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Outcomes in subarachnoid haemorrhage

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Published in
Frontiers in Neurology

ISSN 1664-8714
ISBN 978-2-8325-2435-0
DOI 10.3389/978-2-8325-2435-0

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Outcomes in subarachnoid haemorrhage

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Citation

Nelson, S. E., Rowland, M., Fragata, I., De Oliveira Manoel, A. L., eds. (2023). *Outcomes in subarachnoid haemorrhage*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-2435-0

Table of contents

frontiers | Frontiers in Neurology

TYPE Editorial
PUBLISHED 03 May 2023
DOI 10.3389/fneur.2023.1186473

OPEN ACCESS

EDITED AND REVIEWED BY
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SPECIALTY SECTION
This article was submitted to Endovascular and Interventional Neurology, a section of the journal Frontiers in Neurology

RECEIVED 14 March 2023
ACCEPTED 29 March 2023
PUBLISHED 03 May 2023

CITATION
Nelson SE, Fragata I, Rowland M and de Oliveira Manoel AL (2023) Editorial: Outcomes in subarachnoid hemorrhage.
Front. Neurol. 14:1186473.
doi: 10.3389/fneur.2023.1186473

Editorial: Outcomes in subarachnoid hemorrhage

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KEYWORDS

subarachnoid hemorrhage, outcomes, research, prognostication, biomarker

Editorial on the Research Topic
Outcomes in subarachnoid hemorrhage

Welcome to our ResearchTopic on "*Outcomes in subarachnoid hemorrhage*" in *Frontiers in Neurology*. Although aneurysmal subarachnoid hemorrhage (SAH) represents only 5% of all types of stroke, it carries the highest mortality and disability rates (1–3). Moreover, because SAH affects predominantly young adults, it is associated with huge economic and social burden (4). In addition, a considerable number of patients with an apparent full recovery may experience residual neurocognitive impairment, which are subtle and difficult to recognize, however it may prevent them from returning to work and having a normal life (5). Therefore, the current Research Topic may be of interest to those involved in treating or conducting research in SAH.

Some of the enclosed manuscripts discuss the relationship between clinical factors or biomarkers and SAH outcome directly (Zhang et al.; Wen et al.; Wang et al.). For instance, Zhang et al. found that the C-reactive protein to lymphocytes ratio was associated with unfavorable functional outcome in aneurysmal SAH. Wen et al. observed that parenchymal blood volume maps as acquired by C-arm flat-panel detector CT appear to be associated with discharge outcomes. Wang et al. evaluated factors associated with occurrence of delayed cerebral ischemia and prognosis of patients with aneurysmal SAH associated with hydrocephalus, noting that high Hunt and Hess Grade and surgical clipping were independent risk factors for delayed cerebral ischemia, while older age, higher Hunt and Hess Grade, higher C reactive protein, and increased neutrophil levels were independently associated with unfavorable outcomes at 6 months. Another interesting article discusses the role of the double microcatheter technique as a possible safe and effective treatment for anterior circulation ruptured aneurysms (Zhao et al.). These articles thus add to the literature regarding SAH treatment and prognostication, the latter of which is still fraught with uncertainty (6).

Additionally, two articles included in this series explore the relevance of clinical factors in relation to SAH patients' clinical course (Yuan et al.; Santana et al.), including the development of pneumonia and contribution to early brain injury. For instance, Yuan et al. noted that post-operative pneumonia was more commonly found in those who had undergone surgical clipping vs. endovascular coiling for aneurysm securement and furthermore noted several risk factors for post-operative pneumonia in each of the surgical

clipping and endovascular coiling groups. Also, Santana et al. reviewed the literature on glycemic management and SAH, showing an association between dysglycemia and outcome, and the fact that better knowledge regarding glucose patterns and management surrounding aneurysmal SAH is needed. These articles thus contribute knowledge surrounding the systemic complications that commonly occur in SAH patients, suggesting possible ways in which these medical conditions could be addressed.

Since outcomes can vary even within a single country, Shah et al. presented data examining clinical factors in different areas of the US in relationship to SAH outcomes, and described the variability in SAH care across the country. They also found several clinical factors that appear to affect SAH outcome (Shah et al.). Finally, Andersen, Presseau et al. review what, when, and how to measure in choosing relevant outcomes for aneurysmal SAH as well as initiatives to improve the selection of these outcomes. In a later article, Andersen, English et al. present the results of a survey to assess these outcomes' priorities for different SAH stakeholders (including patients and clinicians). They found that there were several viewpoints concerning optimal aneurysmal SAH outcome measures though patient-reported quality of life was deemed the most important outcome measure (Andersen, English et al.). These articles are important because they point out not only that clinical care in SAH management still appears to be variable (even within one country), but also that choosing appropriate outcomes for this condition is critically important, warranting a thorough evaluation. Hopefully, the articles included in this *Frontiers in Neurology* Research Topic prove to be useful, and in some cases potentially provide the impetus for further research into the topic of SAH outcomes.

Author contributions

SN drafted and edited the manuscript. IF, MR, and AO critically reviewed the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

MR was employed by Novartis Pharmaceuticals.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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ORIGINAL RESEARCH
published: 13 June 2022
doi: 10.3389/fneur.2022.868764

Clinical Value and Prognosis of C Reactive Protein to Lymphocyte Ratio in Severe Aneurysmal Subarachnoid Hemorrhage

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Objective: To investigate the relationship between CLR and disease severity and clinical prognosis of aSAH.

Methods: The authors retrospectively analyzed the clinical data of 221 patients with aSAH, who were admitted to the intensive care unit from January 2017 to December 2020. The indicators of inflammatory factors in the first blood routine examination within 48 h of bleeding were obtained. The prognosis was evaluated by mRS score at discharge, mRS>2 was a poor outcome. Through the receiver operating characteristic (ROC) curve, the area under the curve was calculated and the predicted values of inflammatory factors (CLR, CRP, WBC, and neutrophils) were compared. Univariate and multivariable logistic regression analyses were used to evaluate the relationship between CLR and the clinical prognosis of patients. ROC curve analysis was performed to determine the optimal cut-off threshold, sensitivity, and specificity of CLR in predicting prognosis at admission.

Results: According to the mRS score at discharge, 139 (62.90%) patients were classified with poor outcomes (mRS>2). The inflammatory factor with the best predictive value was CLR, which had an optimal cut-off threshold of 10.81 and an area under the ROC curve of 0.840 (95%CI.788–0.892, $P < 0.001$). Multivariable Logistic regression analysis showed that the Modified Fisher grade, Hunt-Hess grade, and CLR at admission were independent risk factors for poor outcomes of patients with aSAH ($P < 0.05$). According to Hunt-Hess grade, patients were divided into a mild group (Hunt-Hess $\leq$ 3) and a severe group (Hunt-Hess $>$ 3), and the CLR value was significantly higher in severe patients with aSAH than in mild patients. The optimal cut-off threshold of CLR in the severe group was 6.87, and the area under the ROC curve was 0.838 (95% CI.752–0.925, $P < 0.001$).

OPEN ACCESS

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Specialty section:
This article was submitted to Endovascular and Interventional Neurology, a section of the journal Frontiers in Neurology

Received: 03 February 2022
Accepted: 20 April 2022
Published: 13 June 2022

Citation:
Zhang Q, Zhang G, Wang L, Zhang W, Hou F, Zheng Z, Guo Y, Chen Z, Hernesniemi J, Andrade-Barazarte H, Feng G and Gu J (2022) Clinical Value and Prognosis of C Reactive Protein to Lymphocyte Ratio in Severe Aneurysmal Subarachnoid Hemorrhage. Front. Neurol. 13:868764. doi: 10.3389/fneur.2022.868764

Conclusions: The CLR value at the admission of patients with aSAH was significantly associated with Hunt-Hess grade, The higher Hunt-Hess grade, the higher the CL R-value, and the worse the prognosis. Early CLR value can be considered as a feasible biomarker to predict the clinical prognosis of patients with aSAH.

Keywords: aneurysmal subarachnoid hemorrhage (aSAH), C-reactive protein (CRP), lymphocytes, C-reactive protein to lymphocyte ratio (CLR), prognosis, outcome

INTRODUCTION

Aneurysmal subarachnoid hemorrhage (aSAH) has a sudden onset and rapid progression and has high clinical mortality in clinical practice. Previous studies have shown that the mortality rate of aSAH is still as high as 66.7% (1), and the highest rate of permanent disability is about 50% (2). Although mortality and permanent disability rates have decreased with the rapid development of neuro-intensive care techniques, mortality and disability rates remain high for patients with severe conditions at admission and higher Hunt-Hess grades.

There are many factors affecting the clinical prognosis of aSAH patients. In recent years, many clinical studies have used white blood cells, neutrophils, lymphocytes, and C-reactive protein to predict the relationship between them and the clinical prognosis of patients with aSAH (3–7). Güresir et al. (3) reported that the initial inflammatory response was an independent predictor of the clinical prognosis of patients with aSAH. Al-Mufti et al. (7) reported that white blood cell (WBC) count at admission could predict delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage. The higher the WBC count, the greater the probability of delayed cerebral ischemia (DCI), resulting in poor outcomes. However, most of these clinical predictors have low specificity and sensitivity. Therefore, inflammatory factors that can accurately predict the clinical prognosis of patients with aSAH at an early stage are still of great significance for clinical treatment.

C-reactive protein (CRP) is an acute phase protein (8, 9), which is produced by the liver and stimulated by various cells under the action of the body under trauma or inflammatory factors (10, 11). Lymphocytes play a role in promoting the growth and regulation of endothelial cells, which will be consumed in large quantities when the body is traumatized (12). The ratio of C-reactive protein to lymphocytes (CLR) plays a key role in the prognosis of tumors, pancreatic cancer, colorectal cancer, and other related diseases, but there is no study on patients with aSAH. This study mainly explores the clinical value of CLR in patients with aSAH and its relationship with clinical prognosis.

MATERIALS AND METHODS

Patient Population

A retrospective analysis of 307 patients with aSAH was admitted to the intensive care unit from January 2017 to December 2020 was performed. There were 221 patients, who met the criteria, aged 29–88,135 (61.09%) females and 86 (38.91%) males, and with an average age of 58.87 ± 11.99. The inclusion criteria for enrollment were as follows: (1) Acute onset, arrived at our hospital within 48 h and underwent laboratory examination, (2) diagnosed with spontaneous SAH by computed tomography (CT), and the diagnosis of the aneurysm was achieved by computed tomography angiography (CTA) or digital subtraction angiography (DSA), and (3) all of them underwent interventional or surgical clipping treatment.

The study exclusion criteria were as follows: (1) no aneurysm was found by CTA or DSA, (2) more than 48 h after reaching our hospital, (3) patients with incomplete clinical data, (4) complicated with infection, immune dysfunction, blood system diseases, organ function damage, experienced surgery, or major infectious diseases in the past 1 month. This study was approved by the Institutional Review Board. We did not sign the written informed consent, but we obtained the consent of the patient or his family through a telephone interview.

Data Collection

The basic clinical data of all patients were collected, including gender, age, hypertension, diabetes, smoking, drinking history, history of cerebral infarction, mRS at admission, mRS at discharge, modified Fisher score, and Hunt-Hess grade. Venous blood samples were collected within 48 h at admission and stored in tubes containing various anticoagulants for routine blood tests. Routine blood examinations, including examinations of the white blood cell count (reference range, 3.5–9.5 10^9 /L), neutrophil count (reference range, 1.8–6.3 10^9 /L), lymphocyte count (reference range, 1.1–3.2 10^9 /L), and C-reactive protein count (reference range, 0–10 mg/L), were performed for all patients by the routine laboratory assays. The CLR is defined as the number of C-reactive proteins divided by the number of lymphocytes. The status of patients at admission was evaluated according to the modified Fisher scale and Hunt-Hess classification. All subjects were treated with surgery or interventional therapy and discharged from the hospital with a modified Rankin Scale (mRS) score of < 2 for good outcomes and > 3 for poor outcomes.

Statistical Analysis

The SPSS 21.0 statistical software was used for data analysis. Kolmogorov-Smirnov method was used to test whether the data were by the normal distribution. Mean ± standard deviation ($\bar{x} \pm s$) was used for measurement by a normal distribution, and a *t*-test was used for comparison between groups. Median (M) and quartile (P25, P75) were used for measurement data that did not conform to the normal distribution, and the Wilcoxon rank test was used for comparison between groups. Several cases and constituent ratios were used for enumeration

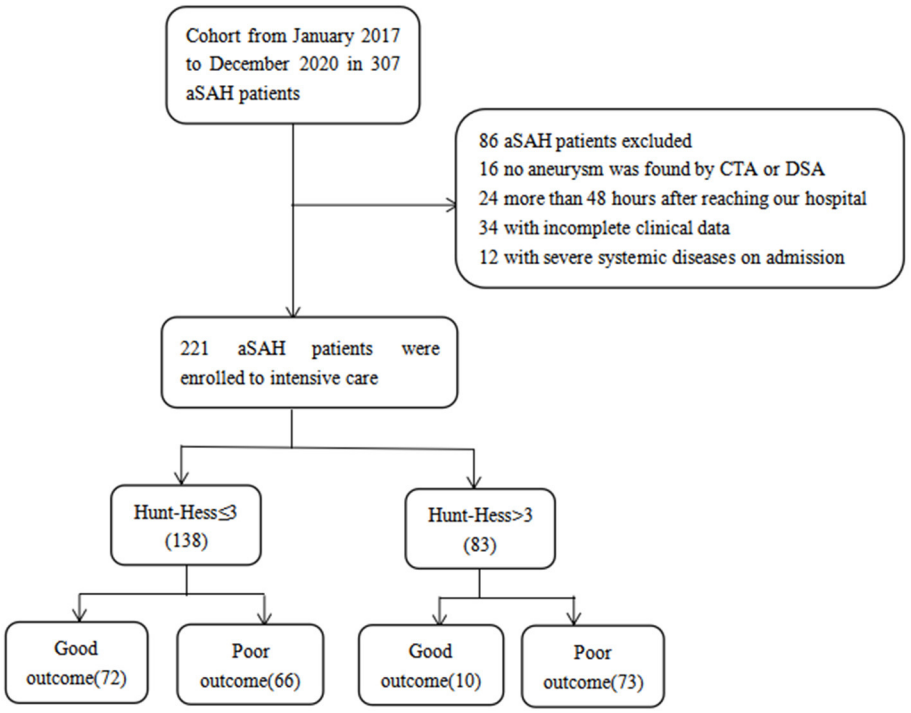

FIGURE 1 | Flowchart illustrating the patient cohort included in this study.

data, $\chi 2$ test was used for comparison between groups. Factors $P < 0.05$ in univariate analysis results were included as dependent variables in multivariable Logistic regression analysis, and receiver operating characteristic (ROC) curve analysis was performed to determine the optimal cut-off value, sensitivity, and specificity of CLR for predicting prognosis at admission. $P < 0.05$ was considered statistically significant (13).

RESULTS

A total of 221 patients with aSAH admitted to the intensive care unit were enrolled, 82 patients with good outcomes and 139 patients with poor outcomes, including 14 deaths. According to Hunt-Hess's grade at admission, 138 cases were mild (Hunt-Hess $\leq$ 3), 72 cases had good outcomes, and 66 cases had poor outcomes. There were 83 cases noted to be severe (Hunt-Hess $>$ 3), with good outcomes in 10 cases and poor outcomes in 73 cases (**Figure 1**).

This study included 82 patients with aSAH in the good outcome group and 139 patients with aSAH in the poor outcome group, including 54 females and 28 males aged 55.72 $\pm$ 11.30 years in the good outcome group and 81 females and 58 males aged 60.29 $\pm$ 12.59 years in the poor outcome group. There were no significant differences in gender, smoking, drinking, or location of aneurysms between good and poor outcome groups ($P > 0.05$). There were statistically significant differences in age, diabetes or hypertension, cerebral infarction, Fisher score at admission, and Hunt-Hess grade between good and poor outcome groups ($P < 0.05$). However, the difference in inflammatory indexes (leukocytes, neutrophils, lymphocytes, and CRP) between the two groups was also statistically significant ($P < 0.05$). In addition, the CLR value of the poor outcome group (35.92 $\pm$ 41.67) was higher than that of patients in the good outcome group (4.44 $\pm$ 7.74), and the difference was statistically significant ($P < 0.05$), as shown in **Table 1**.

Factors associated with poor outcomes in **Table 1** were included in multivariable logistic regression analysis after excluding some confounding factors [due to the high collinearity between CRP and CLR (VIF $>$ 10 after log-conversion), CRP was excluded]. It was found that the improved Fisher score, Hunt-Hess grade, and CLR at admission were independent risk factors for poor outcomes of patients with aSAH ($P < 0.05$), as shown in **Table 2**.

ROC curve analysis showed that white blood cells, neutrophils, CRP, and CLR were 0.633, 0.627, 0.830, and 0.840, respectively. CLR had the highest accuracy in predicting the clinical prognosis of patients with aSAH. The optimal cut-off threshold of CLR was 10.81, the area under the ROC curve was 0.840 (95 % CI 0.788–0.892, $P < 0.001$), the maximum Youden index was 0.627, the sensitivity was 0.676, and the specificity was 0.951 (**Figure 2**).

By comparing the mild with the severe group, it was found that there was a significant correlation between disease severity and patients' age, hypertension, coronary heart disease, history of cerebral infarction, modified Fisher score, WBC, neutrophils, CRP, and CLR ($P < 0.05$). The CLR value (33.96 $\pm$ 44.85) was significantly higher in the severe group than in the mild group

TABLE 1 | Univariate analysis table affecting the clinical prognosis of patients with Aneurysmal subarachnoid hemorrhage (aSAH).

Variables	Total patients (221)		*P* value
	Good outcome (82)	Poor outcome (139)	
Gender			0.264
Female	54 (65.85%)	81 (58.27%)	
Male	28 (34.15%)	58 (41.73%)	
Age, years	55.72 ± 11.30	60.29 ± 12.59	0.006
Smoking	17 (20.73%)	30 (21.58%)	0.881
Drinking	15 (18.29%)	29 (20.86%)	0.644
Diabetes	0 (0.00%)	12 (8.63%)	0.015
Hypertension	38 (46.34%)	90 (64.75%)	0.007
Cerebral infarction	4 (4.88%)	21 (53.85%)	0.034
Coronary arterydisease	4 (4.88%)	19 (13.67%)	0.066
Modified fisher grade			<0.001
Grade 0,1,2	74 (90.24%)	66 (47.48%)	
Grade 3,4	8 (9.76%)	73 (52.52%)	
Hunt-Hess grade			<0.001
Grade 1,2,3	72 (87.80%)	66 (47.48%)	
Grade 4,5	10 (12.20%)	73 (52.52%)	
Location			0.741
Anterior circulation	42 (51.22%)	68 (48.92%)	
Posterior circulation	40 (48.78%)	71 (51.08%)	
Inflammation index			
WBC	11.28 ± 3.87	13.24 ± 4.39	0.001
Neutrophil	9.69 ± 3.73	11.57 ± 4.44	0.002
Lymphocyte	1.11 ± 0.53	1.00 ± 0.56	0.026
CRP	4.21 ± 4.84	28.47 ± 32.76	<0.001
CLR	4.44 ± 7.74	35.92 ± 41.67	<0.001

WBC, white blood cell; CRP, C-reactive protein; CLR, C-reactive protein to lymphocyte ratio.

TABLE 2 | Multivariable logistic regression analysis of poor clinical prognosis of aSAH.

Variables	Total patients (221)		
	OR	95% CI	*P* value
Age, years	0.988	0.949–1.028	0.551
Cerebral infarction	3.157	0.777–12.831	0.108
Hypertension	1.228	0.516–2.918	0.643
Modified fisher grade	6.023	2.045–17.735	0.001
Hunt-Hess grade	5.071	1.840–13.978	0.002
WBC	1.028	0.400–2.646	0.954
Neutrophil	0.958	0.373–2.462	0.929
Lymphocyte	1.495	0.411–5.441	0.542
CLR	1.159	1.087–1.236	<0.001

WBC, white blood cel; CLR, C-reactive protein to lymphocyte ratio.

