in cerebral infarction (irreversible DIND).[5] The treatment of cerebral vasospasm post-SAH includes hematoma removal, systemic pharmacotherapy, improvement of cerebral circulation, and endovascular therapy.

Aneurysmal SAH treatment in Japan has changed over time. Microsurgery was first performed in the 1970s, Guglielmi detach-

Abbreviations: DIND, delayed ischemic neurological deficits; SAH, subarachnoid hemorrhage; FP, the period from 2002 to 2011; SP, the period from 2012 to 2021; PC, the post-clazosentan period in 2022; WFNS, World Federation of Neurosurgical Societies; mRS, modified Rankin scale; OR, odds ratio; CI, confidence interval; GCS, Glasgow Coma Scale.

* Corresponding author at: Department of Neurosurgery, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki 852-8501, Japan (T. Izumo).
E-mail address: go-izumo@hotmail.co.jp (T. Izumo).

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able coils were introduced in 1997, and endovascular treatment was introduced more aggressively following the report of the International Subarachnoid Aneurysm Trial[6] in 2002. A neuro-shaker was used to prevent cerebral vasospasm when clipping was introduced. Regarding changes in pharmacological treatments, ozagrel sodium was introduced in 1988, and fasudil was introduced in 1995. Triple H therapy, comprising induced hypertension, hypervolemia, and hemodilution, was used for some time; however, its use gradually declined after the 2010s as evidence accumulated. In 2010, the efficacy of cilostazol was reported,[7] and its use gradually increased. During the extreme phase of vasospasm, percutaneous transluminal angioplasty and/or superselective arterial administration of fasudil have been reported in endovascular therapy, and their use has increased.

The Japanese Stroke Treatment Guidelines 2021 recommend the systemic administration of fasdil and ozagrel sodium. These therapies are classified as Recommendation B (moderate recommendation), suggesting their reasonable use. However, evidence supporting this recommendation is derived from observational studies, unsystematized clinical experience, and multiple RCTs with major limitations. Therefore, the estimated effects are uncertain. Other available therapies included triple H therapy, intermittent intracisternal urokinase injection, and continuous intravenous infusion of low-dose nicardipine (a calcium channel blocker). Despite several studies reporting the limited efficacy of these therapies, there is no consensus regarding their use for DIND.[8–10] A recent study from Japan indicates that treatment with clazosentan improves patient morbidity/mortality and poor outcomes by 50 % compared with conventional vasospasm treatment.[11] On the other hand, it was reported that it did not improve patient conversion,[12] and add-on fasudil after clazosentan use did not improve conversion and had many side effects.[13]

The Nagasaki SAH Registry, a multicenter cooperative study conducted by Nagasaki University and affiliated institutions, was initiated in 1989. While approximately 350–400 patients were registered annually from 2000 to 2010, the number has gradually decreased. As of 2022, there were 175 registered patients, approximately half of the original number. The registry compiles data on patient background, treatment modalities, and outcomes annually.

Herein, we conducted a retrospective analysis of the complete enumeration data from the Nagasaki SAH Registry[14–16] to elucidate changes in vasospasm therapy and its effects.

2. Method

2.1. Study design and participants

This study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Institutional Review Board of Nagasaki University Hospital (No. 23082109). We obtained verbal informed consent from all participants. If verbal informed consent was not obtainable, we summarized our research on the institute website and allowed the participants to decline their participation.

The study outcomes were the association between vasospasm treatment and the onset of DIND, its reversibility, outcomes, and favorable prognosis (defined as a modified Rankin scale [mRS] score of 0–2, the patient was able to live independently). The study duration was divided into three periods: from 2002 to 2011 (First period: FP); from 2012 to before the introduction of clazosentan in 2021 (Second period: SP); and a subsequent 1-year period in 2022 post-clazosentan introduction (PC). The data used in this study were collected from 3,672 (FP), 2,601 (SP), and 173 (PC) patients who experienced subarachnoid hemorrhage (SAH) and were treated at our university hospital and ten affiliated hospitals in Nagasaki SAH Registry Study group.