(18.39 ± 29.36) (**Table 3**). Univariate analysis of the severe group showed that the age of patients with poor outcomes was generally higher than that of patients with good outcomes. The CLR value of patients with poor outcomes (38.20 ± 46.24) was higher than

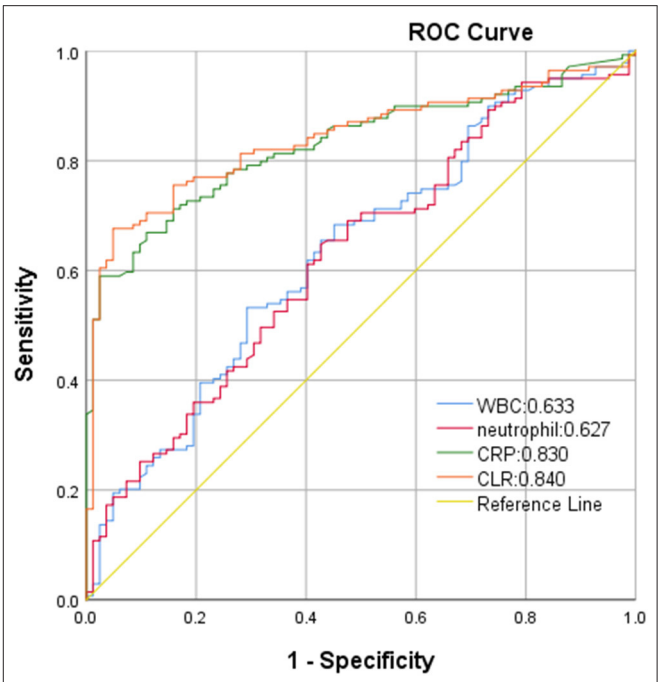

FIGURE 2 | Receiver operating characteristics (ROC) curve of CLR in predicting poor outcome of aSAH patients.

that of patients with good outcomes (2.94 ± 2.05), and the difference had statistical significance ($P < 0.05$, **Table 4**).

The factors associated with poor outcomes in the severe group in **Table 4** are included in the multivariable logistic regression analysis after excluding some confounding factors [due to the high collinearity between CRP and CLR (VIF > 10 after log-conversion), CRP was excluded]. Finally, CLR was found to be an independent risk factor for poor outcomes in patients with severe aSAH (**Table 5**).

In ROC curve analysis, the white blood cells, neutrophils, CRP, and CLR values of patients in the mild group (Hunt-Hess ≤ 3) were 0.569, 0.568, 0.858, and 0.865, respectively. The optimal cut-off threshold of CLR was 10.81, the area under the ROC curve was 0.865 (95% CL0.799–0.931, $P < 0.001$), and the maximum Youden index was 0.686, and its sensitivity was 0.742 and specificity was 0.944 (**Figure 3**). The white blood cell, neutrophil, CRP, and CLR values of patients in the severe group (Hunt-Hess >3) were 0.715, 0.692, 0.817, and 0.838, respectively. The optimal cut-off threshold of CLR was 6.87, the area under the ROC curve was 0.838 (95% CL0.752–0.925, $P < 0.001$), and the maximum Youden index was 0.712, its sensitivity was 0.712 and the specificity was 1 (**Figure 4**).

DISCUSSION

From 221 patients admitted to intensive care due to rapid and severe disease progression at admission, we found that among 83 patients with a Hunt-Hess score of >3 that an elevated baseline systemic inflammatory response was an independent risk factor for poor outcome. Although some patients have

TABLE 3 | Univariate analysis of clinical characteristics of patients in mild and severe groups.

Variables	Hunt-Hess≤3 (138)	Hunt-Hess>3 (83)	*P* value
Gender			0.513
Female	82 (59.42%)	53 (63.86%)	
Male	56 (40.58%)	30 (36.14%)	
Age, years	56.63 ± 11.94	62.59 ± 11.19	<0.001
Smoking	3,021.74%	17 (20.48%)	0.825
Drinking	25 (18.12%)	19 (22.89%)	0.389
Diabetes	5 (3.62%)	7 (8.43%)	0.222
Hypertension	63 (45.65%)	65 (78.31%)	<0.001
Cerebral infarction	8 (5.80%)	17 (20.48%)	0.001
Coronary arterydisease	8 (5.80%)	15 (18.07%)	0.004
Modified fisher grade			<0.001
Grade 0,1,2	108 (78.26%)	32 (38.55)	
Grade 3,4	30 (21.74%)	51 (61.45%)	
Location			0.306
Anterior circulation	65 (47.10%)	45 (54.22%)	
Posterior circulation	73 (52.90%)	38 (45.78%)	
Inflammation index			
WBC	11.77 ± 4.10	13.75 ± 4.36	0.001
Neutrophil	10.21 ± 4.02	11.98 ± 4.49	0.004
Lymphocyte	1.05 ± 0.52	1.04 ± 0.60	0.542
CRP	13.84 ± 18.03	28.82 ± 38.92	0.004
CLR	18.39 ± 29.36	33.96 ± 44.85	0.005

WBC, white blood cell; CRP, C-reactive protein; CLR, C-reactive protein to lymphocyte ratio.

TABLE 4 | Clinical characteristics of clinical prognosis in patients with aSAH with Hunt-Hess of >3.

Variables	Hunt-Hess>3 (83)		*P* value
	Good outcome (10)	Poor outcome (73)	
Gender			0.138
Female	9 (90.00%)	44 (60.27%)	
Male	1 (10.00%)	29 (39.73%)	
Age, years	62.00 ± 8.731	62.67 ± 11.528	0.014
Smoking	0 (0.00%)	17 (23.29%)	0.196
Drinking	1 (10.00%)	18 (24.66%)	0.526
Diabetes	0 (0.00%)	7 (9.59%)	0.677
Hypertension	8 (80.00%)	57 (78.08%)	1.000
Cerebral infarction	2 (20.00%)	15 (20.55%)	1.000
Coronary artery disease	1 (10.00%)	14 (19.18%)	0.788
Modified fisher grade			0.255
Grade 0,1,2	6 (60.00%)	26 (35.62%)	
Grade 3,4	4 (40.00%)	47 (64.38%)	
Location			
Anterior circulation	6 (60.00%)	39 (53.42%)	0.958
Posterior circulation	4 (40.00%)	34 (46.58%)	
Inflammation index			
WBC	10.83 ± 3.29	14.15 ± 4.35	0.028
Neutrophil	9.46 ± 3.53	12.32 ± 4.51	0.050
Lymphocyte	1.08 ± 0.45	1.03 ± 0.62	0.543
CRP	3.33 ± 3.18	32.31 ± 40.26	0.001
CLR	2.94 ± 2.05	38.20 ± 46.24	0.001

WBC, white blood cell; CRP, C-reactive protein; CLR, C-reactive protein to lymphocyte ratio.

TABLE 5 | Multivariable logistic regression analysis of poor clinical prognosis in severe group (Hunt-Hess > 3).

Variables	severe group (83)		*P* value
	OR	95% CI	
Age, years	1.053	0.973–1.139	0.201
WBC	2.850	0.589–13.784	0.193
Neutrophil	0.414	0.089–1920	0.260
CLR	1.280	1.002–1.635	0.048

WBC, white blood cell; CLR, C-reactive protein to lymphocyte ratio.

a better neurological grade on admission, there is still an unpredictable risk of deterioration during treatment, leading to a poor outcome (14, 15). Therefore, the ability to accurately predict prognosis, especially for patients with severe disease and higher Hunt-Hess grade at admission, is important to adjust the management and treatment of patients promptly. Finally, with stepwise validation at baseline, we found that CLR was the strongest independent predictor of prognosis in patients with aSAH. It is a simple and approachable method for early predictability of poor outcomes in patients with aSAH.

The aSAH is a sudden and rapidly progressive disease, especially in patients with severe disease at admission and long hospital stay, it is still a clinical challenge to predict the prognosis of aSAH. After an aneurysm rupture, blood deposition into the subarachnoid cavity will stimulate the brain tissue and activate the immune regulatory cells in the central nervous system, and a large number of inflammatory cells will enter the subarachnoid cavity, which will rapidly cause an inflammatory cascade reaction (16, 17). At present, in clinical practice, inflammatory factors at admission are some of the data we can utilize, and these inflammatory factors are all part of the identifiable data at the admission of patients, avoiding the influencing factors known as sequelae left in the clinical course after aSAH.

Gaastra et al. (18) reported that CRP is an independent predictor of postoperative functional outcome in patients with aSAH, and elevated CRP values at the initial stage of bleeding are closely related to the functional outcome of clinical prognosis (19, 20). CRP is an acute-phase protein produced by the liver (8, 9). Under the action of trauma or inflammatory factors, the liver will rapidly produce CRP and release it into the peripheral blood. At this time, CRP in peripheral blood is elevated (12, 16–18). However, CRP is a non-specific inflammatory marker that can be elevated in the presence of any tissue damage (10, 11),

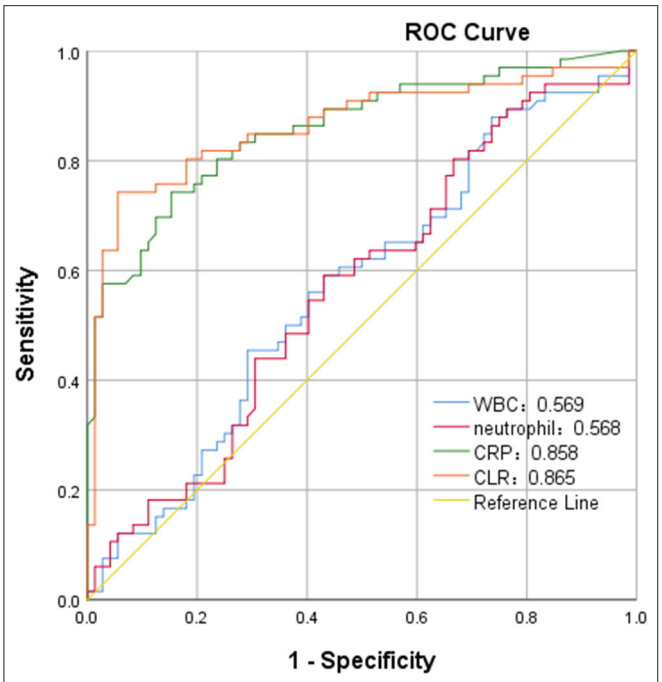

FIGURE 3 | ROC curve of C-reactive protein to lymphocyte ratio (CLR) in predicting poor outcome of patients with aSAH in mild group (Hunt-Hess of ≤ 3).

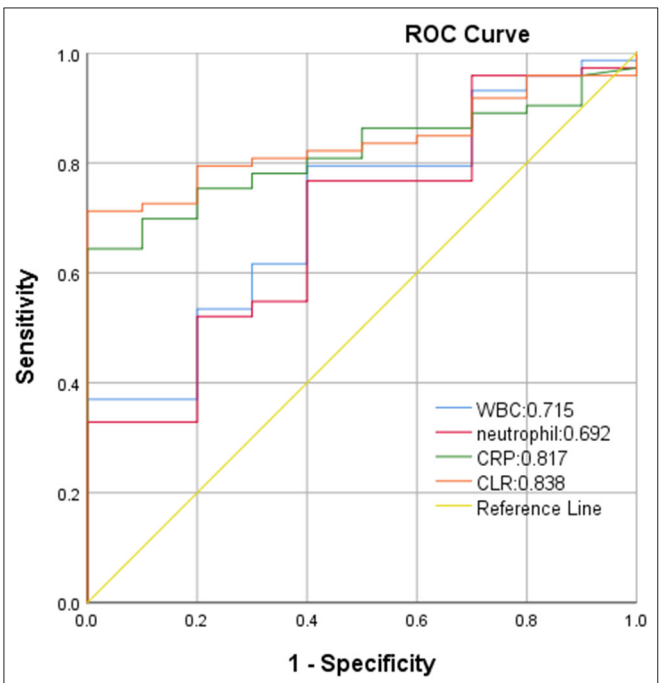

FIGURE 4 | ROC curve of CLR in predicting poor outcome of patients with aSAH in severe group (Hunt-Hess of > 3).

therefore, its clinical value can be improved in combination with other inflammatory indicators.

On the other hand, when the central nervous system is stimulated, the immune system will be activated and a large number of lymphocytes will be released, which can reduce the damage to brain tissue through antigen recognition, cell activation, and immune killing (16). Frösen et al. (21) compared 42 cases of ruptured and 24 cases of unruptured aneurysms in histology and found that lymphocytes actively participate in the inflammatory cascade reaction of the vascular wall of the aneurysm. When aneurysm ruptures, excessive depletion of lymphocytes, results in a decrease in the number of lymphocytes, which is also considered to be a sign of aggravating brain injury with poor clinical outcomes (16). While CLR is a new inflammatory ratio and has been used as one of the prognostic markers of pancreatic and rectal cancer surgery, tumor, and strangulated abdominal hernia (intestinal ischemia) in current studies (22–25). Fan et al. (23) compared the combination of six inflammatory markers, namely neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), C-reactive protein/albumin ratio (CAR), neutrophil/albumin ratio (NAR), platelet/albumin ratio (PAR), and C-reactive protein/lymphocyte ratio (CLR) to predict the accuracy of poor survival rate of pancreatic cancer, and found that CLR was more accurate than NLR, PLR, CAR, NAR and PAR in predicting the survival rate of pancreatic cancer. While CLR has not been reported in the literature in related aspects, such as cerebral hemorrhage and traumatic brain injury. In this study, increased CLR value was related to increased risk for poor outcomes of patients with aSAH, and higher accuracy of CLR relative to WBC, neutrophils, and lymphocytes was observed to predict the prognosis of patients with aSAH.

Our study also found that CLR value is closely related to Hunt-Hess grade, and for patients with higher Hunt-Hess grade and more severe disease, the higher the CLR value, the worse the prognosis. Therefore, CLR values reflect early C-reactive protein excess and lymphocyte depletion in aSAH patients, which may predict preoperative severity and postoperative prognosis. Hunt-Hess grade is used to classify the clinical status of patients with aSAH to select the timing of surgery and determine the prognosis. Related literature has reported that the higher the Hunt-Hess grade of patients at admission, the worse the prognosis (26–28). Frontera et al. showed that in the severe group (Hunt-Hess > 3), patients with aSAH were more prone to ischemic brain injury in the early stage, with higher mortality and disability rates, confirming our findings (26).

However, our study had some limitations. Firstly, the number of patients enrolled in the study is small; second, our analysis is retrospective and carried out in a single center; thirdly, we did not count the blood volume of subarachnoid hemorrhage, therefore, whether the amount of lymphocyte depletion is related to the amount of blood in subarachnoid hemorrhage still requires our further study; and finally, we only investigated the prognosis of patients at discharge. Therefore, long-term perspective and multi-center trials are needed to support our results in the future.

CONCLUSIONS

This study indicated that patients with aSAH with high levels of CLR at admission were at high risk for worse outcomes at

discharge and the higher CLR value was related to the worse prognosis in patients with aSAH with the higher Hunt-Hess grade (>3), which suggests that CLR may be as a potential clinical biomarker to predict prognosis among patients with aSAH with the higher Hunt-Hess grade (>3).

AUTHOR CONTRIBUTIONS

JG contributed to conception and design of the study. QZ and GZ wrote the first draft of the manuscript. LW, WZ, FH, ZZ, and YG wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

FUNDING

This research was supported by Henan Medical Science and Technology Public Relations Program (Joint Construction) Project, Number: LHGJ20190592; by the Senior Specialist Foreign Expert Project, Number: G20190126006; and by Department of Science and Technology of Henan Province.

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frontiers | Frontiers in Neurology

ORIGINAL RESEARCH
published: 16 June 2022
doi: 10.3389/fneur.2022.908609

Regional Variability in the Care and Outcomes of Subarachnoid Hemorrhage Patients in the United States

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Background and Objectives: Regional variability in subarachnoid hemorrhage (SAH) care is reported in physician surveys. We aimed to describe variability in SAH care using patient-level data and identify factors impacting hospital outcomes and regional variability in outcomes.

Methods: A retrospective multi-center cross-sectional cohort study of consecutive non-traumatic SAH patients in the Vizient Clinical Data Base, between January 1st, 2009 and December 30th, 2018 was performed. Participating hospitals were divided into US regions: Northeast, Midwest, South, West. Regional demographics, co-morbidities, severity-of-illness, complications, interventions and discharge outcomes were compared. Multivariable logistic regression was performed to identify factors independently associated with primary outcomes: hospital mortality and poor discharge outcome. Poor discharge outcome was defined by the Nationwide Inpatient Sample-SAH Outcome Measure, an externally-validated outcome measure combining death, discharge disposition, tracheostomy and/or gastrostomy. Regional variability in the associations between care and outcomes were assessed by introducing an interaction term for US region into the models.

Results: Of 109,034 patients included, 24.3% were from Northeast, 24.9% Midwest, 34.9% South, 15.9% West. Mean (SD) age was 58.6 (15.6) years and 64,245 (58.9%) were female. In-hospital mortality occurred in 21,991 (20.2%) and 44,159 (40.5%) had poor discharge outcome. There was significant variability in severity-of-illness, co-morbidities, complications and interventions across US regions. Notable findings were higher prevalence of surgical clipping (18.8 vs. 11.6%), delayed cerebral ischemia (4.3 vs. 3.1%), seizures (16.5 vs. 14.8%), infections (18 vs. 14.7%), length of stay (mean [SD] days; 15.7 [19.2] vs. 14.1 [16.7]) and health-care direct costs (mean [SD] USD; 80,379 [98,999]. vs. 58,264 [74,430]) in the West when compared to other regions (all $p < 0.0001$). Variability in care was also associated with modest variability in hospital mortality and discharge outcome. Aneurysm repair, nimodipine use, later admission-year, endovascular rescue therapies reduced the odds for poor outcome.

OPEN ACCESS

Edited by:
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Specialty section:
This article was submitted to Endovascular and Interventional Neurology, a section of the journal Frontiers in Neurology

Received: *30 March 2022*
Accepted: *25 May 2022*
Published: *16 June 2022*

Citation:
Shah VA, Kazmi SO, Damani R, Harris AH, Hohmann SF, Calvillo E and Suarez JI (2022) Regional Variability in the Care and Outcomes of Subarachnoid Hemorrhage Patients in the United States. Front. Neurol. 13:908609. doi: 10.3389/fneur.2022.908609

Age, severity-of-illness, co-morbidities, hospital complications, and vasopressor use increased those odds (c-statistic; mortality: 0.77; discharge outcome: 0.81). Regional interaction effect was significant for admission severity-of-illness, aneurysm-repair and nimodipine-use.

Discussion: Multiple hospital-care factors impact SAH outcomes and significant variability in hospital-care and modest variability in discharge-outcomes exists across the US. Variability in SAH-severity, nimodipine-use and aneurysm-repair may drive variability in outcomes.

Keywords: clinical practice variation, critical care, clinical practice variability, discharge outcomes, hospital care, subarachnoid hemorrhage (SAH)

INTRODUCTION

Subarachnoid hemorrhage (SAH) patients have high prehospital mortality and those surviving the early phase, experience multiple hospital complications, particularly early brain injury, rebleeding, delayed cerebral ischemic (DCI), cardio-pulmonary complications, nosocomial infections, fluid imbalance and other iatrogenic complications, all of which further impact survival and functional outcomes after SAH and may be related to hospital care (1–5). SAH patients, thus require care by a multidisciplinary group of practitioners, preferably in specialized neurointensive care units (2, 3). However, despite advances in intensive care unit (ICU) care and nearly a 50% reduction in SAH mortality over the last two decades (6), limited scientific data guide therapy in SAH and very few interventions have strong evidence for impacting survival and outcomes (3). As a consequence, significant variability in SAH care is expected and has been reported in prior studies (7–12).

Majority of the studies that assess clinical practice variability in SAH are national and international practice pattern surveys (7–12), that are often subject to recall biases and do not include individual patient data and thus have not been able to determine if variability in care practices are associated with patient outcomes. We, therefore, used the Vizient Clinical Data Base (CDB), that includes patient-level data for this study. We hypothesized that there is significant regional variability in the care of SAH patients in the United States (US) and that this variability is associated with discharge outcomes. The objective of this study was to compare SAH care across different US geographic regions. We also aimed to identify hospital-care factors associated with discharge outcomes in SAH and to determine if regional variability in hospital-care is associated with outcome variability.

MATERIALS AND METHODS

Standard Protocol Approvals, Registrations, and Patient Consents

The Institutional Review Board (IRB) of the Johns Hopkins University School of Medicine deemed the study exempt (Protocol Number: IRB00294595), given that this was a retrospective analysis of deidentified patient data. The study was performed in accordance with the Strengthening The Reporting of OBservational studies in Epidemiology (STROBE) (13) and REporting of studies Conducted using Observational Routinely-collected Data (RECORD) guidelines (14). STROBE and RECORD checklists are included in the **Supplementary Material**.

Study Design and Data Source

We conducted a retrospective analysis of a cross-sectional cohort generated from the Vizient CDB. The Vizient CDB is a multi-center healthcare analytics platform for performance improvement (15) and comprises data from >95% of the US academic medical centers and their affiliated hospitals. It is a collection of patient-level Uniform Bill-04 billing data from all participating hospitals. The discharge abstract data contain information regarding patient demographics, hospital medications, procedures, hospital morbidity, discharge disposition and mortality. Vizient CDB has been previously validated in several observational studies (16–22).

Study Population

In this study, we included all adult patients (age >18 years) with a primary diagnosis of non-traumatic SAH (ICD-9 code: 430 and/or ICD-10 code: I60) in the Vizient CDB between January 1st, 2009 and December 30th, 2018. We chose to assess variability in hospital-care across all forms of non-traumatic SAH and included non-aneurysmal SAH patients as well, in order to ensure that patients are not excluded due to misclassification, given that the ICD codes do not differentiate between aneurysmal and non-aneurysmal hemorrhages. Patients were divided into four groups, based on the US Census Bureau geographic region of the hospital they were admitted to: Northeast (NE), South (S), Midwest (MW) and West (W) (23).

Variable Measurements

Demographics (patient age, race/ethnicity, gender), severity of illness upon admission, year-of-admission, co-morbidities, hospital complications, procedures, neuroimaging modalities, pertinent medications, hospital mortality, discharge disposition, length of stay, health-care direct costs and US census region were extracted from Vizient CDB for all patients. Categories of race and ethnicity followed the CMS methodology (24). Specific diagnoses, imaging modalities and procedures were

identified using International Classification of Diseases, Ninth and Tenth Edition (ICD-9 and ICD-10, Clinical Modification [CM] codes provided in the **Supplementary Material**). Imaging modalities, procedures, medications were flagged as present or absent during the encounter, regardless of the number of times they were used. DCI was defined by linking ICD codes for non-traumatic SAH and cerebral vasospasm, stroke and stroke-related sequalae (**Supplementary Material**). Annual SAH case volume by hospital was calculated, and a flag was created for low-volume SAH centers (<35 cases annually) in each US region (3). The designation of severity of illness (SOI) upon admission was derived from a combination of the 3M All Payer Refined-Diagnosis Related Group (APR-DRG) grouper (25). The SOI and associated risk of mortality is disease-specific and uses a classification for risk stratification consisting of four severity categories: minor, moderate, major, and extreme. In SAH, the APR-DRG risk-of-mortality severity index has been demonstrated to be valid and reliable severity adjustment score (26), with good predictive accuracy (AUC: 0.75) for poor outcome after SAH (27). It has been used previously as an adjustment for severity of illness in the absence of World Federation of Neurological Sciences (WFNS), Glasgow Coma (GCS) or Hunt-Hess scales in prior studies (28, 29).

Outcomes

Primary outcome measures included in-hospital mortality and the Nationwide Inpatient Sample-SAH Outcome Measure (NIS-SOM). NIS-SOM is a dichotomous functional outcome measure that defines good outcome as discharge to home or rehabilitation facility and poor outcome as a composite of in-hospital mortality, discharge to nursing facility/extended care facility/long-term acute care or hospice, placement of tracheostomy and/or gastrostomy (27). The NIS-SOM has been externally validated in a cohort of 716 SAH patients, where a strong correlation was noted between poor outcome defined by NIS-SOM and modified Rankin score (mRS) > 3 at discharge, with a high agreement (95%) and kappa-statistic of 0.84 (27). Secondary outcomes included hospital and ICU length of stay as well as health-care direct costs.

Data Access and Availability Statement

Individual de-identified patient data was available to all investigators through a written agreement with the Center for Advanced Analytics and Informatics, Vizient, Inc. Access to the data can be obtained by submitting a formal proposal in writing to the Center for Advanced Analytics and Informatics, Vizient, Inc.

Statistical Analysis

Patient demographics, comorbidities, care processes, length of stay and outcomes were stratified by US regions and summarized using frequencies (%) for categorical and means (SD) for continuous variables. Variability in these factors across regions was assessed by comparing frequencies/means using the χ^2 test or the analysis of variance (ANOVA) tests, as appropriate. To assess the relationship between variability in care and outcomes, we first fit multivariable logistic regression models, treating the study outcomes as the response and hospital-care factors, including treatment interventions and hospital complication flag as predictors. Hospital-care factors were selected if factors were known to commonly impact SAH outcomes and/or those associated with significant variability across the US regions. In the models, we also adjusted for potential confounders including age, admission SOI, presence of any comorbidity. To adjust for temporal trends in care, we also adjusted for the year-of-admission in the models. Final covariates were chosen if a strong association was noted, judged by p-values ($p < 0.05$) from the Wald test. Subsequently, to assess the impact of regional variability in hospital care and outcome, an interaction effect for US region was included in the logistic regression models. This assessed the relationship between various predictors and outcome by US regions. Performance of the models was tested using a concordance (c) statistic. Statistical analyses were performed using the software SAS (version 9.4, SAS Institute, Inc., Cary, NC), and p-values were two-sided with < 0.05 considered statistically significant.

RESULTS

Baseline Characteristics

We analyzed data from 109,034 non-traumatic SAH patients included in the Vizient CDB. Of these, 26,519 (24.3%) were from the NE; 27,166 (24.9%) from MW; 38,055 (34.9%) from S and 17,294 (15.9%) from W. Regional distribution of patients per year is shown in **Figure 1**. Number of SAH patients in the CDB increased from 2009 to 2018, which is likely due to the inclusion of more hospitals in the Vizient CDB.

Baseline characteristics by US census region are shown in **Table 1**. Mean (SD) age was 58.6 (15.6) years and was marginally higher in the NE (NE: 60.5 [15.9] years vs. mean age 57.9 [15.5] years in other regions). In total of 64,245 (58.9%) patients were female. In the total cohort, 68,492 (62.8%) were White, 19,786 (18.1%) were Black and 20,756 (19.0%) were other races and/or Hispanic ethnicity. Regionally, NE and MW had significantly higher proportions of White patients (NE: 66.3%; MW: 69.2%; S: 57.5%; W: 59.1%; $p < 0.0001$) whereas S had significantly higher proportions of Black patients (NE: 11.5%; MW: 17.5%; S: 28.4%; W: 6.7%; $p < 0.0001$). Higher proportions of other races/ethnicities (Asian, Pacific Islander, American Indian and Hispanic ethnicity) were noted in the W (34.2% vs. other region mean 16.5%; $p < 0.0001$).

Comorbidities are summarized in **Table 1**. Hypertension was the most common comorbidity and present in 71,064 (64.5%) of the total cohort, with highest proportions in the S (NE: 62%, MW: 64.9%, S: 69%, W: 62.4%, $p < 0.0001$).

In total of 91,044 (83.5%) patients were classified as either major or extreme SOI upon admission. SOI upon admission was also highly variable by region, with higher proportions of patients with major SOI in the NE (NE: 53.2%, MW: 51.5%, S: 49%, W: 51.8%; $p < 0.0001$) and extreme SOI in the S (NE: 30.7%, MW: 30.9%, S: 35%, W: 32.2%; $p < 0.0001$).

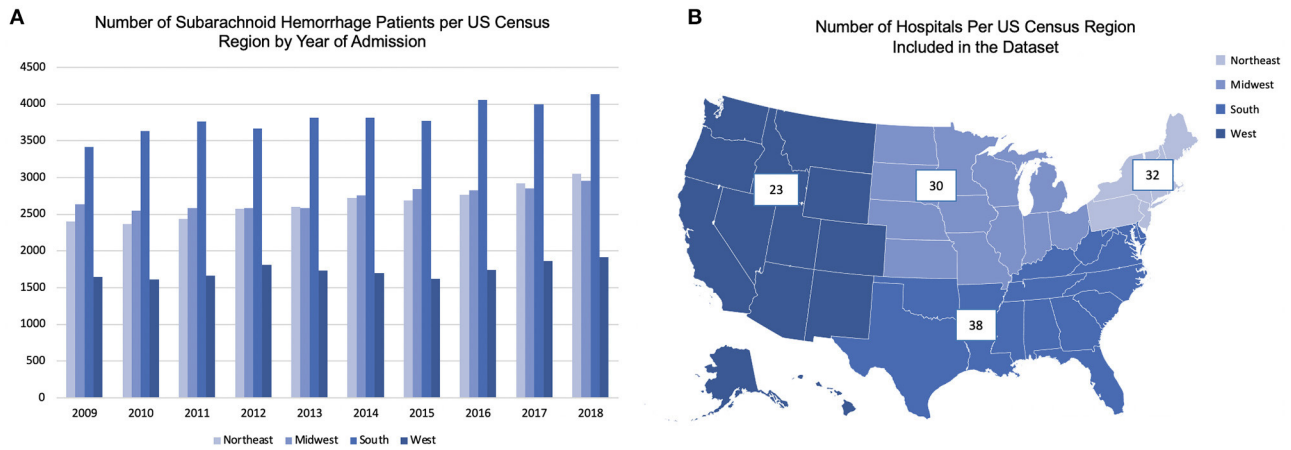

FIGURE 1 | (A) shows distribution of patients per United States Census Bureau region per year; **(B)** shows number of hospitals included in the analysis from the Vizient CDB per United States Census Bureau regions.

Hospital Characteristics

Number of hospitals included from the Vizient CDB in this analysis from each US census region are shown in **Figure 1**. SAH data was available from a total of 123 hospitals, majority (>95%) of which were academic centers. Majority of the hospitals were classified as high-volume SAH centers (annual SAH cases > 35), with 33 (26.8%) hospitals classified as low-volume SAH centers across all regions. The W had a higher proportion of low-volume SAH centers in the Vizient CDB, but this difference was not statistically significant (**Table 1**). However, a significantly higher proportion of SAH patients were admitted to low-volume SAH centers in the W (NE: 2.1%; MW: 3.7%; S: 4.5%; W:8.9%; $p < 0.0001$) (**Table 1**).

Medications

Comparison of medications used among SAH patients across the four US regions are shown in **Table 1**. We studied variability in use of nimodipine, antiepileptic drugs, vasopressors and albumin. Overall, 12,284 (11.3%) patients received nimodipine across all regions with higher use in the S and W (NE: 10.6%, MW: 10.7%, S: 12.0%, W: 11.7%; $p < 0.0001$). In total of 19,397 (17.8%) patients received antiepileptic drugs (AED), of which levetiracetam was most commonly used followed by phenytoin. With respect to regional variability, phenytoin use was twice more common in the W compared to other regions (NE: 1.1%; MW: 1.0%, S: 1.1%, W: 2.0%; $p < 0.0001$). Vasopressor and inotrope use (NE: 11.2%, MW: 13.3%, S: 13.9%, W: 13.9%; $p < 0.0001$) as well as albumin use (NE: 3%, S: 3.6%, MW: 4.1%, S: 4.0%; $p < 0.0001$) were less common in the NE compared to other regions.

Hospital Procedures

Hospital procedures by US census regions are summarized in **Table 1**. Aneurysmal surgical clipping was used in 13,866 (12.7%) patients, while endovascular coiling was used in 11,146 (10.2%) of the total cohort. Surgical clipping was significantly more common in the W (NE: 9.1%; MW: 12.9%; S: 12.4%; W: 18.8%; $p < 0.0001$). In general, as shown in **Table 2**, higher proportions of patients with major SOI received surgical clipping and minor/moderate SOI received endovascular coiling. However, across all grades of SOI, the W had higher proportions of patients receiving surgical clipping than endovascular coiling (**Table 2**).

With respect to DCI rescue therapies, intra-arterial (IA) vasodilator use was noted in 12,392 (11.4%) patients of the total cohort and was more common than cerebral angioplasty (3,294 [3.0%]). Significant regional variability in intra-arterial vasodilator use was noted (NE: 8.2%; MW: 13.1%; S: 11.9%; W: 12.4%; $p < 0.0001$). Among other procedures, notably, tracheostomy was significantly more common in the S (NE: 2%, MW: 2.7%; S: 4.6%, W: 2.7%; $p < 0.0001$).

Hospital Complications

There was significant variability in hospital complications across US regions as outlined in **Table 3**. Hydrocephalus (NE: 32.7%, MW: 34.2%, S: 37.9%, W: 35%; $p < 0.0001$) and cerebral edema (NE: 27.5%, MW: 26.1%, S: 35.2%, W: 29%; $p < 0.0001$) were more common in the S, whereas seizures/status epilepticus (NE: 15.2%, MW: 15.0%, S: 14.5%, W: 17%; $p < 0.0001$) and DCI (NE: 3.1%, MW: 3.8%, MW: 2.7%, W: 4.3%; $p < 0.0001$) were more common in the W.

Cardiopulmonary complications were significantly lower in the NE and higher in the S (NE: 44.6%, MW: 47.8%; S: 49.6%, W: 47.3%; $p < 0.0001$). Among these, acute respiratory failure was much more common in the S (NE: 31.6%, MW: 34.1%, S: 38.4%, W: 35%; $p < 0.0001$) and acute respiratory distress syndrome in W (NE: 0.8%, MW: 1.0%; S: 1.2% and W: 2.1%; $p < 0.0001$). Hyponatremia (NE: 18.1%, MW: 21.8%, S: 21.4%, W: 22%; $p < 0.0001$) and acute kidney injury (NE: 11.9%, MW: 13.2%, S: 12.3%, W: 14%; $p < 0.0001$) were less common in NE and more common in the W compared to other regions. Systemic infections were much more prevalent in the W (NE: 14.7%, MW: 15.2%, S: 14.4%, W: 18%; $p < 0.0001$) with a higher prevalence of aspiration pneumonia, sepsis and central nervous system infections ($p < 0.0001$).

TABLE 1 | Variability in baseline characteristics and hospital care variables by US Region.

Variables	NE (n = 26,519)	MW (n = 27,166)	S (n = 38,055)	W (n = 17,294)	p value
Baseline characteristics and Care Variables for Subarachnoid Hemorrhage patients across United States (2009 to 2018)[a]					
Age, mean (SD), y	60.5 (15.9)	58.7 (15.6)	57.5 (15.3)	57.7 (15.7)	<0.0001
Sex – Female	15,568 (58.7)	15,990 (58.9)	22,817 (60)	9,870 (57.1)	<0.0001
Race: White	17,585 (66.3)	18,784 (69.2)	21,898 (58)	10,225 (59.1)	<0.0001
Black	3,043 (11.5)	4,766 (17.5)	10,817 (28)	1,160 (6.7)	
Other/unknown[b]	5,891 (22.2)	3,616 (13.3)	5,340 (14)	5,909 (34.2)	
No. of low volume SAH centers[c]	8 (25.0)	8 (26.7)	9 (23.7)	8 (34.8)	0.80
Patients in low volume SAH-centers[c]	547 (2.1)	1,009 (3.7)	1,713 (4.5)	1,480 (8.9)	<0.0001
Medical co-morbidities					
Hypertension	16,437 (62.0)	17,627 (64.9)	26,213 (69)	10,787 (62.4)	<0.0001
Diabetes mellitus	4,341 (16.4)	4,720 (17.4)	7,076 (18.6)	2,999 (17.3)	<0.0001
Congestive heart failure	2,235 (8.4)	2,484 (9.1)	3,057 (8.0)	1,294 (7.5)	<0.0001
Smoking	3,966 (15.0)	5,193 (19.1)	6,998 (18.4)	2,297 (13.3)	<0.0001
Admission severity-of-illness[d]					
Minor	1,047 (4.0)	1,002 (3.7)	1,384 (3.6)	513 (3.0)	<0.0001
Moderate	2,832 (10.7)	2,748 (10.1)	3,830 (10.1)	1,903 (11.0)	
Major	14,107 (53.2)	13,998 (51.5)	18,623 (49)	8,963 (51.8)	<0.0001
Extreme	8,144 (30.7)	8,389 (30.9)	13,250 (35)	5,570 (32.2)	<0.0001
Radiology/procedures/medications[e]					
Cerebral angiogram/arteriogram	14,519 (54.8)	14,073 (51.8)	20,144 (53)	9,375 (54.2)	<0.0001
Extra-ventricular drain	5,694 (21.5)	5,927 (21.8)	9,192 (24.2)	4,181 (24.2)	<0.0001
Cerebral aneurysm clipping	2,419 (9.1)	3,500 (12.9)	4,701 (12.4)	3,246 (18.8)	<0.0001
Cerebral aneurysm coiling	2,737 (10.3)	2,668 (9.8)	4,138 (10.9)	1,603 (9.3)	<0.0001
Cerebral angioplasty	801 (3.0)	902 (3.3)	1,084 (2.9)	507 (2.9)	0.01
Ventriculo-peritoneal shunt	313 (1.2)	391 (1.4)	385 (1.0)	215 (1.2)	<0.0001
Tracheostomy	523 (2.0)	724 (2.7)	1,746 (4.6)	472 (2.7)	<0.0001
Gastrostomy tube placement	188 (0.7)	291 (1.1)	239 (0.6)	129 (0.8)	<0.0001
Electroencephalogram	3,755 (14.2)	4,005 (14.7)	4,870 (12.8)	2,771 (16.0)	<0.0001
Vasopressor and inotrope use[f]	2,964 (11.2)	3,617 (13.3)	5,306 (13.9)	2,411 (13.9)	<0.0001
Intra-arterial vasodilator therapy[g]	2,168 (8.2)	3,569 (13.1)	4,515 (11.9)	2,140 (12.4)	<0.0001
Nimodipine	2,808 (10.6)	2,904 (10.7)	4,557 (12.0)	2,015 (11.7)	<0.0001
Levetiracetam	4,192 (15.8)	4,075 (15.0)	5,587 (14.7)	2,513 (14.5)	0.0002
Phenytoin/fosphenytoin	265 (1.0)	258 (1.0)	431 (1.1)	321 (1.9)	<0.0001
Valproic acid	208 (0.8)	137 (0.5)	205 (0.5)	97 (0.6)	<0.0001
Albumin	802 (3.0)	968 (3.6)	1,575 (4.1)	693 (4.0)	<0.0001

NE, Northeast; MW, Midwest; S, South; W, West; SD, Standard Deviation; SAH, Subarachnoid Hemorrhage; MRI, Magnetic Resonance Imaging. [a]Unless otherwise specified, values are listed as number and percentage of total number of patients per region. [b]Other race/ethnicity includes Asian race, Pacific Islander, Native American, Hispanic Ethnicity. [c]Defined as annual SAH case load of less than 35 cases. [d]Defined by the All Patients Refined Diagnosis Related Groups (APR-DRG) disease-specific risk-of-mortality index. [e]Defined as at least one encounter for each modality or medication during hospital admission. [f]Included intravenous norepinephrine, epinephrine, dopamine, vasopressin, dobutamine, milnirone. [g]Included intra-arterial nicardipine, verapamil, milnirone, papaverine.

Outcomes

Patient outcomes are highlighted in **Table 2**. Overall hospital mortality occurred in 21,991 (20.2%), with modest but statistically significant variability across US regions (NE: 20.4%; MW: 19.5%; S: 20.2%; W: 20.8%; $p = 0.004$). Poor outcome by NIS-SOM occurred in 44,119 (40.5%) of the total cohort, with modest but statistically significant regional variability (NE: 40.4%; MW: 41.7%; S: 39.6%; W: 40.4%; $p < 0.0001$). Odds for hospital mortality and poor discharge outcome decreased significantly through the study period and every year in the cohort (approximately 5% per annum when compared to 2009) (**Figure 2**).