2.2. Diagnostic procedures and patient management

Herein, SAHs were primarily due to aneurysm ruptures. Other causes included intracranial arterial dissection, arteriovenous malformations, dural arteriovenous malformations, and unknown bleeding sources.. Patients under 18 years of age were excludes because they are atypical and may have different courses than those with ruptured aneurysms in normal adults. Those patients who were in poor condition at the time of the visit and did not receive treatment were excluded because they were not eligible for treatment comparisons. The registry included patient background information such as the presence of hypertension, diabetes mellitus, previous cerebrovascular disease, and heart disease, SAH severity as per the World Federation of Neurosurgical Societies (WFNS) 1–5 scale, vasospasm treatment, presence of ischemic symptoms due to vasospasm, reversibility of ischemic symptoms, and patient outcomes. Patients' prognosis was evaluated using the modified Rankin scale, with a modified Rankin scale of 0–2 defined as an independent activity of daily living (ADL) and indicating a good prognosis.

Neurosurgical patients are first evaluated at the time of presentation with Glasgow coma scale (GCS) for level of consciousness and neurological findings. Patients with sudden headache, vomiting, and consciousness disturbances indicative of SAH were promptly diagnosed using computed tomography or magnetic resonance imaging upon arrival at the hospital. Contrast-enhanced computed tomography angiography was performed using an intravenous contrast medium to identify the source of the bleeding. Magnetic resonance angiography was also performed as required. Patients with known SAH are evaluated for WFNS grade based on neurological findings and level of consciousness, and the Fisher group is determined from initial Computed tomography imaging. The WFNS grade is determined as follows; Grade1: GCS 15, Grade2: GCS13-14, without focal neurological deficit, grade3: GCS 13–14, with focal neurological deficit, grade4: GCS7-12, grade5: GCS3-6. The Fisher group, on the other hand, is determined follows; Group1: no bleeds detected, Group2: a diffuse deposition or thin layer with all vertical layers of blood less than 1 mm thick, Group3: Localized clots and/or ventrical layers of blood 1 mm or greater in thickness, Group4: Diffuse no arachnoid blood, but with intracerebral or intraventricular clots. Although there is no Group5 in the original classification, we newly defined Group5 as group3 with intracerebral hematoma. Based on the cause of bleeding and factors such as the location, size, and shape of the ruptured aneurysm, a decision between surgical or endovascular treatment was made, usually within 72 h, to prevent re-rupture. Bed rest with systolic blood pressure maintained below 120 mmHg, controlled lighting, and sedation (light or complete), as deemed appropriate, were maintained until surgery. Usually, after prophylaxis against re-rupture, treatment to prevent subsequent cerebral vasospasms continues for two to three weeks. Before the introduction of clazosentan, fasudil and ozagrel sodium were commonly administered according to expert consensus and the Japanese Guidelines for the Management of Stroke (2004), along with cilostazol and hypervolemic therapy, as needed. In our institute, before the introduction of clazosentan, ozagrel was used first if endovascular re-rupture prevention surgery was performed, and fasdil was added approximately 1 week after the spasm tendency became more apparent. Fasdil was used first in patients who underwent direct surgery, and ozagrel was added approximately 1 week later. After the launch of clazosentan in 2022, clazosentan was the primary treatment for vasospasm, except in specific cases, for example, if the patient was old, had a heart condition, or had allergies.

Endovascular percutaneous transluminal angioplasty or superselective arterial injection of fasdil was used for significant vasospasm and DIND. In patients who underwent surgery, cerebral cistern drainage was used for SAH clearance or intracranial pressure control; in contrast, spinal drainage was used in patients who underwent endovascular management. Cerebrospinal fluid management spanned 1–2 weeks, with drainage replacement or extension performed due to infection or obstruction. Although currently less common due to a lack of evidence, intermittent intracisternal urokinase injection therapy through a cisternal drainage tube was employed in the past. Stable patients received rehabilitation to prevent disuse and improve activities of daily living (ADLs) during the early postoperative period. Following stabilization of vasospasm, patients with enlarged ventricles were evaluated for ventriculoperitoneal or lumber arachnoid-peritoneal shunting if necessary. Finally, patients were discharged if they were capable of independent standing for ADLs (good outcome, the modified Rankin Scale (mRS) score 0–2), transferred to a rehabilitation hospital if needed, or moved to a convalescent hospital if no improvement occurred. The final ADLs were assessed using the modified Rankin scale (mRS) score at discharge.

2.3. Statistical analysis

The demographic and clinical data are presented as frequencies and percentages for categorical variables and medians (interquartile range) for continuous variables. GCS, WFNS and Fisher grades on admission were considered ordinal variables. Logistic regression analyses were performed to evaluate DIND incidence, DIND reversibility, and patient outcomes (a good outcome was defined mRS 0–2). Intergroup differences were assessed using Fisher's exact test for categorical variables. Characteristics of patients with SAH and vasospasm therapy-related variables associated with the logistic regression analyses were investigated, and odds ratios (ORs) and 95 % confidence intervals (CIs) were estimated. Small p-values were evaluated using logWorth (-log10[p-value]); a smaller p-value corresponded to a greater logWorth value and vice versa. If the logWorth value was zero, the p-value was set to 1. If the logWorth value was > 2, the p-value was $\leq$ 0.01.