There was significant regional variability in discharge disposition. Overall, 43.6% patients were discharged home with highest proportions in the S followed by the W (**Table 3**). In total of 18.3% of patients were discharged to an acute rehabilitation facility, but significantly lower in the W: 10.4% were discharged to a skilled nursing facility with highest proportions in MW and

TABLE 2 | Aneurysmal coiling vs. clipping by admission severity of illness (SOI) in each US region.

Region	Coiling	Clipping	*p*-value
Coiling vs. clipping by admission severity of illness (SOI)			
Minor SOI (n; Northeast = 1,047, Midwest = 1,002, South = 1,384, West = 513)			
Northeast	319 (30.4)	<5	
Midwest	320 (31.9)	<5	
South	455 (32.9)	<5	
West	149 (29.1)	<5	
Moderate SOI (n; Northeast = 2,832, Midwest = 2,748, South = 3,830, West = 1,903)			
Northeast	563 (19.9)	397 (14.0)	<0.0001
Midwest	544 (19.8)	532 (19.3)	0.928
South	827 (21.6)	687 (17.9)	0.0004
West	292 (15.3)	540 (28.4)	<0.0001
Major SOI (n; Northeast = 14,107, Midwest = 13,998, South = 18,623, West = 8,963)			
Northeast	1131 (8.0)	1397 (9.9)	<0.0001
Midwest	1136 (8.1)	2122 (15.2)	<0.0001
South	1614 (8.7)	2551 (13.7)	<0.0001
West	599 (6.7)	1782 (19.9)	<0.0001
Extreme SOI (n; Northeast = 8,144, Midwest = 8,389, South = 13,250, West = 5,570)			
Northeast	632 (7.8)	524 (6.4)	0.004
Midwest	572 (6.8)	696 (8.3)	0.0001
South	1096 (8.3)	1258 (9.5)	0.0001
West	346 (6.2)	679 (12.2)	<0.0001

W: 3.6% were discharged to a long-term acute care facility and 3.2% to hospice. Mean length of stay was higher in the W (mean [SD] days; NE: 14.2 [19.7], MW: 13.6 [13.3], S: 14.4 [16.6], W: 15.7 [19.2]; $p < 0.0001$), as were the ICU length of stay (mean [SD] days; NE: 8.3 [9.9], MW: 8.5 [9.7], S: 8.8 [10.3], W: 9.6 [12.6]; $p < 0.0001$) and health-care direct costs (mean [SD] USD; NE: 58,574 [93,223], MW: 57,183 [59.576], S: 59,036 [66,179], W: 80,379 [98,999]; $p < 0.0001$).

Predictors of Hospital Outcomes

Factors independently associated with lower hospital mortality included subsequent years of admission (2014-18 vs. 2009-13: adjusted odds ratios [aOR], 0.72, 95% confidence intervals [CI], 0.69–0.74), aneurysmal repair by coiling (aOR, 0.50, 95% CI, 0.46–0.53) or clipping (aOR, 0.37, 95% CI, 0.35–0.40), presence of a co-morbidity flag (aOR, 0.75, 95% CI, 0.71–0.79), nimodipine use (OR, 0.41, 95% CI, 0.38–0.44), intra-arterial vasodilator rescue therapy (aOR, 0.48, 95% CI, 0.45–0.51) and cerebral angioplasty (aOR, 0.75, 95% CI, 0.68–0.83). Higher age (aOR per y, 1.02, 95% CI, 1.019–1.021), worse APR-DRG admission SOI (extreme vs. minor: aOR, 13.53, 95% CI, 11.60–15.78) any hospital complication flag (aOR, 1.53, 95% CI, 1.47–1.59), vasopressor use (aOR, 2.38, 95% CI, 2.24–2.54) and hospital US region West (W vs. NE: aOR, 1.12, 95% CI, 1.07–1.18) were independently associated with higher hospital mortality (c-statistic for hospital mortality model: 0.765). Regional variability in hospital mortality predictors with corresponding aOR and 95% CI by each US region are shown in **Table 4**. Regional interaction effect revealed that factors contributing to regional variability in hospital mortality included variability in aneurysm repair and admission SOI.

Factors independently associated with reduced odds for poor discharge outcome included subsequent years of admission (2014-18 vs. 2009-13: aOR, 0.69, 95% CI, 0.66–0.71), aneurysmal repair by clipping (aOR, 0.89, 95% CI, 0.85–0.93), nimodipine use (0.44, 95% CI, 0.41–0.47) and intra-arterial vasodilator rescue therapy (aOR, 0.66, 95% CI, 0.64–0.72), whereas factors increasing odds for poor outcome included higher age (aOR per y, 1.045, 95% CI, 1.044–1.046), presence of a comorbidity flag (aOR, 1.21, 95% CI, 1.15–1.27), higher APR-DRG admission SOI (extreme vs. minor: aOR, 20.64, 95% CI, 18.52–23.00), any hospital complication flag (aOR, 3.05, 95% CI, 2.94–3.15), vasopressor use (aOR, 1.74, 95% CI, 1.64–1.85) and hospital US region MW (MW vs. NE: aOR 1.13, 95% CI, 1.09–1.18) and W (W vs. NE: aOR, 1.09, 95% CI, 1.04–1.14) (c-statistic for discharge outcome model: 0.809). Regional variability in discharge outcome predictors with corresponding aOR and 95% CI by each US region are shown in **Table 5**. Regional interaction effect revealed that factors contributing to regional variability in poor discharge outcomes included variability in aneurysm repair, admission SOI and nimodipine use.

DISCUSSION

In this 10-year retrospective cross-sectional cohort study of 109,034 non-traumatic SAH patients, we found significant regional variability in patient characteristics and hospital interventions across the US. While there was only a modest variability in hospital outcomes, hospital complications also had significant variability across the US. Factors contributing to variability in discharge outcomes included variability in admission SOI, nimodipine use and aneurysm repair. Our study also demonstrated a continued progressive improvement in hospital mortality and discharge outcome every year, indicating an overall improvement in SAH care across the US, consistent with prior studies (6).

Strengths and Limitations

Strengths of this study include data from a large cohort of non-traumatic SAH patients admitted to majority of academic institutions in the US. Such a very large cohort of SAH patients from multiple academic centers and affiliated hospitals across the US over a 10-year period, with updated data through 2018, has allowed us to provide insights into more recent trends in care practices, complications and outcomes across the nation. The Vizient CDB comprise detailed information on hospital care and hospital charges associated with resources used. In addition, the risk adjustment model available in the database has been validated and commonly used for comparison of institutions and estimations of quality of care delivered (10, 15, 17–21), providing a unique insight into SAH care in the country.

TABLE 3 | Variability in hospital complications and patient outcomes by US Region.

Variables	NE (n = 26,519)	MW (n = 27,166)	S (n = 38,055)	W (n = 17,294)	*P* value
Complications and outcomes in subarachnoid hemorrhage patients across the United States (2009-2018)[a]					
Complications					
Hydrocephalus	8,673 (32.7)	9,286 (34.2)	14,437 (37.9)	6,075 (35)	<0.0001
Delayed cerebral ischemia	830 (3.1)	1034 (3.8)	1024 (2.7)	737 (4.3)	<0.0001
Seizures/status epilepticus	4,025 (15.2)	4,081 (15.0)	5,515 (14.5)	2,844 (17)	<0.0001
Cerebral edema	7,304 (27.5)	7,099 (26.1)	13,382 (35.2)	5,043 (29)	<0.0001
Cerebral ventriculitis	637 (2.4)	785 (2.9)	1,084 (2.9)	655 (3.8)	<0.0001
Cardio-pulmonary complications	11,836 (44.6)	12,974 (47.8)	18,877 (49.6)	8,181 (47)	<0.0001
Neurogenic stress cardiomyopathy	408 (1.5)	446 (1.6)	539 (1.4)	304 (1.8)	0.0026
Volume/fluid overload	618 (2.3)	1,059 (3.9)	1,156 (3.0)	676 (3.9)	<0.0001
Acute myocardial infarction	3,856 (14.5)	3,968 (14.6)	4,782 (12.6)	2,279 (13)	<0.0001
Pulmonary edema	263 (1.0)	387 (1.4)	398 (1.1)	223 (1.3)	<0.0001
ARDS	213 (0.8)	262 (1.0)	462 (1.2)	356 (2.1)	<0.0001
Acute respiratory failure	8,389 (31.6)	9,272 (34.1)	14,595 (38.4)	6,010 (35)	<0.0001
Pulmonary embolism	527 (2.0)	623 (2.3)	704 (1.9)	366 (2.1)	0.0009
Deep venous thrombosis	47 (0.2)	70 (0.3)	69 (0.2)	31 (0.2)	0.0988
Hyponatremia	4,811 (18.1)	5,915 (21.8)	8,141 (21.4)	3,841 (22)	<0.0001
Acute kidney injury	3,160 (11.9)	3,587 (13.2)	4,673 (12.3)	2,418 (14)	<0.0001
Systemic infectious complications	3,908 (14.7)	4,138 (15.2)	5,483 (14.4)	3,112 (18)	<0.0001
Aspiration pneumonia	1,135 (4.3)	977 (3.6)	1,306 (3.4)	954 (5.5)	<0.0001
Sepsis	1,649 (6.2)	1,807 (6.7)	2,436 (6.4)	1373 (7.9)	<0.0001
Bacteremia	551 (2.1)	630 (2.3)	817 (2.2)	289 (1.7)	<0.0001
Clostridium difficile enteritis	607 (2.3)	646 (2.4)	692 (1.8)	450 (2.6)	<0.0001
Discharge outcomes					
In-Hospital mortality	5,404 (20.4)	5,304 (19.5)	7,689 (20.2)	3,594 (21)	0.0081
Home	10,724 (41.0)	10,999 (41.0)	17,334 (46.5)	7,426 (45)	<0.0001
Rehabilitation facility	5,674 (21.7)	5173 (19.3)	6278 (16.8)	2413 (15)	<0.0001
Skilled nursing facility	2,743 (10.5)	3,169 (11.8)	3,145 (8.4)	2,027 (12)	<0.0001
Long-term acute care	735 (2.8)	1,212 (4.5)	1,408 (3.8)	491 (3.0)	<0.0001
Hospice	826 (3.2)	922 (3.4)	1,326 (3.6)	380 (2.3)	<0.0001
Unknown/other	24 (0.1)	67 (0.3)	97 (0.3)	48 (0.3)	<0.0001
NIS-SOM poor outcome[b]	10,710 (40.4)	11,337 (41.7)	15,085 (39.6)	6,987 (40)	<0.0001
Length of hospital stay, mean (SD), days	14.23 (19.7)	13.60 (13.3)	14.42 (16.6)	15.66 (19.2)	<0.0001
Length of ICU stay, mean (SD), days	8.27 (9.9)	8.52 (9.7)	8.84 (10.3)	9.63 (12.6)	<0.0001
Health-care direct cost, mean (SD), US dollars	58,574 (93,223)	57,183 (59,576)	59,036 (66,179)	80,379 (98,999)	<0.0001

NE, Northeast; MW, Midwest; S, South; W, West; ARDS, Acute Respiratory Distress Syndrome; NIS-SOM, Nationwide Inpatient Sample-Subarachnoid Outcome Measure; SD, Standard Deviation; US, United States. [a]Unless otherwise specified, values are listed as number and percentage of total number of patients per region; [b]defined as discharge to hospice, nursing facility, long-term acute care, death, need for tracheostomy and/or gastrostomy.

There are several limitations of this study which need to be highlighted. First, it is important to acknowledge that our cohort had lower proportions of patients who underwent aneurysmal clipping/coiling, than one would expect in a cohort of non-traumatic SAH patients. There are several reasons that may have contributed to this. The use of ICD codes to identify patients may be associated with reporting and misclassification biases, as ICD codes rely on appropriate coding by hospital providers. This may have led to traumatic and other non-aneurysmal SAH cases being wrongly classified into this cohort, increasing the denominator. In addition, billing codes were used for identification of aneurysmal repair interventions. These may be subject to under-, or over-coding and may also have led to a misclassification bias, leading to lower proportions of endovascular coiling and surgical clipping. To mitigate this, we used validated ICD codes and procedural codes. However, we do hypothesize that the lower proportions of coiling/clipping procedures in this cohort may, at least in part, truly reflect SAH care across the country, given that aneurysmal repair was independently associated with improved outcomes in multivariable models. Notably, in this cohort patients with a higher clinical severity-of-illness index (SOI) on admission were less likely to receive aneurysmal repair interventions. Thirty one percent with minor SOI underwent aneurysmal repair vs. only

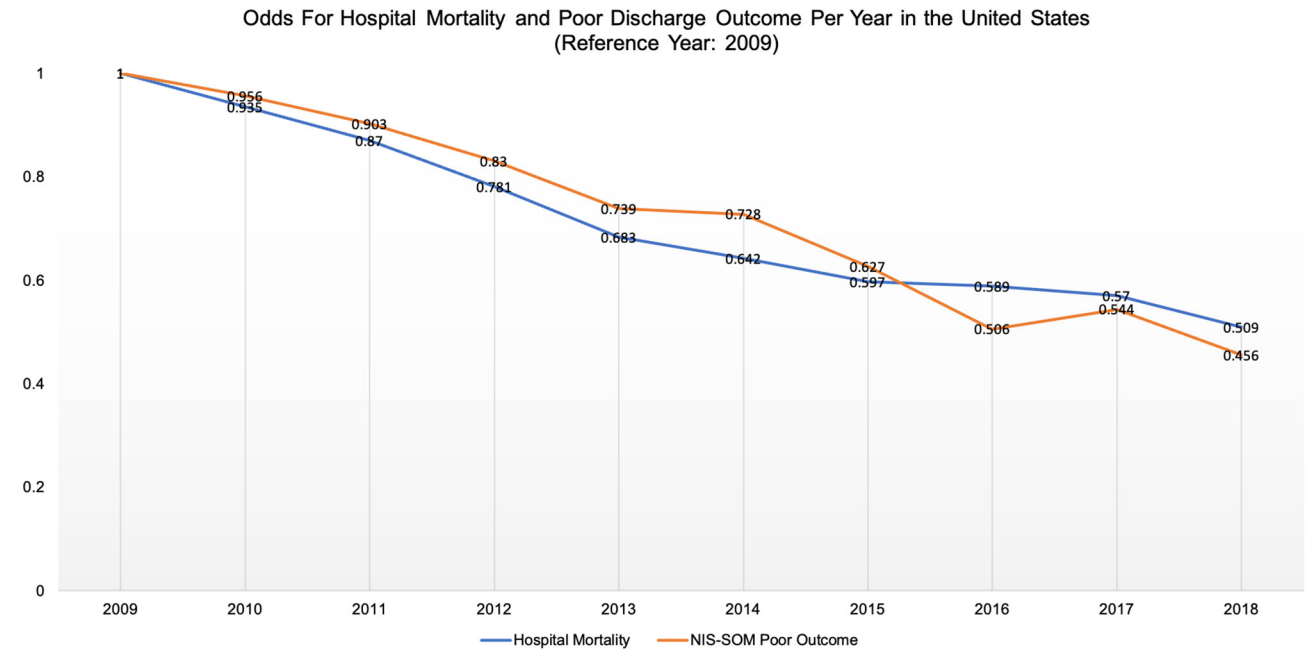

FIGURE 2 | Shows sustained reduction in odds for hospital mortality and poor Nationwide Inpatient Sample SAH-Outcome Measure (NIS-SOM) per year from 2009 to 2018.

TABLE 4 | Multivariable logistic regression models predicting hospital mortality by US region.

Variable	Adjusted odds ratio estimates (95% confidence intervals)				*P* value	
Hospital mortality						
Years: 2014–2018 vs. 2009–2013	0.71 (0.69–0.74)				<0.0001	
	Northeast	**Midwest**	**South**	**West**	**Main effect**	**Regional interaction Effect**
Aneurysm repair						
Any procedure	0.25 (0.12–0.54)	0.24 (0.11–0.54)	0.61 (0.39–0.96)	0.68 (0.46–1.02)	<0.0001	0.001
Endovascular coiling	0.53 (0.47–0.61)	0.50 (0.44–0.57)	0.41 (0.37–0.46)	0.53 (0.45–0.63)		
Surgical clipping	0.34 (0.30–0.40)	0.33 (0.28–0.37)	0.37 (0.34–0.42)	0.42 (0.37–0.48)		
Age, per year	1.02 (1.02–1.024)	1.02 (1.02–1.021)	1.02 (1.02–1.022)	1.02 (1.02–1.023)	<0.0001	0.192
Presence of a comorbidity flag[a]	0.77 (0.69–0.85)	0.74 (0.66–0.83)	0.7 (0.66–0.80)	0.82 (0.72–0.94)	<0.0001	0.528
Severity of illness (SOI) on admission[b]						
Moderate SOI	2.36 (1.7–3.3)	1.9 (1.41–2.67)	1.91 (1.42–2.55)	1.66 (1.08–2.56)	<0.0001	0.002
Major SOI	3.25 (2.39–4.42)	2.76 (2.05–3.70)	2.92 (2.23–3.81)	2.73 (1.82–4.09)		
Extreme SOI	15.1 (11.1–20.5)	11.90 (8.9–16.0)	14.4 (11.0–18.8)	13.13 (8.8–19.7)		
Presence of a hospital complication flag[c]	1.53 (1.42–1.65)	1.64 (1.52–1.77)	1.43 (1.34–1.53)	1.58 (1.44–1.73)	<0.0001	0.068
Nimodipine use	0.40 (0.35–0.47)	0.43 (0.37–0.50)	0.39 (0.35–0.45)	0.48 (0.40–0.58)	<0.0001	0.289
Vasopressor use[d]	2.58 (2.3–2.94)	2.55 (2.24–2.90)	2.60 (2.33–2.91)	2.45 (2.09–2.87)	<0.0001	0.943
Use of intra–arterial vasodilator therapy[e]	0.48 (0.41–0.56)	0.51 (0.45–0.58)	0.47 (0.42–0.52)	0.50 (0.42–0.59)	<0.0001	0.725
Cerebral angioplasty	0.77 (0.64–0.94)	0.71 (0.58–0.86)	0.81 (0.68–0.96)	0.71 (0.54–0.92)	0.009	0.715

SOI, Severity of Illness. [a]Defined as any medical comorbidity prior to ictus. [b]Defined by the All Patients Refined Diagnosis Related Groups (APR-DRG) disease-specific risk-of-mortality severity index; reference group: minor SOI. [c]Defined as any hospital complication during admission. [d]Included intravenous norepinephrine, epinephrine, dopamine, vasopressin, dobutamine, milnirone. [e]Included intra-arterial nicardipine, verapamil, milnirone, papaverine.

TABLE 5 | Multivariable logistic regression models predicting poor discharge outcome (NIS-SOM) by US region.

Variable	Adjusted odds ratio estimates (95% confidence intervals)				*P* value	
Year of admission: 2014–2018 versus 2009–2013	0.69 (0.66–0.71)				<0.0001	
	Northeast	**Midwest**	**South**	**West**	**Main effect**	**Regional interaction Effect**
Aneurysm repair						0.001
Endovascular coiling	0.96 (0.87–1.07)	1.14 (1.03–1.27)	0.84 (0.77–0.92)	0.96 (0.84–1.11)	0.605	
Surgical clipping	0.96 (0.87–1.07)	0.90 (0.82–0.98)	0.88 (0.81–0.95)	0.82 (0.74–0.90)		
Age, per year	1.05 (1.04–1.05)	1.05 (1.04–1.05)	1.05 (1.04–1.05)	1.04 (1.04–1.05)	<0.0001	0.171
Presence of a comorbidity flag[a]	1.181(1.07–1.30)	1.28 (1.16–1.42)	1.16 (1.06–1.26)	1.28 (1.14–1.45)	0.001	0.305
Severity of illness (SOI) on admission[b]						
Moderate SOI	1.91 (1.54–2.4)	2.02 (1.60–2.54)	1.91 (1.56–2.34)	1.70 (1.24–2.33)	<0.0001	<0.0001
Major SOI	3.05 (2.50–3.73)	3.98 (3.21–4.93)	3.28 (2.73–3.96)	3.34 (2.50–4.47)		
Extreme SOI	18.49(15.1–22.7)	22.6 (18.2–28.1)	21.8 (18.1–26.3)	18.7 (13.9–25.2)		
Presence of a complication flag[c]	2.98 (2.78–3.20)	3.08(2.878–3.30)	3.08 (2.90–3.27)	3.01 (2.76–3.28)	<0.0001	0.886
Nimodipine use	0.43 (0.38–0.50)	0.48 (0.42–0.55)	0.39 (0.34–0.43)	0.49 (0.42–0.58)	<0.0001	0.025
Vasopressor use[d]	1.63 (1.44–1.84)	1.75 (1.55–1.97)	1.81 (1.63–2.01)	1.79 (1.54–2.08)	<0.0001	0.615
Use of intra-arterial vasodilator therapy[e]	0.65 (0.57–0.74)	0.70 (0.63–0.79)	0.66 (0.60–0.73)	0.65 (0.56–0.75)	<0.0001	0.771

SOI, Severity of Illness. [a]Defined as any medical comorbidity prior to ictus. [b]Defined by the All Patients Refined Diagnosis Related Groups (APR-DRG) disease-specific risk of mortality severity index; reference group: Minor SOI. [c]Defined as any hospital complication during admission. [d]Included intravenous norepinephrine, epinephrine, dopamine, vasopressin, dobutamine, milnirone. [e]Included intra-arterial nicardipine, verapamil, milnirone, papaverine.

9% with major/extreme SOI, and majority of this cohort were classified as major and extreme SOI patients. This may be due to the withholding of aneurysmal repair among higher SAH grade patients, which has been considered a common practice in many centers (30–32).

Other limitations include identification of DCI as complication, given that there is no valid ICD code and DCI was defined by combining ICD codes for vasospasm and ischemic stroke with SAH. Additionally, we used mortality, discharge disposition and procedural codes for tracheostomy/gastrostomy to define poor discharge-outcome (NIS-SOM), as the database did not include functional outcome measures such as mRS or Glasgow outcome scale. Although this is not ideal, definitive end-points such as mortality, discharge disposition and procedural codes are not often impacted by misclassification bias, due to their association with billing. In addition, NIS-SOM is an externally validated outcome measure with a strong correlation and high agreement with poor mRS defined as mRS 4–6 (27). Nonetheless, we acknowledge that discharge outcomes are less meaningful when compared to longer-term outcomes such as 90 or 180-day outcomes, limiting our understanding of the true impact of variability in care on recovery after SAH. Moreover, regional variation in availability of different types of post-acute care discharge facilities, regional socioeconomic disparities and geographical impediments leading to delay in access to advanced SAH care, may have also confounded this study findings, which was not accounted for in this study. Finally, the database also did not include information on well-known SAH severity measures such as Hunt-Hess or WFNS grades, although the APR-DRG admission SOI risk-of-mortality index is disease-specific (25) and has also been shown previously to be a good predictor of functional outcome and mortality after SAH (27). We could not account for unmeasured confounders such as location of the aneurysm, timing of aneurysm treatment, granular information regarding neuroimaging characteristics of SAH, dosing/frequency and duration of medications used as these were not available in the administrative data. Hence, more detailed analyses were not feasible. Most importantly, ICD-9 and 10 codes could not differentiate non-aneurysmal from aneurysmal SAH and thus our cohort of patients included all non-traumatic SAH patients, regardless of etiology. We acknowledge that variability in care practices and outcomes may be related to variability in the geographic distribution of aneurysmal vs. non-aneurysmal SAH patients, however the goal of this study was to assess hospital-care across all SAH patients, regardless of etiology.

Implications of the Study

While variability in outcome has been studied previously (33–35), this is the first study evaluating regional variability in care among SAH patients using patient-level data in the US. Reasons for variability in care remain unclear, but may be

related to limited Class I data guiding therapy in SAH as well as significant variability in access to specialized care. A prior study showed that patients admitted to low-volume SAH centers have worse outcomes when compared to high volume centers (36). The W had a lower proportion of high-volume SAH centers compared to other regions in our cohort. This may explain the higher use of aneurysmal surgical clipping in the W, and consequent complications, particularly DCI, seizures and CNS infections. High-volume SAH centers are most often designated comprehensive stroke centers, and thus, have round-the-clock availability of endovascular neurointerventionalists, providing easy access to endovascular coiling. There is a national shortage of neurointerventionalists, with most US centers unable to meet the required neurointerventional procedure volume to ensure adequate operator experience (37). In a recent study, there was significant geographic disparity in proximity to certified stroke centers with higher disparity in the W compared to other regions (38). Majority of the central hub stroke-centers in the W are located in the more populous states of California, Oregon and Washington, with significant geographic impediments delaying access to advanced care, including prolonged travel times due to mountain travel, long distances, and weather impediments. This hypothesis needs further exploration including evaluation of population-to-neurointerventionalist and population-to-comprehensive-stroke-center ratios in different US regions and their relation to SAH care and outcomes. A prior study showed that higher population-to-neurosurgeon ratio and higher per-capita GDP were associated with lower mortality and better neurological outcomes in SAH likely due to centralized care and better resource availability (35).

Despite variability in care, we found only a modest variability in hospital mortality and discharge outcomes across US geographic regions. This is largely consistent with prior literature that found no significant difference in outcomes in SAH patients between countries and continents (11, 33), although there were differences in outcome between centers (33), which may be related to variability in experience in management of SAH patients. Our study, however, found significant regional variability in hospital complications, length of stay, likelihood of discharge to home/acute rehabilitation and health-care expenditure, which may be an influence of differences in care practices. For example, the W had higher incidence of DCI, seizures and systemic infections which are more commonly associated with surgical clipping after SAH (39). Higher length of stay in the W may be due to higher use of surgical clipping and its consequent complications. Similarly, lower prevalence of cardio-pulmonary complications in the NE, may be due to lower use of albumin and vasopressors as well as variability in fluid therapy (40), although we did not study volume and type of intravenous crystalloids used. Baseline patient characteristics, such as admission SOI and co-morbidities may also contribute to the variability in complications. For example, the S had a higher proportion of patients with extreme admission SOI, which may explain higher prevalence of cerebral edema, hydrocephalus and consequently, respiratory failure and need for tracheostomy. Vasopressor use was also higher in the S and this is associated with higher risk for global cerebral edema (41).

The most important factor associated with hospital outcome included SOI upon admission, a surrogate marker for SAH severity (27). This is consistent with prior studies which have shown that SAH severity grade remains the most important predictor of outcome (42). Patients with extreme SOI had an 11–22 fold higher risk for death and poor discharge outcome in our study. Consequently, admission SOI was also an independent factor driving regional variability in outcomes. Other patient characteristics associated with variability in outcome included age, hospital complications and co-morbidities. Presence of a co-morbidity reduced odds for hospital mortality but increased odds for poor discharge outcome, which may be a consequence of survival in a poor functional state. A prior study evaluating impact of co-morbidities on SAH outcome, however, did not find any association with outcome after SAH (43).

Among hospital interventions, aneurysm repair, nimodipine use, vasopressor use and EVT for DCI were associated with outcome. The benefits of early aneurysm repair have been known for decades (3, 44). Our study also demonstrated that aneurysm repair by surgical clipping or endovascular coiling significantly reduced odds for hospital mortality.

Nimodipine use was associated with reduction in mortality and poor discharge outcome, consistent with prior studies (45–47). Moreover, variability in nimodipine use also contributed to variability in discharge outcomes across US regions. In contrast, vasopressor use was associated with higher odds for death and poor discharge outcome. We were unable to delineate whether vasopressors were used for induced hypertension to treat DCI or to treat shock and hypotension. It is possible that the inverse relationship between vasopressor use and outcome may be due to higher incidence of hypotension and other complications among patients that needed vasopressors. However, even after adjusting for admission SOI and any complication flag, vasopressor use was independently associated with poor outcome in multivariable models. This is the first study showing worse outcomes with vasopressor use in SAH, however, prior studies have shown higher incidence of neurocardiogenic injury and cerebral edema in SAH patients receiving vasopressors (41, 48).

EVT for DCI, particularly intra-arterial vasodilator therapy, significantly reduced odds for hospital mortality and poor discharge outcome. There are no randomized trials that have assessed outcome benefit with EVT in DCI, however a large meta-analysis of 55 smaller observational studies showed significant radiographic benefit with only a modest clinical benefit (49). This is the first large multicenter study of more than hundred thousand patients that has shown significant improvement in discharge outcomes with EVT for DCI. Another recent study of 1,000 patients showed that early and more frequent EVT increased odds for favorable outcome compared to a more restrictive strategy (50) in DCI.

Other factors of significance that warrant discussion include variability in management of post-SAH pain and headache (51) as well as elevated intracranial pressure (ICP) (52). Our ability to study these was limited due to limited availability of more granular inpatient data in the Vizient data-base, including patient-reported pain, behavioral pain scores, ICP recordings and related interventions. We

did find variability in the use of extra-ventricular drains for ICP management, with higher use in S and W (24%) vs. NE and MW (21%). It is however likely, that there is significant variation in management of these SAH-related complications, including in the use of steroids and hyperosmolar therapy.

CONCLUSIONS AND FUTURE RESEARCH

Our study suggests that significant regional variability in care of SAH patients exists in the US. In addition, our data demonstrates a significant association between such variability and a modest worsening in hospital outcomes and complications. Our findings need further confirmation in well-conducted prospective observational studies, which should incorporate detailed information regarding SAH severity, imaging data, and long-term clinical outcomes. Such prospective, observational studies will afford the opportunity for comparative-effectiveness research (CER) analyses to determine which treatments/interventions may have a significant effect on long-term outcomes and overall resource use and cost.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: The dataset includes individual de-identified patient-level data from more than 95% of academic centers in the US that participate in the Vizient Clinical DataBase. The data is collected and stored by Vizient Inc. and can be obtained by providing a written research proposal directly to Vizient Inc. Requests to access these datasets should be directed to clinicalanalytics@vizientinc.com.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Johns Hopkins Institutional Review Board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

VS participated in conceptualizing study, data collection, planning data analysis, interpretation and presentation of results, and wrote the first draft of the manuscript. SK, RD, and EC participated in data collection and review and editing of manuscript. AH performed data collection, data analysis, participated in interpretation and presentation of results, and review and editing of manuscript. SH participated in data analysis, interpretation and presentation of results, and review and editing of manuscript. JS conceptualized the study, formulated hypothesis, participated in data collection, analysis, and review and editing of manuscript. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.908609/full#supplementary-material

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Conflict of Interest: AH and SH are employed by Center for Advanced Analytics and Informatics, Vizient, Inc. None of the authors had any financial relationships except JS, who is the Chair of the DSMB for the INTREPID Study funded by BARD, member of the CEC for the REACT Study funded by Idorsia, member of the Editorial Board of Stroke, and an ex-officio member of the Board of Directors of the Neurocritical Care Society.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers | Frontiers in Neurology

ORIGINAL RESEARCH
published: 24 June 2022
doi: 10.3389/fneur.2022.893516

Pre-Operative Predictors for Post-Operative Pneumonia in Aneurysmal Subarachnoid Hemorrhage After Surgical Clipping and Endovascular Coiling: A Single-Center Retrospective Study

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Objective: Postoperative pneumonia (POP) is one of the major complications after aneurysmal subarachnoid hemorrhage (aSAH) associated with postoperative mortality, prolonged hospitalization, and increased medical cost. Early recognition of pneumonia and more aggressive management may improve patient outcomes.

Methods: We retrospectively reviewed all patients with aSAH who were admitted to our institution between January 2015 and December 2020. Baseline clinical characteristics, imaging data, and inflammatory biomarkers were reviewed. The risk factors derived from multivariate logistic regression of surgical clipping (SC) and endovascular coiling (EC) were analyzed. The area under the receiver operating characteristic (ROC) curve (AUC) was used to calculate each independent predictor's prediction ability.

Results: A total of 843 patients were enrolled. Compared with patients in the EC group, the incidence of POP was higher in the SC group [143/414 (34.54%) vs. 114/429 (26.57%), $p = 0.015$]. In the EC group, multivariate analysis revealed that age [$p = 0.001$; odds ratio (OR) = 1.04, 95% CI = 1.02–1.07], posterior circulation aneurysms ($p = 0.021$; OR = 2.07, 95% CI = 1.14–3.83), higher neutrophil (NEUT; $p < 0.001$; OR = 1.13, 95% CI = 1.06–1.21), World Federation of Neurosurgical Societies (WFNS) grade 4 or 5 ($p < 0.001$; OR = 4.84, 95% CI = 2.67–8.79), modified Fisher Scale (mFS) grade 3 or 4 ($p = 0.022$; OR = 2.60, 95% CI = 1.15–5.89), and acute hydrocephalus ($p = 0.048$; OR = 1.74, 95% CI = 1.01–3.00) were independent risk factors for POP. In the SC group, multivariate analysis revealed that age ($p = 0.015$; OR = 1.03, 95% CI = 1.01–1.05), WFNS grade 4 or 5 ($p = 0.037$; OR = 1.76, 95% CI = 1.03–3.00), heart disease

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Edited by:
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Specialty section:
This article was submitted to Endovascular and Interventional Neurology, a section of the journal Frontiers in Neurology

Received: *10 March 2022*
Accepted: *30 May 2022*
Published: *24 June 2022*

Citation:
Yuan K, Li R, Zhao Y, Wang K, Lin F, Lu J, Chen Y, Ma L, Han H, Yan D, Li R, Yang J, He S, Li Z, Zhang H, Ye X, Wang H, Li H, Zhang L, Shi G, Zhou J, Zhao Y, Zhang Y, Li Y, Wang S, Chen X, Zhao Y and Hao Q (2022) Pre-Operative Predictors for Post-Operative Pneumonia in Aneurysmal Subarachnoid Hemorrhage After Surgical Clipping and Endovascular Coiling: A Single-Center Retrospective Study. Front. Neurol. 13:893516. doi: 10.3389/fneur.2022.893516

($p < 0.001$; OR = 5.02, 95% CI = 2.03–12.45), higher white blood cell (WBC; $p < 0.001$; OR = 1.13, 95% CI = 1.07–1.20), and mFS grade 3 or 4 ($p = 0.019$; OR = 2.34, 95% CI = 1.15–4.77) were independent risk factors for POP.

Conclusion: Patients treated with SC are more likely to develop POP. Comprehensive preoperative evaluation of patients may help physicians to better predict POP and implement preventive measures to improve outcomes.

Keywords: aneurysmal subarachnoid hemorrhage, post-operative pneumonia, risk factors, endovascular coiling, surgical clipping

INTRODUCTION

Aneurysmal subarachnoid hemorrhage (aSAH) is a severe neurosurgical emergency with a high mortality rate of 22–50% (1–3). Even patients receiving surgical clipping (SC) or endovascular coiling (EC) therapy also left approximately one-third of the patients to suffer from being severely disabled and functionally dependent. Early and reliable prediction of the patients' condition after SAH is important in clinical practice for decision-making about treatment options and providing information for the patients and their families (4, 5).

Severe in-hospital complications may affect the prognosis of patients and increase the medical burden on patients' families and countries. Therefore, early identification of complications associated with poor patient prognosis has considerable clinical importance (6, 7). Postoperative pneumonia (POP) is one of the major complications after aSAH surgery and is associated with postoperative mortality, prolonged hospitalization, and increased medical cost (5, 8).

Three large studies have shown that patients with SC had a higher incidence of hospital complications than those with EC, leading to a higher risk of poor discharge outcomes and even long-term disability (9–12). Our team's research showed that POP may have a long-lasting impact on the prognosis of patients (5). Thus, early identification and active prevention of POP become critical. Some studies have tried to identify risk factors associated with POP; however, the two treatment modalities' preoperative indicators related to risk factors for POP have not been reported (13, 14).

This study retrospectively reviewed the preoperative indicators associated with POP in SC and EC groups. Further, we analyzed the potential causes of pneumonia due to these factors to provide clinical evidence for preventing and treating POP.

MATERIALS AND METHODS

Study Design

We retrospectively reviewed the patient data from consecutive patients with aSAH who were admitted to our institution between January 2015 and December 2020. All patient data were from the Long-Term Prognosis of Emergency Aneurysmal Subarachnoid Hemorrhage (LongTEAM) study. The registry is listed at ClinicalTrials.gov (registration no. NCT 04785976).

This study was approved by the Institutional Review Board of Beijing Tiantan Hospital, Capital Medical University (KY 2021-008-01). All participants or their authorized representatives obtained informed consent for clinical analyses. All the analyses were performed by the Declaration of Helsinki and the local ethics policies. Both procedures were performed by specific senior neurosurgeons, with an annual average of more than 250 procedures per neurosurgeon. All patients were managed according to the American Heart Association/American Stroke Association guidelines (15).

Inclusion and Exclusion Criteria

All patients had angiographically documented aSAH caused by intracranial aneurysm confirmed by computed tomography (CT) or lumbar puncture. The inclusion criteria were as follows: (1) age $\geq$18 years; (2) single aneurysm; (3) emergency admission without previous aneurysm rupture; (4) only patients treated by clipping or interventional; (5) complete 90-day follow-up; and (6) no missing data. The exclusion criteria were as follows: (1) admitted over 72 h from rupture to the emergency department; (2) other neurological diseases (tumor, vascular malformation, Parkinson's disease, multiple sclerosis, and primary epilepsy), and functional or neurological deficit of the extremities due to any cause; (3) history of neurosurgery before rupture; and (4) treatments, such as external ventricular drainage, lumbar puncture, angiography, intubation, and mechanical ventilation, at other hospitals before presentation to our hospital.

Procedures

Baseline clinical characteristics and imaging data were reviewed, such as age, sex, location of the ruptured aneurysm, Graeb score, acute hydrocephalus, and medical and medication history. The severity of aSAH was assessed based on the initial World Federation of Neurosurgical Societies (WFNS) grade and the modified Fisher Scale (mFS) grade. We also collected inflammatory markers, such as white blood cell (WBC), systemic inflammation response index (SIRI), neutrophil (NEUT), monocyte (MONO), monocyte-to-lymphocyte ratio (MLR), platelet-to-white blood cell ratio (PWR), platelet-to-neutrophil ratio (PNR), and neutrophil-to-lymphocyte ratio (NLR).

Postoperative clinical complications, such as rebleeding, delayed cerebral ischemia (DCI), seizures, intracranial infection, stress ulcer bleeding, abnormal hepatic function, urinary tract infection, anemia, hypoproteinemia, POP, and deep vein thrombosis (DVT), during hospitalization were collected. The modified Rankin Scale (mRS) scores were collected at discharge and 90 days after discharge.

Outcome Assessment

The primary outcome was the occurrence of POP. POP was defined as fever, increased WBC and C-reactive protein (CRP) levels, and chest radiograph showed pulmonary infiltrates within 30 days after surgery, which required antibiotic therapy by a surgeon, according to the modified Centers for Disease Control and Prevention criteria (16).

The secondary outcome was the mRS [a stroke outcome scale with scores ranging from 0 (no symptoms) to 6 (dead)] score at discharge and 90 days after discharge (the neurosurgeon followed up with patients *via* telephone or an outpatient appointment 90 days after discharge). Unfavorable outcomes were defined when the mRS score was ≥3.

Statistical Analysis

Categorical variables were presented as frequency (percentages), and continuous variables were presented as the means ± standard deviations (SD) or median and interquartile range (IQR). In comparing baseline characteristics and outcomes between groups, the Pearson's chi-square test or Fisher's exact test was used to compare categorical variables as appropriate. After testing for normality, continuous variables were analyzed using the independent Student's *t*-test or Mann-Whitney U rank-sum test (as appropriate). According to the diagnosis of POP, we divided the patients into two groups and performed the univariate regression analysis. Only variables with $p < 0.05$ in univariate analysis were entered in multivariate logistic regression analysis, with adjustments for other characteristics, a forward stepwise model was used to identify the independent predictors of POP between groups. The odds ratio (OR) and 95% confidence intervals (CIs) of variables were calculated. The sensitivities and specificities of predictive factors were calculated from the receiver operating characteristic (ROC) curve analyses. The area under the ROC curve (AUC) was calculated to measure each independent predictor's prediction ability. $p < 0.05$ was considered to be statistically significant. Statistical analyses were performed using the R statistical program (R studio; version 3.3.3), SPSS Statistics version 26.0 (IBM Corp.), and GraphPad PRISM 8.3.0 (GraphPad Software Inc.).