3. Results

3.1. Demographic and clinical data

A total of 6,446 patients who developed SAH between January 1, 2002, and December 31, 2022, were assessed for eligibility. After applying the exclusion criteria, the final analysis included 2,878 patients in the FP group, 2,016 patients in the SP group, and 152 patients in the PC group. The key patient characteristics are summarized in Table 1. The mean ages of the FP, SP, and PC groups were 64 (57–74), 66 (54–76), and 68 (57–77) years, respectively. Approximately 70 % of the patients in all groups were women. The underlying conditions included hypertension in approximately 50 % of patients, diabetes mellitus in approximately 5 % of patients, heart disease in approximately 7 % of patients, and previous cerebrovascular disease in 6.7–7.5 %. The prevalence of smoking was 25–29 %. Incidence of hyperlipidemia increased from 4.3 % in the FP group to 8.7 % in the SP group and was present in 9.9 % of patients in the PC group. In the FP, SP, and PC groups, patients with WFNS grade 1–2 and mild disease accounted for approximately 60 % of patients (60.9 %, 57.1 %, and 55.9 %, respectively), while those with grade 4–5 and severe disease accounted for 34.3 %, 29.5 %, and 38.1 %, respectively. Fisher group 3 represented approximately 70 % of the cases; hematomas were present in approximately 8.5–10 % of patients.

Table 1
Summary of various stratified by generations.

Characteristics	FP	SP	PC
No	2878	2016	152
Age	64.0(54–74)	66(54–76)	68(57–77)
Sex			
Male	836	608	46
Female(%)	2038(70.9)	1408(69.8)	106(69.7)
Aneurysm location			
AcoA	767(26.7)	497(24.7)	38(25)
ICA	854(29.7)	640(31.7)	47(30.9)
MCA	715(24.8)	484(24.0)	39(25.7)
AC distal	171(5.9)	103(5.1)	5(3.3)
BA	124(4.3)	72(3.6)	6(3.9)
VA	123(4.2)	123(6.1)	8(5.2)
Others	113(3.9)	91(4.5)	7(4.6)
Unknown	11(3.8)	6(0.3)	2(1.3)
Anterior circulation	2534(88.4)	1750(87.1)	133(87.5)
Posterior circulation	333(11.6)	260(12.9)	19(12.5)
Missing	11	6	0
Size			
≧5mm	919(32.6)	801(40.1)	55(36.7)
5–9 mm	1478(52.5)	947(47.4)	67(44.7)
10–24 mm	393(14.0)	240(12.0)	27(18.0)
≦25 mm	26(0.9)	11(0.6)	1(0.7)
Missing	62	17	2
mRS (Pre)			
0–2	–	1259(94.7)	136(92.5)
Missing	All	687	5
Past history			
HTN	1353(47.6)	1052(48.7)	74(48.7)
DM	117(4.1)	125(6.2)	9(5.9)
CVD	204(7)	211(10.5)	10(6.6)
HD	194(6.7)	150(7.5)	11(7.2)
HL	123(4.3)	174(8.7)	15(9.9)
Smoking	694(25.4)	556(28.1)	44(28.9)
WFNS grade			
1	1001(34.8)	617(30.6)	44(28.9)
2	750(26.1)	534(26.5)	41(27.0)
3	109(3.8)	84(4.2)	9(5.9)
4	531(18.5)	363(18)	18(11.8)
5	483(16.8)	418(20.7)	40(26.3)
Missing	4	0	0
Fisher group			
1,2	622(21.7)	293(14.6)	8(5.2)
3	2004(69.8)	1506(74.9)	107(70.4)
4	204(7.1)	160(8.0)	14(9.2)
5	40(1.4)	52(2.6)	23(1.5)
Missing	12	5	0

Figures in () in the table indicate percentages. AP; First period, SP; Second period, PC; Post clazosentan period, AcoA; Acom artery aneurysm, ICA; Internal carotid artery aneurysm, MCA; Middle cerebral aneurysm, AC distal; Anterior cerebral artery distal aneurysm, BA; Basilar artery aneurysm,VA; Vertebral artery aneurysm, mRS; modified Rankin scale, HT; Hypertention, DM; Diabetas mellitas, CVD; Cerebral vascular disease, HD; Heart disease, HL; Hyper lipidemia.
Information on mRS were all missing during the AP phase.