RESULTS

Patient Characteristics

A total of 843 patients in the retrospective cohort who had their hospitalization between January 2015 and December 2020 were enrolled in the present study (**Figure 1**). Compared with the SC group, patients in the EC group had a higher proportion of female patients [265/429 (61.8%) vs. 226/414 (54.6%), $p = 0.041$] and a higher proportion of posterior circulation aneurysms [77/429 (18.0%) vs. 12/414 (2.9%), $p < 0.001$; **Table 1**].

In-Hospital Complications

Compared with the EC group, patients in the SC group had higher incidences of DCI [136/414 (32.9%) vs. 90/429 (21.0%), $p < 0.001$], intracranial infection [83/414 (20.25%) vs. 10/429 (2.33%), $p < 0.001$], anemia [173/414 (41.79%) vs. 85/429 (19.81%), $p < 0.001$], hypoproteinemia [194/414 (46.86%) vs. 94/429 (21.91%), $p < 0.001$], and POP [143/414 (34.54%) vs. 114/429 (26.57%), $p = 0.015$] and a lower incidence of urinary tract infection [4/414 (0.97%) vs. 19/429 (4.43%), $p = 0.004$; **Table 2**]. The SC group had a higher incidence of unfavorable outcome at discharge [201/414 (48.55%) vs. 150/429 (34.97%), $p < 0.001$] and 90 days after discharge [92/414 (22.22%) vs. 62/429 (14.45%), $p < 0.001$].

Independent Risk Factors Associated With POP in All Patients

Multivariate analysis showed that age ($p < 0.001$; OR = 1.03, 95% CI = 1.01–1.04), female patients ($p = 0.012$; OR = 1.53, 95% CI = 1.10–2.14), WFNS grade 4–5 ($p < 0.001$; OR = 4.43, 95% CI = 3.09–6.37), mFS grade 3 or 4 ($p < 0.001$; OR = 3.04, 95% CI = 1.82–5.07), and SC ($p = 0.031$; OR = 1.43, 95% CI = 1.03–1.98) were independently associated with POP (**Table 3**).

Patient Characteristics in the EC Group

Patients who had POP in the EC group were more likely to have intraventricular hemorrhage on admission [94/114 (82.46%) vs. 173/315 (54.92%), $p < 0.001$], a higher incidence of WFNS grade 4 or 5 [57/114 (50.00%) vs. 30/315 (9.52%), $p < 0.001$], a higher incidence of mFS grade 3 or 4 [106/114 (92.98%) vs. 219/315 (69.52%), $p < 0.001$], a higher incidence of acute hydrocephalus [106/114 (62.28%) vs. 109/315 (34.60%), $p < 0.001$], a higher incidence of posterior circulation [33/114 (28.95%) vs. 44/315 (13.97%), $p < 0.001$], a higher incidence of hypertension [88/114 (77.19%) vs. 185/315 (58.73%), $p < 0.001$], a higher incidence of heart disease [19/114 (16.67%) vs. 21/315 (6.67%), $p = 0.003$], and higher level of inflammatory biomarkers, such as WBC [14.94 (11.32–17.96) vs. 11.55 (9.32–14.39), $p < 0.001$], MONO [0.45 (0.30–0.67) vs. 0.36 (0.25–0.54), $p < 0.001$], NEUT [13.10 (10.02–16.19) vs. 10.20 (7.63–12.91), $p < 0.001$], SIRI [6.17 (3.58–10.32) vs. 3.56 (2.25–5.77), $p < 0.001$], MLR [0.47 (0.35–0.67) vs. 0.36 (0.26–0.51), $p < 0.001$], a lower level of PWR [15.98 (13.17–22.74) vs. 19.58 (15.76–23.47), $p = 0.004$], and a lower level of PNR [17.95 (14.61–19.65) vs. 22.44 (17.50–28.40), $p = 0.002$; **Table 4**).

Patient Characteristics in the SC Group

Patients who had POP in the SC group were more likely to have intraventricular hemorrhage on admission [102/143 (71.33%) vs. 156/271 (57.56%), $p = 0.008$], a higher incidence of WFNS grade 4 or 5 [52/143 (36.36%) vs. 43/271 (15.87%), $p < 0.001$], a higher incidence of mFS grade 3 or 4 [131/143 (91.61%) vs. 205/271 (75.65%), $p < 0.001$], a higher incidence of heart disease 19/143 (13.29%) vs. 8/271 (2.95%), $p < 0.001$], a higher incidence of current use of anti-platelet aggregation drugs [12/143 (8.39%) vs. 7/271 (2.58%), $p = 0.015$], and higher level of inflammatory biomarkers, such as WBC [13.59 (11.51–17.37) vs. 11.57 (8.78–14.31), $p < 0.001$], MONO [0.47 (0.32–0.74) vs. 0.40 (0.27–0.56), $p < 0.001$], NEUT [11.60 (9.87–16.00) vs. 10.18 (7.52–12.93), $p < 0.001$], SIRI [5.44 (3.23–10.49) vs. 3.43 (2.34–6.24), $p < 0.001$], MLR [0.50 (0.32–0.73) vs. 0.38 (0.25–0.55), $p < 0.001$], PNR [18.29 (13.92–23.39) vs. 22.21 (17.02–28.98), $p = 0.005$], NLR [12.71 (8.56–20.33) vs. 11.06 (6.32–15.90), $p = 0.007$], and a lower level of PWR [2.00 (1.37–3.15) vs. 19.37 (14.98–23.83), $p < 0.001$; **Table 5**].

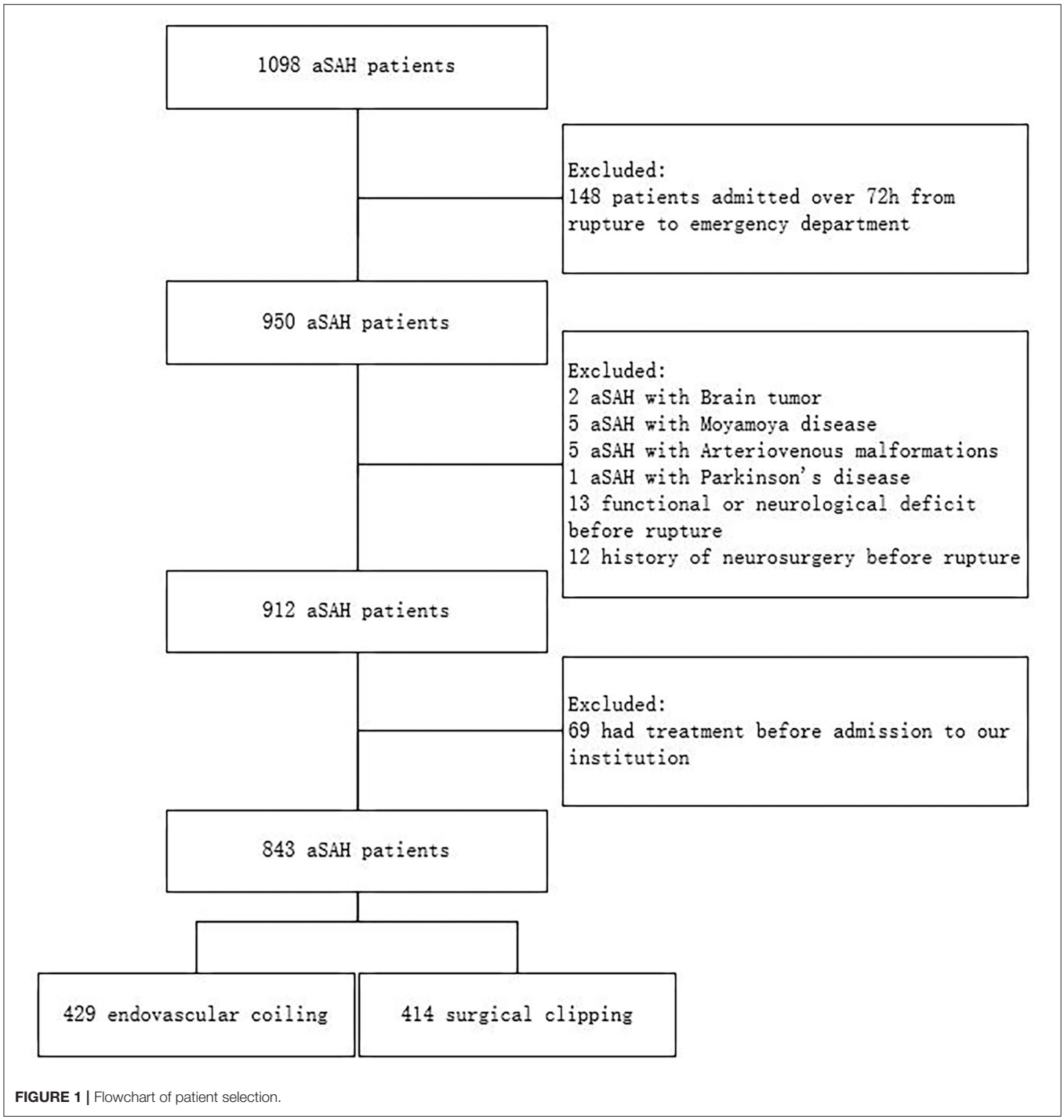

FIGURE 1 | Flowchart of patient selection.

Independent Risk Factors Associated With POP in the EC Group

Multivariate analysis showed that age ($p = 0.001$; OR = 1.04, 95% CI = 1.02–1.07), posterior circulation aneurysms ($p = 0.021$; OR = 2.07, 95% CI = 1.14–3.83), higher NEUT ($p < 0.001$; OR = 1.13, 95% CI = 1.06–1.21), WFNS grade 4 or 5 ($p < 0.001$; OR = 4.84, 95% CI = 2.67–8.80), mFS grade 3 or 4 ($p = 0.022$; OR = 2.60, 95% CI = 1.15–5.89), and acute hydrocephalus ($p = 0.048$; OR = 1.74, 95% CI = 1.01–3.00) were independently associated with POP in the EC group (**Table 6**).

Independent Risk Factors Associated With the Assurance of POP in the SC Group

Multivariate analysis showed that age ($p = 0.015$; OR = 1.03, 95% CI = 1.01–1.05), WFNS grade 4 or 5 ($p = 0.037$; OR 1.76, 95% CI

TABLE 1 | Baseline characteristics and group comparisons between the two treatment modalities.

Patient characteristics	Overall *N* = 843	Endovascular coiling *N* = 429	Surgical clipping *N* = 414	*P*
Age, y, mean ± SD	54.7 ± 11.1	55.4 ± 12.0	54.0 ± 10.2	0.067
Female, *n* (%)	491 (58.2)	265 (61.8)	226 (54.6)	0.041
WFNS grade 4–5, *n* (%)	182 (21.6)	87 (20.3)	95 (23.0)	0.391
mFS grade 3–4, *n* (%)	661 (78.4)	325 (75.8)	336 (81.2)	0.069
Intraventricular hemorrhage, *n* (%)	525 (62.3)	267 (62.2)	258 (62.3)	>0.99
Acute hydrocephalus, *n* (%)	338 (40.1)	180 (42.0)	158 (38.2)	0.292
Posterior circulation, *n* (%)	89 (10.6)	77 (18.0)	12 (2.9)	<0.001
Current smoking, *n* (%)	244 (29.0)	127 (29.6)	117 (28.3)	0.724
Current alcohol abuse, *n* (%)	187 (22.2)	104 (24.2)	83 (20.1)	0.167
Diabetes mellitus, *n* (%)	82 (9.7)	44 (10.3)	38 (9.2)	0.681
Hypertension, *n* (%)	510 (60.5)	273 (63.6)	237 (57.3)	0.068
Hyperlipidemia, *n* (%)	76 (9.0)	41 (9.6)	35 (8.5)	0.661
Heart disease, *n* (%)	67 (8.0)	40 (9.3)	27 (6.5)	0.169
Current use of anti-platelet aggregation drugs, *n* (%)	43 (5.1)	24 (5.6)	19 (4.6)	0.613

WFNS, World Federation of Neurological Societies; mFS, modified Fisher Scale.

TABLE 2 | The comparison of in-hospital complications between two treatment modalities.

Patient characteristics	Overall *N* = 843	Endovascular coiling *N* = 429	Surgical clipping *N* = 414	*p*
Rebleeding, *n* (%)	5 (0.59)	4 (0.93)	1 (0.24)	0.391
Delayed cerebral ischemia, *n* (%)	226 (26.81)	90 (20.98)	136 (32.85)	<0.001
Seizures, *n* (%)	9 (1.07)	5 (1.17)	4 (0.97)	>0.99
Intracranial infection, *n* (%)	93 (11.03)	10 (2.33)	83 (20.05)	<0.001
Stress ulcer bleeding, *n* (%)	192 (22.78)	104 (24.24)	88 (21.26)	0.341
Abnormal hepatic function, *n* (%)	244 (28.94)	116 (27.04)	128 (30.92)	0.244
Urinary tract infection, *n* (%)	23 (2.73)	19 (4.43)	4 (0.97)	0.004
Anemia, *n* (%)	258 (30.60)	85 (19.81)	173 (41.79)	<0.001
Hypoproteinemia, *n* (%)	288 (34.16)	94 (21.91)	194 (46.86)	<0.001
Postoperative pneumonia, *n* (%)	257 (30.49)	114 (26.57)	143 (34.54)	0.015*
Deep vein thrombosis, *n* (%)	73 (8.66)	32 (7.46)	41 (9.90)	0.254
mRS 3–6 at discharge, *n* (%)	351 (41.64)	150 (34.97)	201 (48.55)	<0.001
mRS 3–6 90 days after discharge, *n* (%)	154 (18.27)	62 (14.45)	92 (22.22)	0.005

*$P < 0.05$, *significant difference.*

1.03–3.00), heart disease ($p < 0.001$; OR = 5.02, 95% CI = 2.03–12.45), higher WBC ($p < 0.001$; OR = 1.13, 95% CI = 1.07–1.20), and mFS grade 3 or 4 ($p = 0.019$; OR = 2.34, 95% CI = 1.15–4.77) were independently associated with POP in the SC group (**Table 5**).

ROC Curve Analysis

In ROC analysis, when the AUC of a variable was >0.7, the predictor variable was defined as a good predictor. The AUC values for each independent risk factor that predicts POP in the SC group and EC group are shown in **Figures 2**, **3**, respectively.

Among preoperative indicators, WFNS grade 4 or 5 showed good predictive ability for POP in the EC group (AUC = 0.702, 2.67–8.80; $p < 0.001$).

DISCUSSION

Postoperative pneumonia is one of the major complications after aSAH surgery associated with postoperative mortality, prolonged hospitalization, and increased medical cost (6, 17–19). Our previous study revealed that among in-hospital complications, the occurrence of POP showed good predictive efficacy of 90-day unfavorable outcomes in the SC group and EC group (AUC > 0.7) (5). Therefore, trying to identify the occurrence of POP at an early stage is of great significance to improve patient outcomes.

In previous studies, SC was an independent risk factor for the occurrence of POP after aSAH (13). Therefore, we should pay more attention to the baseline characteristics and laboratory tests before the occurrence of POP after SC and EC to predict the occurrence of POP in advance and take preventive measures in

time. Unlike previous studies, this study paid more attention to distinguish between groups with different treatment modalities. Our study showed that age, WFNS grade 4 or 5, and mFS grade 3 or 4 were common independent risk factors associated with POP in both groups.

Aspiration of oropharyngeal fluid containing pathogenic microorganisms is the most common cause of POP (20). In addition, the more bacteria inhaled, the greater the likelihood of aspiration pneumonia (21, 22). Most aSAH operations are emergency operations with inadequate preoperative preparation, and patients often have symptoms of vomiting. Preoperative respiratory exercise and oral care are rarely performed, resulting in more oral bacteria and an increased risk of POP. With the increase in age, the immune function of the human body gradually decreases, the tracheal ciliary protective movement and cough reflex become worse, and the bacterial colonization of the oral and upper respiratory tract is significantly increased, leading to a significant increase in the risk of aspiration. At the same time, the increase in age will also lead to organ function failure, resulting in slower drug metabolism after general anesthesia, prolonged neuromuscular block time after anesthesia, and increased the probability of aspiration, ultimately leading to an increased incidence of POP (23, 24). Patients with a higher initial WFNS grade are more likely to stay in the hospital longer, increasing the probability of aspiration, which in turn increases the potential risk of POP. Previous studies have shown that poor postoperative awareness may be a risk factor for poor prognosis, which may also be partly related to the increased incidence of POP (14). Meanwhile, we analyzed the

TABLE 3 | Independent risk factors associated with postoperative pneumonia (POP) in all patients ($N = 843$).

Variables	OR (95%CI)	*p*
Age	1.03 (1.01–1.04)	<0.001
Female	1.53 (1.10–2.14)	0.012
WFNS grade 4–5	4.43 (3.09–6.37)	<0.001
mFS grade 3–4	3.04 (1.82–5.07)	<0.001
Surgical clipping	1.43 (1.03–1.98)	0.031

OR, odds ratio; CI, confidence interval; WFNS, World Federation of Neurological Societies; mFS, modified Fisher Scale.

TABLE 4 | Baseline characteristics and inflammatory biomarkers in the endovascular coiling EC group.

Variable	Overall *N* = 429	No-POP *N* = 315	POP *N* = 114	*p*
Age, y, mean ± SD	55.4 ± 12.0	54.1 ± 11.8	58.8 ± 11.9	<0.001*
Female, *n* (%)	265 (61.8)	201 (63.8)	64 (56.1)	0.183
WFNS grade 4–5, *n* (%)	87 (20.3)	30 (9.5)	57 (50.0)	<0.001*
mFS grade 3–4, *n* (%)	325 (75.8)	219 (69.5)	106 (93.0)	<0.001*
Graeb 5–12, *n* (%)	40 (9.3)	15 (4.76)	25 (21.9)	<0.001*
Acute hydrocephalus, *n* (%)	180 (42.0)	109 (34.6)	71 (62.3)	<0.001*
Posterior circulation, *n* (%)	77 (18.0)	44 (14.0)	33 (29.0)	<0.001*
Current smoking, *n* (%)	127 (29.6)	92 (29.2)	35 (30.7)	0.857
Current alcohol abuse, *n* (%)	104 (24.2)	74 (23.5)	30 (26.3)	0.635
Diabetes mellitus, *n* (%)	44 (10.3)	30 (9.5)	14 (12.3)	0.515
Hypertension, *n* (%)	273 (63.6)	185 (58.7)	88 (77.2)	<0.001*
Hyperlipidemia, *n* (%)	41 (9.6)	30 (9.5)	11 (9.7)	>0.99
Heart disease, *n* (%)	40 (9.3)	21 (6.7)	19 (16.7)	0.003*
Current use of anti-platelet aggregation drugs, *n* (%)	24 (5.6)	16 (5.1)	8 (7.0)	0.594
White blood cell count[a], median (IQR)	12.4 (9.67–15.53)	11.55 (9.32–14.39)	14.94 (11.32–17.96)	<0.001*
Lymphocyte count[a], median (IQR)	0.96 (0.70–1.34)	0.98 (0.69–1.33)	0.94 (0.71–1.36)	0.649
Monocyte count[a], median (IQR)	0.39 (0.27–0.57)	0.36 (0.25–0.54)	0.45 (0.30–0.67)	<0.001*
Neutrophil count[a], median (IQR)	11.03 (8.17–13.81)	10.20 (7.63–12.91)	13.10 (10.02–16.19)	<0.001*
Platelet count[a], median (IQR)	228.50 (183.75–269.50)	226.50 (181.00 −262.25)	232.50 (195.25–292.25)	0.028*
SIRI, median (IQR)	4.24 (2.44–7.02)	3.56 (2.25–5.77)	6.17 (3.58–10.32)	<0.001*
MLR, median (IQR)	0.26 (0.20–0.32)	0.36 (0.26–0.51)	0.47 (0.35–0.67)	<0.001*
PWR, median (IQR)	18.36 (14.52–23.25)	19.58 (15.76–23.47)	15.98 (13.17–22.74)	0.004*
PNR, median (IQR)	21.17 (16.17–27.33)	22.44 (17.50–28.40)	17.95 (14.61–19.65)	0.002*
NLR, median (IQR)	11.52 (7.61–17.05)	10.37 (6.12–15.72)	13.60 (9.47–19.65)	0.215

POP, postoperative pneumonia; mRS, modified Rankin scale; SD, standard deviation; IQR, interquartile range; WFNS, World Federation of Neurological Societies; mFS, modified Fisher Scale; SIRI, systemic inflammation response index; MLR, monocyte-to-lymphocyte ratio; PWR, platelet-to-white blood cell ratio; PNR, platelet-to-neutrophil ratio; NLR, neutrophil-to-lymphocyte ratio.