3.2. Cause of bleeding and aneurysm characteristics

Ruptured aneurysms exhibited a similar distribution across the three periods. Aneurysms in the anterior communicating and middle cerebral arteries accounted for approximately 25 % of all cases each, whereas those in the internal carotid artery were observed in approximately 30 % of cases. Anterior circulation was involved in less than 90 % of the cases. Ruptured aneurysms measuring $\leq$ 10 mm constituted approximately 85 % of cases, with aneurysms $\leq$ 5 mm constituting 32.6 %, 40.1 %, and 36.7 % cases in FP, SP, and PC groups.

3.3. Surgical procedures to prevent rebleeding (Fig. 1)

In the FP group, 79 % of patients underwent clipping, 16 % underwent coiling, and 4.6% underwent other procedures such

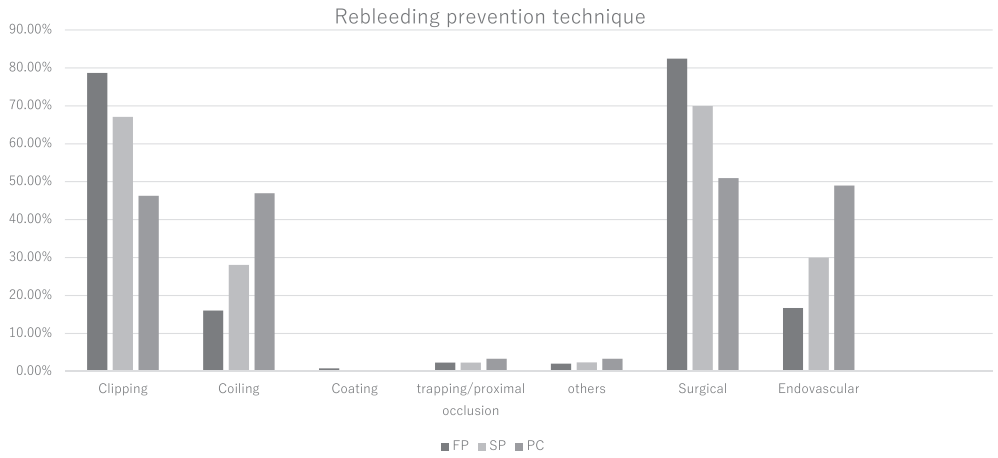

Fig. 1. Prophylactic methods for SAH rebleeding. Other procedures include drainage surgery, internal or external decompression surgery, and trial craniotomies. Trapping involves both surgical and endovascular procedures. FP: First Period, SP: Second Period, PC: post-clazosentan period.

as coating, trapping, and drainage. However, over the years, the prevalence of endovascular procedures, including coiling, has increased and surpassed clipping in 2022 (clipping vs. coiling, 46.3 % vs. 47.0 %). Endovascular therapy has become the primary approach to prevent rebleeding.

3.4. Spasm prevention therapy (Fig. 2)

Before the introduction of clazosentan, in the FP group, treatment modalities included hypervolemia/hypertension (2H) in 16.9 % of cases, intravenous fasudil (Fas) in 81.9 %, intravenous ozagrel (Oza) in 54.8 %, intracisternal urokinase injection therapy through a drainage tube (UK) in 15.8 %, oral cilostazol (CSZ) in 1.0 %, and low-dose continuous intravenous administration of nicardipine (Nic) in 0.8 % of patients. In the subsequent decade (SP group), these treatment percentages changed as follows; 16.6 % (2H), 84.25 % (Fas), 54.04 % (Oza), 7.98 % (UK), 14.71 % (CSZ), and 4.0 % (Nic), respectively. However, after the introduction of clazosentan, the use of fasudil decreased to 63.8 %, the use of ozagrel almost remained unchanged at 53.3 %, cilostazol was used in 224.3 % of patients, hypervolemia/hypertension in 9.2 % of patients, nicardipine in 3.3 % of patients, and the urokinase use was almost discontinued (in 0.66 % of patients).

3.5. DIND and reversibility (Fig. 3)

In the FP, SP, and PC groups, DIND was observed in 1803 (37.4 %), 489 (24.2 %), and 25 (16.7 %) patients, respectively, and it was irreversible in 577 (53.3 %), 225 (46.1 %), and 11 (45.8 %) patients, respectively. The most relevant factor was shunt surgery (OR 2.49; 95 % CI 2.18–2.85; P < 0.0001), followed by Fisher group, generation, Glasgow Coma Scale (GCS) at presentation (unit OR 1.08; 95 %CI 1.53–3.73; p < 0.001), WFNS grade (Unit OR1.15; 95 %CI 1.04–1.26; p = 0.004). The presence of DIND was not significantly associated with the surgical method, age, and direct surgery or endovascular surgery. Fisher groups 2, 3, 4, and 5 were compared with group 1. The results of the analysis are as follows: group 2 (OR 1.99; 95 % CI 1.03–3.84; p = 0.041), group 3 (OR 3.81; 95 % CI 2.00–7.24; p < 0.0001), group 4 (OR 2.16; 95 % CI1.29–4.92; p < 0.007), group 5 (OR 3.41; 95 % CI 1.57–7.43; p < 0.001). Significant reduction in generation was observed in the comparison of FP and SP groups (OR 0.60; 95 % CI 0.53–0.70; P < 0.001) and the comparison of FP and PC group (OR 0.42; 95 % CI 0.27–0.66; P < 0.001) (Table 2a).

In addition, age was most strongly associated with the irreversibility of DIND (logWorth 3.095, unit OR1.01; 95 % CI 1.01–1.02; p < 0.0001). DIND irreversibility was not significantly associated with shunt surgery, GCS, Fisher group, operation method,

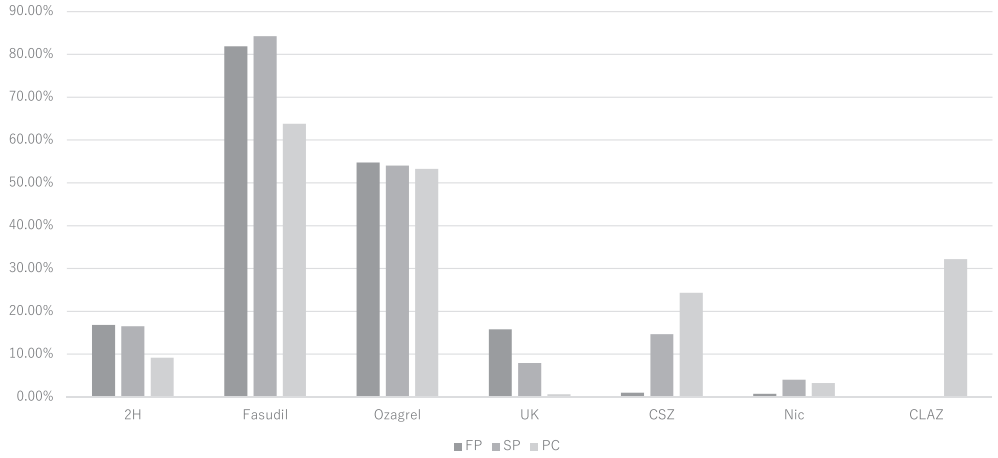

Fig. 2. The therapeutic agents used to treat spasm per period are shown. 2H: Hypervolemia/Hypertension therapy, UK: intracisternal urokinase injection, CSZ: Cilostazol, Nic: Nicardipine low-dose continuous intravenous infusion, CLAZ: Clazosentan.

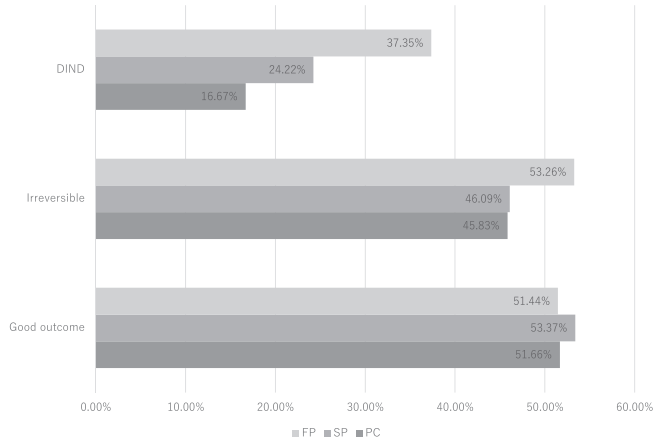

Fig. 3. Percentage of symptomatic spasm (DIND), its irreversibility, and good prognosis in generation. DIND: delayed ischemic neurological deficits, FP: First Period, SP: Second Period, PC: post-clazosentan period.

Table 2
A-c. Result of logistic regression analysis.