[a]*Unit of measurement: 10^9/L.*

*$p < 0.05$.

TABLE 5 | Baseline characteristics and inflammatory biomarkers in the surgical clipping (SC) group.

Variable	Overall *N* = 414	No-POP *N* = 271	POP *N* = 143	p
Age, y, mean ± SD	54.0 ± 10.2	53.1 ± 10.1	55.7 ± 10.1	0.012*
Female, *n* (%)	226 (54.6)	154 (56.8)	72 (50.4)	0.248
WFNS grade 4–5, *n* (%)	95 (23.0)	43 (15.9)	52 (36.4)	<0.001*
mFS grade 3–4, *n* (%)	336 (81.2)	205 (75.7)	131 (91.6)	<0.001*
Graeb 5–12, *n* (%)	24 (5.8)	9 (3.3)	15 (10.5)	0.003*
Acute hydrocephalus, *n* (%)	158 (38.2)	97 (35.8)	61 (42.7)	0.207
Posterior circulation, *n* (%)	12 (2.9)	8 (3.0)	4 (2.8)	>0.99
Current smoking, *n* (%)	117 (28.3)	69 (25.5)	48 (33.6)	0.104
Current alcohol abuse, *n* (%)	83 (20.1)	51 (18.8)	32 (22.4)	0.465
Diabetes mellitus, *n* (%)	38 (9.2)	20 (7.4)	18 (12.6)	0.117
Hypertension, *n* (%)	237 (57.3)	147 (54.2)	90 (62.9)	0.111
Hyperlipidemia, *n* (%)	35 (8.5)	27 (10.0)	8 (5.6)	0.182
Heart disease, *n* (%)	27 (6.5)	8 (3.0)	19 (13.3)	<0.001*
Current use of anti-platelet aggregation drugs, *n* (%)	19 (4.6)	7 (2.6)	12 (8.4)	0.014*
White blood cell count[a], median (IQR)	12.32 (10.02–15.60)	11.57 (8.78–14.31)	13.59 (11.51–17.37)	<0.001*
Lymphocyte count[a], median (IQR)	0.97 (0.70–1.40)	0.98 (0.69–1.46)	0.96 (0.70–1.40)	0.252
Monocyte count[a], median (IQR)	0.43 (0.29–0.60)	0.40 (0.27–0.56)	0.47 (0.32–0.74)	<0.001*
Neutrophil count[a], median (IQR)	10.83 (8.60–13.90)	10.18 (7.52–12.93)	11.60 (9.87–16.00)	<0.001*
Platelet count[a], median (IQR)	225.00 (194.50–268.50)	224.50 (190.25–267.50)	228.00 (198.50–269.50)	0.413
SIRI, median (IQR)	4.10 (2.61–8.09)	3.43 (2.34–6.24)	5.44 (3.23–10.49)	<0.001*
MLR, median (IQR)	0.40 (0.26–0.61)	0.38 (0.25–0.55)	0.50 (0.32–0.73)	<0.001*
PWR, median (IQR)	18.16 (14.10–23.13)	19.37 (14.98–23.83)	2.00 (1.37–3.15)	<0.001*
PNR, median (IQR)	21.18 (15.88–26.94)	22.21 (17.02–28.98)	18.29 (13.92–23.39)	0.005*
NLR, median (IQR)	11.67 (7.35–17.78)	11.06 (6.32–15.90)	12.71 (8.56–20.33)	0.007*

POP, postoperative pneumonia; mRS, modified Rankin scale; SD, standard deviation; IQR, interquartile range; WFNS, World Federation of Neurological Societies; mFS, modified Fisher Scale; SIRI, systemic inflammation response index; MLR, monocyte-to-lymphocyte ratio; PWR, platelet-to-white blood cell ratio; PNR, platelet-to-neutrophil ratio; NLR, neutrophil-to-lymphocyte ratio.

[a]*Unit of measurement: 10^9/L.*

**p < 0.05.*

correlation between WFNS grade and inflammatory indicators and found that WBC and NEUTs were significantly higher in WFNS grade 4–5 patients than in WFNS grade 1–3 patients, that is to say, patients with high WFNS grade may have a more severe inflammatory response.

Studies in mouse models have shown that NEUTs may be important mediators of early cortical hypoperfusion and oxidative stress after aSAH (25). Depletion of NEUTs 3 days after SAH mitigates tissue inflammation and reverses cerebral vasoconstriction in the middle cerebral artery (26); thus, NEUTs are closely associated with oxidative stress and cerebral vasoconstriction. Increased NEUTs or WBCs in the blood before surgery may set the stage for a more intense early systemic inflammatory response in the early stages of brain injury, increasing susceptibility to systemic infections, such as POP. Meanwhile, our data showed that patients with high WFNS grade or high mFS grade had a severe inflammatory response (**Figure 4**).

Hydrocephalus caused by aSAH can also manifest as high cranial pressure, which can lead to Cushing's reaction (CR). CR compensates for hypothalamic-mediated acute hyperemic

TABLE 6 | Independent risk factors associated with postoperative pneumonia (POP) in the endovascular coiling (EC) and surgical clipping (SC) groups.

Variables	OR (95%CI)	p
Independent risk factors associated with POP in the EC groups		
Age	1.04 (1.02–1.07)	0.001
Posterior circulation	2.07 (1.12–3.83)	0.021
NEUT	1.13 (1.06–1.21)	<0.001
WFNS grade 4–5	4.84 (2.67–8.79)	<0.001
mFS grade 3–4	2.60 (1.15–5.89)	0.022
Acute hydrocephalus	1.74 (1.01–3.00)	0.048
Independent risk factors associated with POP in the SC groups		
Age	1.03 (1.01–1.05)	0.015
Heart disease	5.02 (2.03–12.45)	<0.001
WFNS grade 4–5	1.76 (1.03–3.00)	0.037
WBC	1.13 (1.07–1.20)	<0.001
mFS grade 3–4	2.34 (1.15–4.77)	0.019

OR, odds ratio; CI, confidence interval; NEUT, neutrophil; WBC, white blood cell; WFNS, World Federation of Neurological Societies; mFS, modified Fisher Scale.

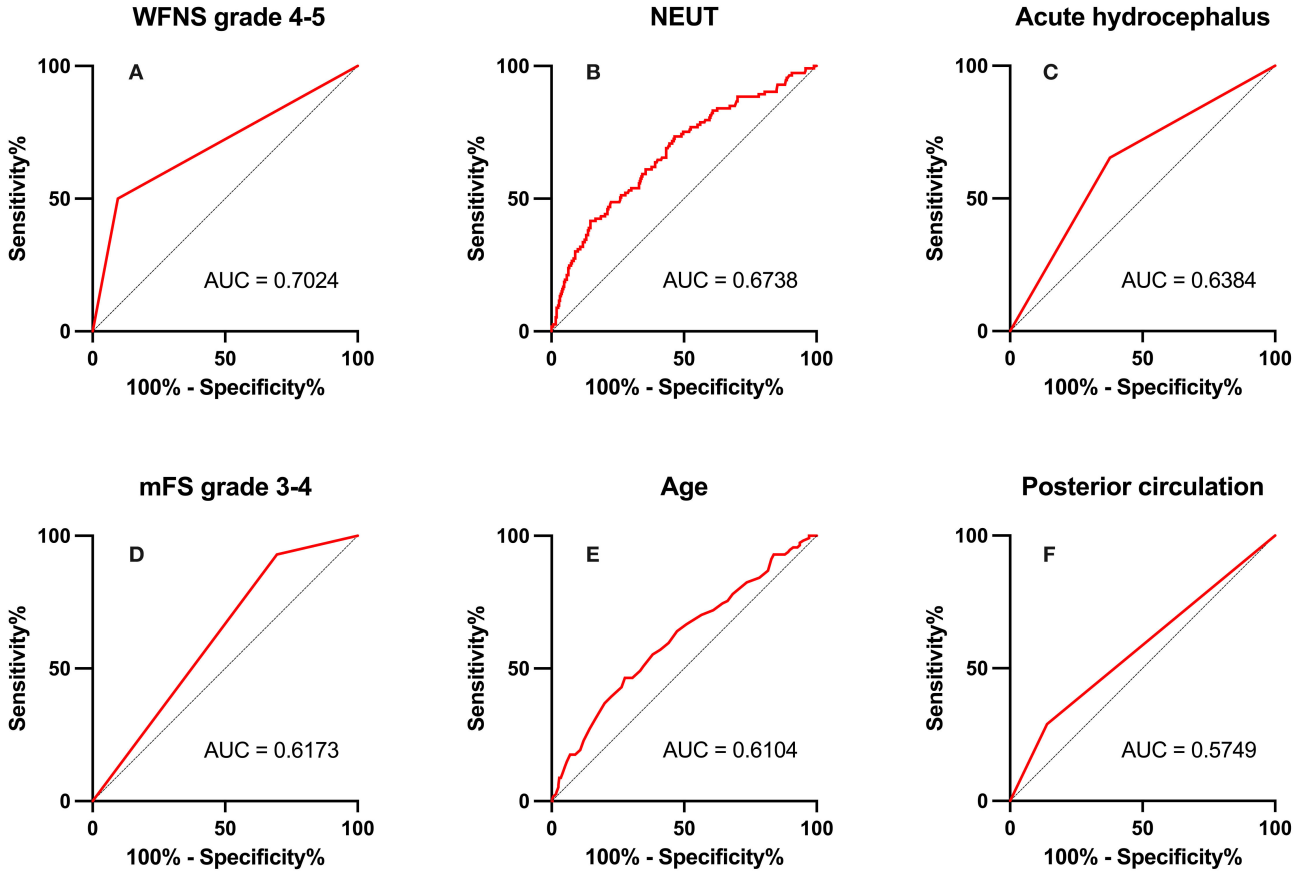

FIGURE 2 | Area under the receiver operating characteristic (AUC) values for preoperative factors that predicted postoperative pneumonia in the endovascular coiling (EC) group. **(A)** World Federation of Neurosurgical Societies (WFNS) grade 4–5 (AUC = 0.702, 95% CI = 2.67–8.80; $p < 0.001$). **(B)** Neutrophil (NEUT; AUC = 0.674, 95% CI = 1.06–1.22; $p < 0.001$). **(C)** Acute hydrocephalus (AUC = 0.638, 95% CI = 1.01–3.00; $p = 0.048$). **(D)** modified Fisher Scale (mFS) grade 3–4 (AUC = 0.617, 95% CI = 1.15–5.89; $p = 0.022$). **(E)** Age (AUC = 0.610, 95% CI = 1.02–1.07; $p = 0.001$). **(F)** Posterior circulation (AUC = 0.575, 95% CI = 1.12–3.83; $p = 0.021$).

response to intracranial pressure (ICP) increment. In patients with aSAH, CR mainly presents as sympathetic peaks with increased serum epinephrine and/or norepinephrine levels. High levels of these two hormones mediate early lymphocyte activation defects leading to POP (27). The severity of CR at SAH depends on the height of ICP and depends on the amount of blood that ruptured into the subarachnoid space (20, 28). Patients with high mFS grade may develop a persistent and excessive systemic inflammatory response syndrome that leads to immunosuppression and is more prone to POP.

Since posterior circulation aneurysms originate anteriorly in the brain stem, rupture and bleeding of posterior circulation aneurysms may affect the brain stem. Both the International Subarachnoid Aneurysm Trial (ISAT) (9) and International study of Unrupted intracranial Aneurysms (ISUIA) (29) studies confirmed that the complication rate of SC for posterior circulation aneurysms is much higher than that of EC treatment. The posterior circulation aneurysm in our center is also mainly treated by EC. At the same time, posterior circulation aneurysms are more likely than other aneurysms to cause an increase in ICP and hydrocephalus. In this case, the EC treatment itself does not improve the condition of hydrocephalus. All of these aggravated CR and increased the risk of POP. Rupture of posterior circulation aneurysm can also increase the incidence of cerebral vasospasm, which affects the cerebral nerves in the posterior approach group, thereby increasing the risk of vomiting and aspiration, leading to an increased incidence of POP (30). Patients with posterior circulation aneurysms with other risk factors of POP, such as a high WFNS grade and a high mFS grade, can be considered an early routine ICP reduction, such as lumbar cistern drainage, in addition to EC therapy.

For patients with pre-existing heart disease, cardiac dysfunction will lead to decreased lung function, significantly increase the probability of cardiogenic pulmonary edema, seriously impair lung ventilation and ventilation function, and reduce the ability of the lung to fight infection (31). They are more likely to develop POP after a traumatic craniotomy.

Therefore, we should pay more attention to preoperative indicators, especially preoperative laboratory indicators, such as WBC and NEUT, which may be of great significance for the

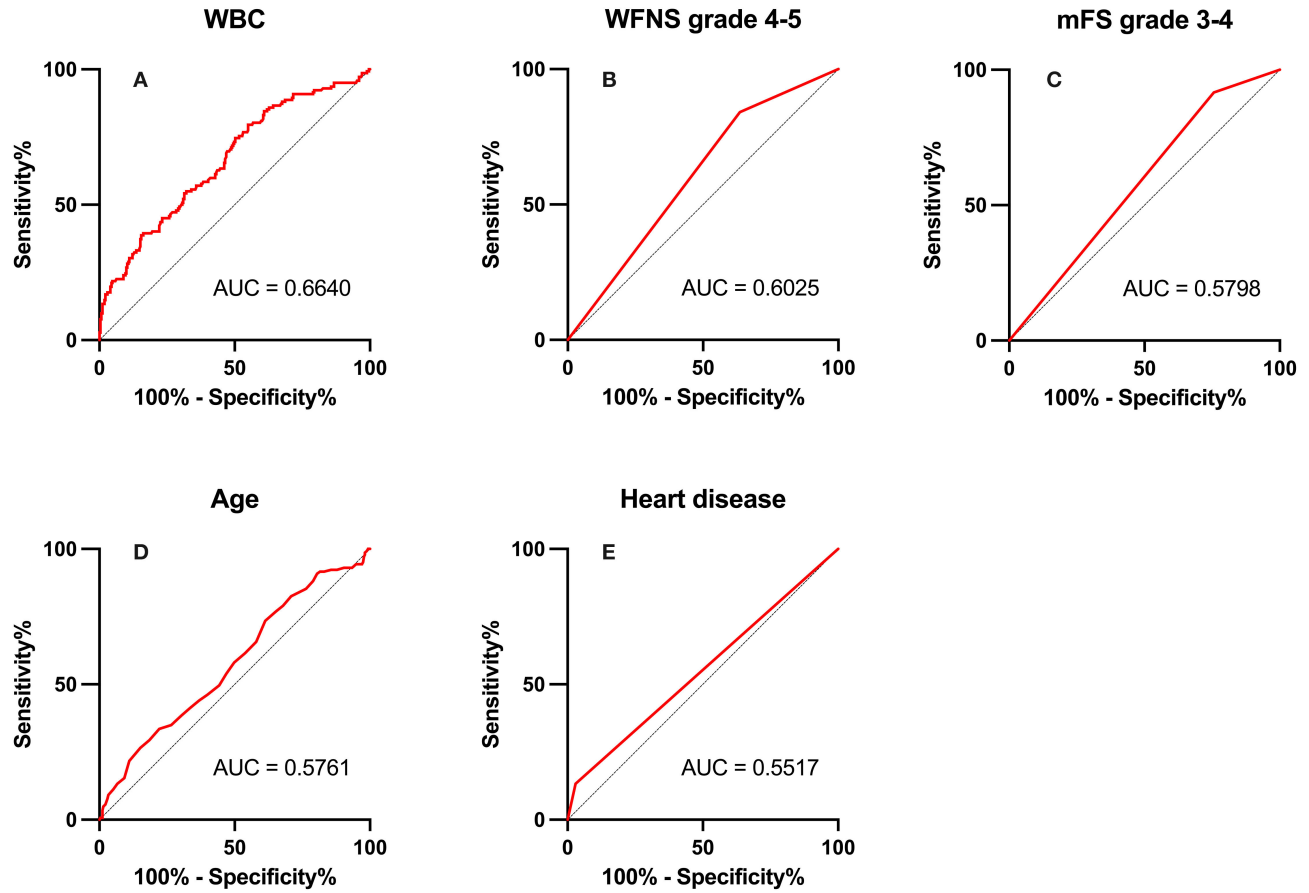

FIGURE 3 | Area under the receiver operating characteristic (AUC) values for preoperative factors that predicted postoperative pneumonia in the surgical clipping (SC) group. **(A)** White blood count (WBC; AUC = 0.664, 95% CI = 1.07–1.20; $p < 0.001$). **(B)** World Federation of Neurosurgical Societies (WFNS) grade 4–5 (AUC = 0.603, 95% CI = 1.03–3.00; $p = 0.037$). **(C)** Modified Fisher Scale (mFS) grade 3–4 (AUC = 0.580, 95% CI = 1.15–4.77; $p = 0.019$). **(D)** Age (AUC = 0.576, 95% CI = 1.01–1.05; $p = 0.015$). **(E)** Heart disease (AUC = 0.552, 95% CI = 2.03–12.45; $p < 0.001$).

identification of early POP. More prospective trials should be conducted in the future to confirm our results.

For patients who underwent elective coronary artery bypass-grafting surgery, a previous study has proved that taking some preventive, tailored interventions to improve inspiratory muscle function can reduce the incidence of POP by 50%. This raises the possibility of preoperatively identifying patients at high risk for POP and taking preventive measures to reduce the incidence of POP after surgery (32). However, aSAH is mostly emergency surgery, which makes our time even more stressful. Advances in surgical techniques have improved patient outcomes, meanwhile, another challenge is the periprocedural management of patients for anesthesiologists and intensivists (33). At present, there is no recognized effective measure to prevent the occurrence of POP. This is also the goal of our further study, starting with preoperative inflammatory parameters and serum epinephrine and/or norepinephrine levels to reduce the secondary attack of surgery on the lungs. We also plan to collect prospective data and build a scoring model for pneumonia in further studies to make it easier for all newly admitted patients to identify the potential risk of pneumonia as early as possible.

Once associated preoperative risk factors are identified, patients at high risk should take targeted preventive measures, such as quitting smoking as soon as physical examination reveals an unruptured aneurysm, initiating doctor-directed prophylaxis with inhale steroids and bronchodilators at the onset of symptoms, and pay attention to respiratory physical therapy and circulatory management. Strategies to inhibit catecholamine in the hyperacute phase may help to prevent vasospasm and improve patient outcomes (34).

Limitations

The study has several limitations. First, our data were collected retrospectively. Second, differences in preoperative baseline information between the two groups may lead to different risk factors for POP. Third, our study was a single-center study, lacking multicenter validation.