DIND

Factor	LogWorth	P value	Odds ratio
Shunt	44.693	<0.0001	2.59
Generation	13.901	<0.0001	0.6(SP/FP) 0.4(PC/SP)
GCS	4.559	<0.0001	1.08*
Fisher group	3.498	<0.0001	
WFNS grade	2.842	0.001	1.15*
Operation method	2.033	0.009	
Age	0.743	0.181	1.30*
Direct/Endovascular therapy(D/E)	0.572	0.268	0.64(D/E)

Irreversible DIND

Factor	LogWorth	P value	Odds ratio
Age	3.095	<0.0001	1.18*
Generation	2.644	0.002	0.68(SP/FP) 0.54(PC/SP)
Shunt	1.298	0.05	1.23
GCS	1.278	0.05	0.94*
Fisher	0.881	0.13	
Operation method	0.317	0.48	
WFNS	0.248	0.58	1.19
Direct/Endovascular therapy(D/E)	0.173	0.67	0.66(D/E)

Good outcome

Factor	LogWorth	P value	Odds ratio
Age	115.110	<0.0001	0.94*
Shunt	42.055	<0.0001	0.36
GCS	15.873	<0.0001	1.18*
Fisher group	8.969	<0.0001	
Operation method	5.831	<0.0001	
WFNS	3.562	<0.0001	0.83*
Generation	2.721	0.002	0.77(SP/FP) 0.88(PC/FP)
Direct/Endovascular therapy	1.739	0.019	2.49(D/E)

Association of each item with Table 2a: DIND, Table 2b:whether DIND is irreversible, and Table 2c: whether the prognosis is favorable.
LogWorth means -Log10(p-Value).
* indicate unit odds ratio. Unit odds ratio indicates how the odds change with a 1 unit increase in that variable, holding all other variables constant.

WFNS, and direct or endovascular surgery. Regarding DIND irreversibility, the SP group was superior to the FP group (OR 0.68; 95 % CI 0.54–0.85; p < 0.0001); however, there was no difference between the FP and PC groups (OR 0.54; 95 % CI 0.22–1.27; p = 0.16) and between the SP and PC groups (OR 0.79; 95 % CI 0.33–1.88; p = 0.60) (Table2b).

3.6. Outcome (Fig. 4)

Good prognosis, defined as mRS score 0–2 at discharge, was observed in 1479/2875 (51.4 %) patients in the FP group, 1069/2003 (53.4 %) in the SP group, and 73/151 (48.3 %) in the PC group. Logistic regression analysis for good prognosis showed that age was the most relevant factor (logWorth 115.1; unit OR; 0.94; 95 % CI 0.93–0.94; p < 0.0001), followed by shunt surgery (logWorth 42.1; OR 0.36; 95 % CI 0.31–0.41; p < 0.001), GCS (logWorth 15.9; unit OR 0.14; 95 % CI 0.09–0.23; p < 0.0001), the Fisher group (logWorth 9.0; unit OR 0.14; 95 % CI 0.09–0.23; p < 0.0001), operation method (logWorth 5.8), WFNS score (logWorth 3.6; unit OR 0.85; 95 % CI 0.82–0.88; p < 0.0001), and generation (logWorth 2.7; unit OR 0.85; 95 % CI 0.82–0.88; p < 0.0001). Fisher groups 2, 3, 4, and 5 were compared with group 1. The results of the analysis are as follows: group 2 (OR 1.43; 95 % CI 0.84–2.44; p = 0.178), group 3 (OR 0.87; 95 % CI 0.53–1.46; p = 0.62), group 4 (OR 0.54; 95 % CI 0.31–0.96; p = 0.034), group 5 (OR 0.33; 95 % CI 0.15–0.72; p = 0.0006). Regarding surgical techniques, clipping was associated with a better prognosis compared with coiling (coiling/clipping: OR 0.30; 95 % CI 0.14–0.65) in all age groups analyzed in this study; however, the difference became less significant with each newer generation (SP: OR 0.55; 95 % CI 0.45–0.67, p < 0.001; FP: OR 0.79 95 % CI 0.65–0.97p = 0.02, PC: OR 1.33; 95 % CI 0.68–2.62; p = 0.39) (Table 2c).

4. Discussion

According to this analysis of the Nagasaki SAH registry data accumulated over the past 20 years, SAH patient management has evolved regarding patient demographics, shift from clipping to coiling, and introduction of new spasm prevention treatments such as clazosentan. In our study, we found that the most relevant factor associated with DIND was shunt surgery (OR 2.49; 95 % CI 2.18–2.85; P < 0.0001), followed by Fisher group, generation, Glasgow Coma Scale (GCS) at presentation (unit OR 1.08; 95 %CI 1.53–3.73; p < 0.001), WFNS grade (Unit OR1.15; 95 %CI 1.04–1.26; p = 0.004). However, Shunt surgery is not the cause of DIND but rather a result of its increase occurrence. The presence of DIND was not significantly associated with surgical method, age, and direct surgery or endovascular surgery. Although DIND decreased as the generation became more recent, it did not improve outcome, and age remained the most important factor related to outcomes. The high prevalence of aneurysmal SAH in Japan and Finland is well-known.[17] In a Western study of unruptured cerebral aneurysms, ISUIA,[18] and in the UCAS study in Japan,[19] Japanese patients were found to be 10 years older on average. These patients also had a higher prevalence of smaller aneurysms. Moreover, the risk of aneurysm rupture in Japan is higher than that in Western countries. However, as reported by Ikawa et al., the number of patients with SAH in Japan has declined from 31.34 cases per 100,000 in 2003 to 27.63 cases per 100,000 in 2015.[20] Herein, the number of patients with SAH in the registry peaked at 400 in 2003 and continued to decline, reaching 173 in 2022, which is less than half of the number of patients in 2003. The condition of patients with SAH eligible for treatment has been worsening with generations; however, more aggressive treatments are also being administered. Notably, the use of endovascular therapies has increased, with coiling nearly surpassing clipping in 2022.

In Japan, owing to the unavailability of nimodipine, medications unique to the Japanese clinical practice, such as fasudil and ozagrel, have been used. However, with the introduction of clazosentan in 2022, new treatment protocols are being adopted. Clazosentan effectively prevents symptoms and complications of SAH in patients. However, its use presents several challenges, especially

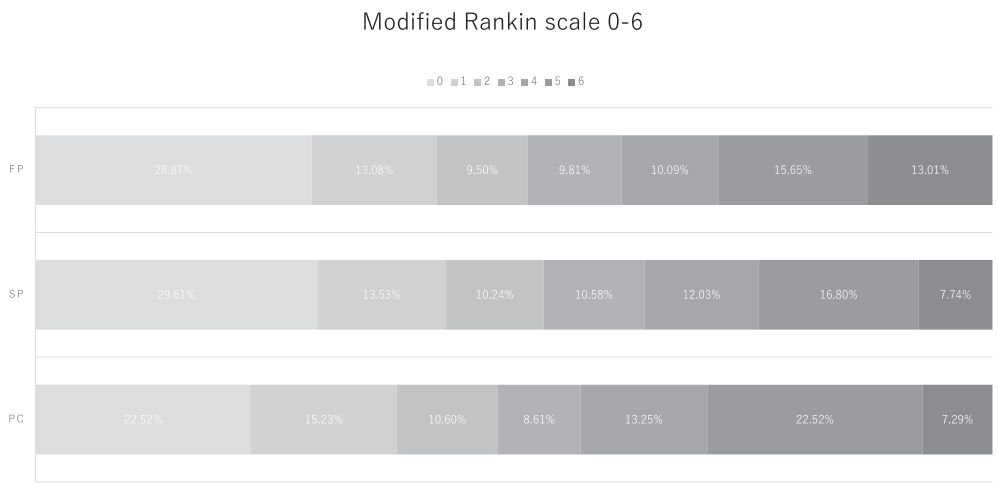

Fig. 4. Modified Rankin scale (mRS) score at discharge or after 3 months for each group. mRS 0–2; good outcome, 3–4; moderate outcome, 5,6; bad outcome.

in older patients or those with heart failure, and there is a risk of adverse effects. The reported adverse events of clazosentan include vomiting, signs of hemodilution or fluid retention (hyponatremia, hypoalbuminemia, anemia, pleural effusion, cerebral edema, and pulmonary edema), blood and lymphatic system disorder (placebo vs. clazosentan; 10.8 % vs. 17.9 %), anemia (9,5% vs 16.5 %), pleural effusions (3.6 % vs 11.9 %) and pulmonary edema (4.5 % vs 11.9 %); the use of clazosentan also requires careful fluid management.[13] In addition, according to the COMPASS1 study, the incidence of ischemic symptoms due to cerebral vasospasm was capacity-dependent (placebo vs. 1 mg/h vs. 5 mg/h vs. 15 mg/h: 66 % vs. 43 % vs. 39 % vs. 23 %).[21] Although the indicated volume in Japan is 10 mg/h, the body weights and heights of individual patients differ, which may result in different effects. The differences in results according to patient height and weight need to be investigated.

As the Nagasaki SAH Registry has no dedicated section to record information regarding patient height and weight, pulmonary edema, pleural effusion complications, or infusion management, further studies are needed to determine the relationship between the effects and adverse events of clazosentan.

Numerous reports have suggested that cilostazol is effective in preventing post-SAH complications and improving the prognosis. Recent meta-analyses have also confirmed the efficacy of cilostazol.[22–23] However, the effects of clazosentan have not been thoroughly evaluated.

Several studies report that clazosentan is effective in preventing delayed ischemic neurological deficit (DIND). Pontes et al. reported that in dataset from 2778 patients, clazosentan reduced the risk of DIND (Risk ratio [RR] 0.63, 95 % CI 0.50–0.80) and angiographic vasospasm (RR 0.54, 95 % CI 0.47–0.61), but did not significantly affect the likelihood of good clinical outcomes (RR 0.99, 95 % CI 0.79–1.24) or the risk of death (RR 1.03 95 % CI 0.71–1.49). Additionally, adverse events were increased in the clazosentan group (RR 1.54 95 % CI 1.35–1.76).[12] In another study, Muraoka et al. reported 47 cases where clazosentan was used in combination with other drugs for the treatment of vasospasm. The combination including clazosentan resulted in vasospasm in 30 % of the patients, but delayed ischemic complications occurred in fewer than 7 % of the cases. However, the addition of fasudil to the clazosentan regimen did not further reduce the incidence of DCI and it led to an increased in side effects.

Although there is little evidence regarding the efficacy of clazosentan in spasm treatment, this survey demonstrated its effectiveness in reducing DIND after various treatments. In the future, as the use of clazosentan increases, further studies are needed to determine its impact on treatment outcomes and prognosis of patients with SAH. In addition, a detailed examination of the efficacy and safety of combination therapy with clazosentan and other medications is required.

Because the initial damage of SAH significantly affects the outcome, improving prognosis with spasm treatment alone is difficult. As the population ages and the patient population changes, further efforts are needed to provide satisfactory treatment results.

4.1. Study limitations and future directions

Although this study provides valuable insights, it has some limitations. The retrospective nature of the study and the presence of potential confounders necessitate a cautious interpretation of the findings. Additionally, the evolving landscape of treatment interventions and changes in clinical practice over time may have influenced the observed outcomes. Since the Registry relies on real-world treatment data, multiple spasm treatments are often administered to the same patient, which makes it difficult to assess the effectiveness of each spasm medication, including clazosentan. Another limitation is the significantly smaller number of patients in the PC group compared to the FP and SP groups.

Further studies, including prospective studies and randomized controlled trials, are required to validate our findings and establish causal relationships.

5. Conclusions

Between 2002 and 2022, 6,446 SAH patients with SAH were evaluated over three distinct periods, revealing an increasing average age, especially in the most recent period. Although the aneurysm location and size distribution remained consistent across the periods, there was a notable shift in rebleeding prevention methods used, with endovascular treatments, particularly coiling, becoming more prevalent and nearly surpassing clipping in 2022. The introduction of clazosentan also marked a change in spasm prevention treatments used. While the incidence of DIND varied across periods, it was notably reduced in the most recent period. Despite these changes, the proportion of patients with favorable outcomes remained at approximately 50 %, with age and other factors being significant determinants of outcomes. This study underscores the evolving approaches to the management of patients with SAH, influenced by the introduction of clazosentan and changes in treatment modalities.

CRediT authorship contribution statement

Hajime Maeda: Conceptualization, Methodology, Software, Writing – review & editing, Writing – original draft. **Tsuyoshi Izumo:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing, Formal analysis, Funding acquisition, Methodology, Project administration, Resources, Validation, Visualization. **Kazuaki Okamura:** Investigation, Software. **Susumu Yamaguchi:** Investigation, Visualization. **Yoichi Morofuji:** Investigation, Visualization. **Takayuki Matsuo:** Supervision, Validation.

Ethical approval

Helsinki and approved by the Institutional Review Board of Nagasaki University Hospital (No. 23082109).

Consent to participate

This study was conducted in accordance with the principles of the Declaration of We obtained verbal informed consent from all participants. If verbal informed consent was not obtainable, we summarized our research on the institute website and allowed the participants to decline their participation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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