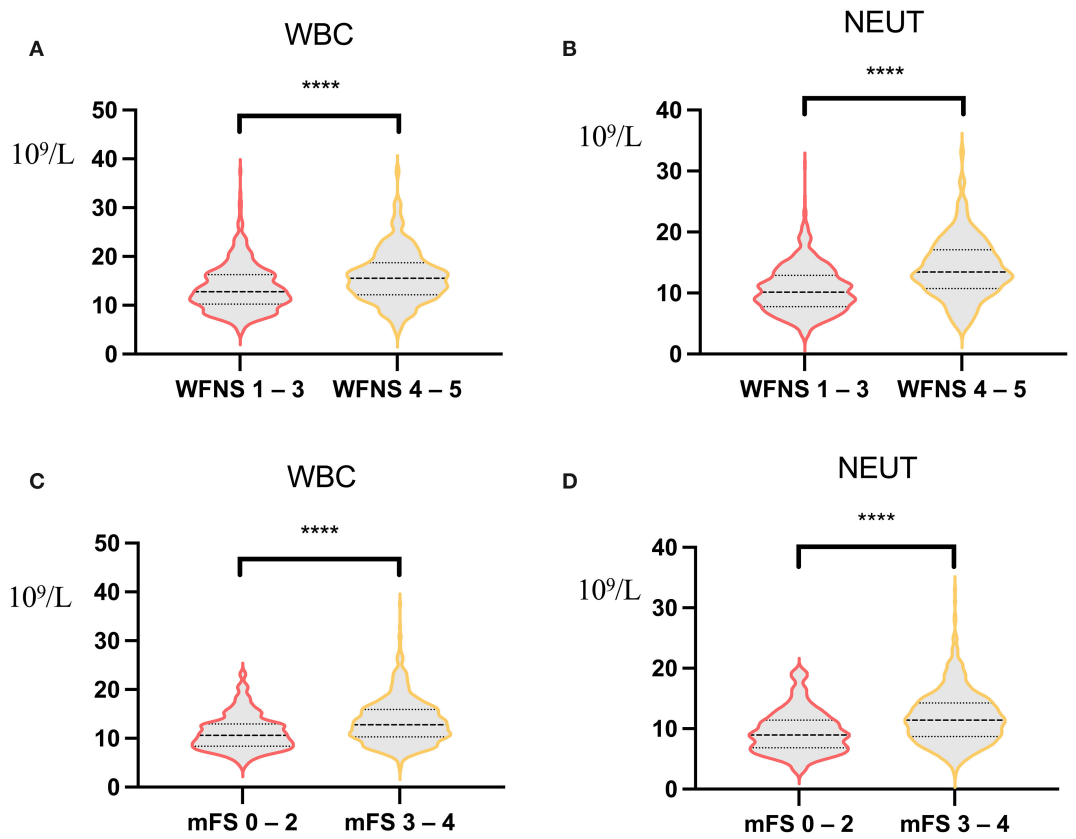

FIGURE 4 | Correlation analysis of World Federation of Neurosurgical Societies (WFNS) score, modified Fisher Scale (mFS) score, and inflammatory indicators. **(A)** Correlation analysis of white blood count (WBC) between WFNS grade 1–3 and WFNS grade 4–5 [12.14 (3.88) vs. 15.88 (5.19), $p < 0.001$]. **(B)** Correlation analysis of neutrophil between WFNS grade 1–3 and WFNS grade 4–5 [10.59 (3.78) vs. 14.03 (4.82), $p < 0.001$]. **(C)** Correlation analysis of WBC between mFS grade 0–2 and mFS grade 3–4 [11.18 (3.59) vs. 13.44 (4.57), $p < 0.001$]. **(D)** Correlation analysis of neutrophil between mFS grade 0–2 and mFS grade 3–4 [9.50 (3.52) vs. 11.85 (4.31), $p < 0.001$]. ****$p < 0.001$.

CONCLUSION

In summary, this large, single-center retrospective cohort study demonstrated that patients with aSAH treated with SC are more likely to develop POP. Patients with high preoperative inflammatory factors, high WFNS grade, and high mFS grade should be more alert to the occurrence of POP. Comprehensive preoperative evaluation of patients may help physicians to better predict POP and implement preventive measures to improve their outcomes.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of Beijing Tiantan Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

QH and YuaZ: conception, design, and reviewed submitted version of manuscript. KY, RunL, FL, YC, JL, HH, DY, RuiL, JY, ZL, HZ, HL, LZ, YanZ, and YukZ: acquisition of data. KY and RunL: drafting the article. KY, RunL, FL, YC, JL, and QH: statistical analysis. YL, SW, GS, and JZ: administrative, technical, and material support. QH, XC, and YuaZ: study supervision. All authors: analysis, interpretation of data, contributed to the article, and approved the submitted version.

FUNDING

This study was supported by the National Key Research and Development Program of China (Grant Nos. 2021YFC2501101 and 2020YFC2004701), the National Natural Science Foundation of China (Grant Nos. 82071296, 81671129, and

81471210), the Beijing Municipal Administration of Hospitals Incubating Program, Beijing, China (Grant No. pX2020023), and the Natural Science Foundation of Beijing, China (Grant No. 7204253).

ACKNOWLEDGMENTS

The authors acknowledge the contribution of all staff who participated in the present study.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
published: 14 July 2022
doi: 10.3389/fneur.2022.888369

Feasibility of FDCT Early Brain Parenchymal Blood Volume Maps in Predicting Short-Term Prognosis in Patients With Aneurysmal Subarachnoid Hemorrhage

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Specialty section:
This article was submitted to Endovascular and Interventional Neurology, a section of the journal Frontiers in Neurology

Received: 02 March 2022
Accepted: 16 June 2022
Published: 14 July 2022

Citation:
Wen L, Zhou L, Wu Q, Zhou X and Zhang X (2022) Feasibility of FDCT Early Brain Parenchymal Blood Volume Maps in Predicting Short-Term Prognosis in Patients With Aneurysmal Subarachnoid Hemorrhage. Front. Neurol. 13:888369. doi: 10.3389/fneur.2022.888369

Purpose: Aneurysmal subarachnoid hemorrhage (SAH) is accompanied by cerebral perfusion changes. We aimed to measure the parenchymal blood volume (PBV) maps acquired by C-arm flat-panel detector CT (FDCT) to assess the cerebral blood volume at an early stage in aneurysmal SAH and to explore the correlation with the outcomes at discharge.

Methods: Data of 66 patients with aneurysmal SAH who underwent FDCT PBV examination were retrospectively analyzed. The PBV of regions of interest, including the cortices of the bilateral frontal lobe, the parietal lobe, the occipital lobe, and the cerebral hemisphere, as well as the basal ganglia, were measured and quantitatively analyzed. The clinical and imaging data of the patients were also collected, and logistic regression analysis was performed to explore the correlation between the perfusion parameters and outcomes at discharge.

Results: The favorable and poor outcomes at discharge were found in 37 (56.06%) and 29 (43.94%) patients, respectively. The whole-brain PBV was significantly correlated with the Hunt-Hess grades ($p < 0.005$) and the WFNSS grades ($p < 0.005$). The whole-brain PBV of the poor prognosis was significantly higher than that of the favorable prognosis (35.17 ± 7.66 vs. 29.78 ± 5.54, $p < 0.005$). The logistic regression analysis showed that the PBV of the parietal lobe at the bleeding side (OR = 1.10, 95%CI: 1.00–1.20, $p = 0.04$) was an independent risk factor predicting the short-term prognosis.

Conclusions: Parenchymal blood volume (PBV) maps could reflect the cerebral blood volume throughout the brain to characterize its perfusion status at an early stage in aneurysmal SAH. It enables a one-stop imaging evaluation and treatment in the same angio-suite and may serve as a reliable technique in clinical assessment of aneurysmal SAH.

Keywords: perfusion, parenchymal blood volume, digital subtraction angiography, outcome, subarachnoid hemorrhage

INTRODUCTION

Aneurysmal SAH is a life-threatening disease with high mortality and disability rates (1–4). Increasing fundamental and clinical research has suggested that early brain injury (EBI) is the most critical cause of the subsequent delayed cerebral vasospasm, delayed neurological dysfunction, and mortality and disability in patients (5–10). EBI, which involves a series of microcirculation dysfunctions that occur within 72 h after SAH, was correlated with early cerebral hypoperfusion, which was responsible for the subsequent delayed cerebral infarct (DCI) and poor prognosis of patients (11, 12).

Several investigators have found that about 60% of patients showed abnormal perfusion on MR perfusion (MRP) at an early stage of aneurysmal SAH, which was correlated with the Hunt-Hess grade and neurological prognosis (13, 14). Also, several studies reported that, after aneurysmal SAH, CT perfusion (CTP) can reflect the severity of brain injury and predict the occurrence of delayed cerebral ischemia (DCI) (15–22), in which decreased CBF and prolonged mean transit time (MTT) in the early stage of aneurysmal SAH were found to be related to the DCI and the poor outcome (18, 21). Given the fact that the reversal of vasospasm does not appear to improve patient outcomes, it could be argued that the earlier diagnosis and treatment of EBI may attenuate some of the devastating secondary injuries and improve the outcome of patients with SAH (5).

However, both MRP and CTP involve a relatively long waiting time before the examination and require the patients to be transferred to the special examination room, which are both challenging for patients with aneurysmal SAH (especially high-grade patients) when they are in a serious condition and need emergent surgery. Therefore, clinical applications of MRP and CTP are still limited. An alternative to MRP or CTP that is easily accessible, effective, and accurate is of great importance in clinical practice.

The C-arm flat-panel detector CT (FDCT) *syngo* DynaPBV Neuro is a 3D imaging application that provides the cerebral blood volume parameter intraoperatively for perfusion status assessment developed with the advancement of computer and imaging technology in recent years (23–28). The application visualizes the contrast-enhanced blood volume distribution of the whole brain in 3D color-coded cross-sectional images based on a steady-state contrast injection. It also allows measurements of PBV to quantitatively assess the perfusion changes caused by treatment or the biological processes. The PBV measurement can be performed in the same angio suite together with the interventional surgery in a one-stop fashion, which is safe and convenient for patients. Several authors reported that the cerebral blood volume calculated by PBV software compared favorably with that measured with CTP, and PBV's ability in cerebral perfusion evaluations is similar to CTP (26, 29). PBV has been found useful in evaluating perfusion in patients with acute ischemic stroke (AIS) (24–26, 28), yet its application in aneurysmal SAH is still in its infancy (23, 30).

In this study, we used the C-arm FDCT *syngo* DynaPBV Neuro application to measure the cerebral PBV and evaluate the association between the cerebral perfusion status at an early stage in aneurysmal SAH and the clinical manifestations in patients, as well as the functional outcomes at discharge. We hypothesized that PBV would serve as a reliable technique for the evaluation of hemorrhage severity and prediction of short-term prognosis in patients with aneurysmal SAH.

Abbreviations: EBI, early brain injury; DCI, delayed cerebral infarct; PBV, parenchymal blood volume; FDCT: flat-panel detector CT; CBF, cerebral blood flow; MTT, mean transit time; AIS, acute ischemic stroke; WFNSS, world federation of neurological societies scale; mFisher, modified Fisher; mRS, modified rankin score.

MATERIALS AND METHODS

Patients

The study was approved by the institutional research ethics committee of Jinling Hospital, Nanjing University, Nanjing, China. Written informed consent was obtained from a legally authorized representative of all patients. Data of patients diagnosed with aneurysmal SAH who underwent C-arm FDCT PBV examination in the early stage (<48 h) in the Jinling Hospital between 1 January 2016 and 31 December 2018 were retrospectively analyzed. The exclusion criteria were the following: DSA or CTA suggested the presence of intracranial hematoma with local mass effect, cerebrovascular malformation, moyamoya disease, moderate or higher degree cerebral artery stenosis, or other cerebrovascular diseases and patients who had already received external ventricular drain. Clinical records related to functional outcomes including age, gender, Hunt-Hess grade, World Federation of Neurological Societies Scale (WFNSS) grade, modified Fisher (mFisher) grade, as well as the location of the aneurysm, were collected for analysis.

Methods

All patients received a whole-brain perfusion examination on the C-arm FDCT (Artis Zee Biplane, Siemens Healthineers, Forchheim, Germany) through the transfemoral artery approach within 48 h after hemorrhage. C-arm FDCT PBV was acquired after general anesthesia in the angio-suite. As previously described (25, 31), PBV acquisition includes two 3D rotations: mask and fill runs. For both runs, the C-arm rotated 200° in 6 s, with an angle increment of 0.5°.

The first 3D mask run was acquired with no contrast filling. When the C-arm returned to the initial position after the mask run, 80 ml of 1:1 diluted contrast media (iodixanol, Visipaque 320 mg I/ml, GE Healthcare, Ireland) was injected through a 5F pigtail catheter placed at the aorta root at 8 ml/s, 600 psi for 10 s. To ensure the contrast filling in the brain tissue has reached the steady-state, the second 3D fill run was not triggered until superior sagittal sinus filling was observed during "bolus watching" (32).

Post-processing of the 3D data to generate color-coded PBV maps was performed using the *syngo* DynaPBV Neuro software (Siemens Healthineers, Forchheim, Germany) on the clinical workstation (*syngo* X workplace, Siemens Healthineers, Forchheim, Germany). In brief, PBV map reconstruction includes a subtraction of the mask image (1st run) from the fill

image (2nd run) and detection of the arterial input (33). The PBV values were measured in units of ml/1,000 ml of cerebral tissue and viewed with a thickness of 10 mm using MPR. Then, five symmetrical regions of interest (ROIs), excluding hematoma, were drawn on the perfusion maps on the bilateral cerebral hemispheres for each patient: (1) Third ventricle level: the bilateral frontal pole cortex, the occipital cortex, and the basal ganglia (**Figure 1A**); (2) 4.5 cm above third ventricle level: the bilateral frontal cortex and the parietal cortex (**Figure 1B**).

$PBV_{hemisphere} = 0.2^{*}(PBV_{fontal\ pole} + PBV_{frontal\ lobe} + PBV_{parietal\ lobe} + PBV_{occipital\ lobe} + PBV_{Basal\ ganglia})$, $PBV_{whole\ brain} = 0.5^{*}(PBV_{left\ hemisphere} + PBV_{right\ hemisphere})$. The whole cerebrum was divided into the bleeding side hemisphere and the non-bleeding side hemisphere according to the location of the aneurysm. If the aneurysm was located in the basilar artery, the hemisphere with more hemorrhage was determined as the bleeding side hemisphere.

Clinical Outcomes

The modified Rankin score (mRS) of the patients at discharge was used for the evaluation of functional outcomes. The mRS of 0–2 points indicated favorable outcomes and 3–6 points indicated poor outcomes.

Statistical Analysis

Continuous variables in this study (PBV values) are presented as mean with standard deviation (SD). Comparisons between groups were performed with analysis of *t*-tests or the Mann-Whitney-U-test for continuous parameters and the $\chi 2$ test for categorical parameters. Significant univariate factors with a *p*-value ≤ 0.1 were entered into multivariable logistic regression (forward). Odds ratios (OR) and associated 95% confidence intervals (CI) are reported for regression analysis. Statistical analysis was performed using IBM SPSS Statistics software Version 19.0 (IBM, Armonk, New York, USA). A p-value < 0.05 was considered statistically significant.

RESULTS

A total of 66 patients (24 men [36.4%] and 42 women [63.6%] with the mean age of 55.98 $\pm$ 9.99 years) were included in this study. Fifty-five patients (83.33%) were diagnosed with an anterior circulation aneurysm and 11 patients (16.67%) with a posterior circulation aneurysm. Favorable outcomes were achieved in 37 patients (56.06%) at discharge, while 29 patients (43.94%) were discharged with poor outcomes (**Table 1**).

Blood volumes of the parietal lobe and the cerebral hemisphere on the bleeding side were significantly higher than those on the non-bleeding side, with 35.14 $\pm$ 9.71 vs. 33.17 $\pm$ 94, $p = 0.01$ for the parietal lobe and 32.59 $\pm$ 7.36 vs. 31.70 $\pm$ 04, $p = 0.02$ for the cerebral hemisphere. Although blood volume at the frontal lobe, the occipital lobe, and the basal ganglia on the bleeding side was higher than those on the non-bleeding side, statistical significance was not found (**Table 2**).

Whole-brain PBV values increased significantly as the Hunt-Hess grades ($p < 0.005$) and the WFNSS grades ($p < 0.005$) increased. The whole-brain PBV of the poor outcome group was significantly higher than that of the favorable outcome group (35.17 $\pm$ 7.66 vs. 29.78 $\pm$ 5.54, $p < 0.005$) (**Table 3**).

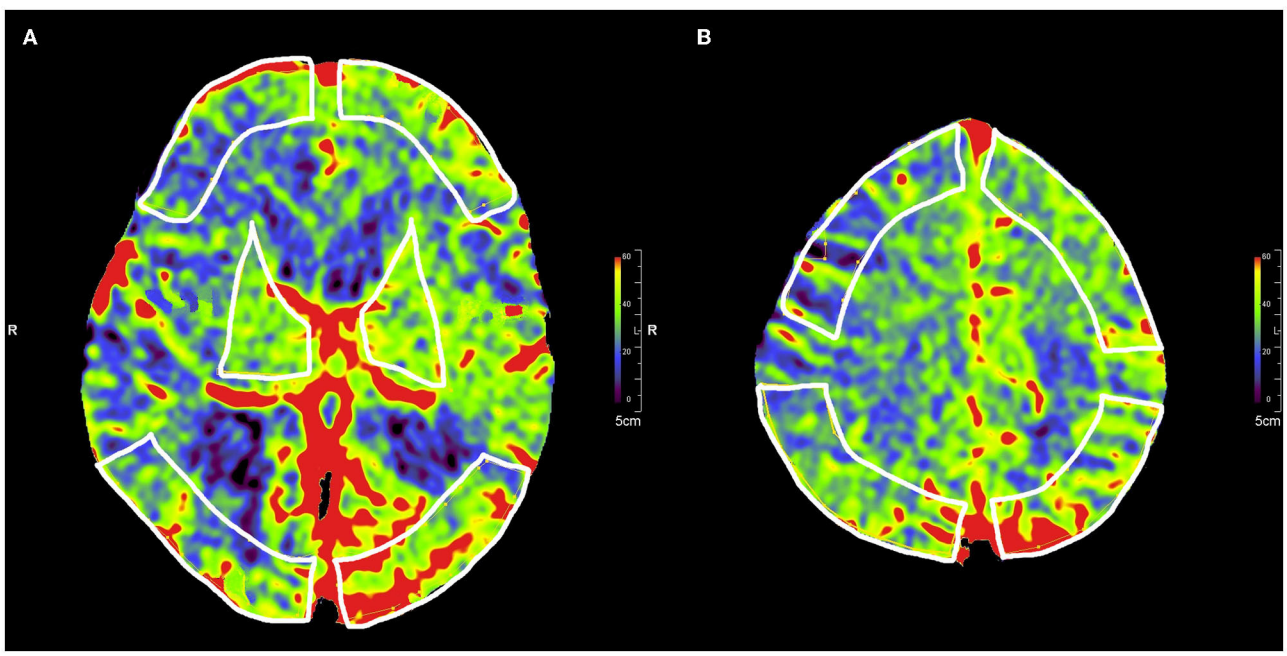

FIGURE 1 | Selection of five symmetrical ROIs in color-coded parenchymal blood volume maps. **(A)** ROIs of the frontal pole cortex, the occipital cortex, and the basal ganglia in the third ventricle level. **(B)** ROIs of the frontal cortex and the parietal cortex at 4.5 cm above the third ventricle level.

TABLE 1 | Demographics and clinical features of patients with aSAH.

Characteristics	All patients ($N = 66$)	Favorable outcome ($n = 37$)	Poor outcome ($n = 29$)	*P*-value
Age (years), mean ± SD	55.98 ± 9.99	52.95 ± 9.33	59.85 ± 9.58	<0.005
Gender, *n* (%)				0.61
Men	24 (36.36%)	12 (32.43%)	12 (41.38%)	
Women	42 (63.64)	25 (67.57%)	17 (58.62%)	
Hunt-Hess, *n* (%)				<0.005
I	1 (1.5%)	1 (2.70%)	0 (0%)	
II	25 (37.9%)	22 (59.46%)	3 (10.34%)	
III	11 (16.7%)	7 (18.92%)	4 (13.79%)	
IV	20 (30.3%)	4 (10.81%)	16 (55.17%)	
V	9 (13.6%)	3 (8.10%)	6 (20.67%)	
WFNSS, *n* (%)				<0.005
I	25 (37.9%)	23 (62.16%)	2 (6.90%)	
II	9 (13.6%)	5 (13.51%)	4 (13.79%)	
III	3 (94.5%)	2 (5.41%)	1 (3.45%)	
IV	12 (18.2%)	2 (5.41%)	10 (34.48%)	
V	17 (25.8%)	5 (13.51%)	12 (41.38%)	
mFisher, *n* (%)				0.25
0	3 (4.5%)	3 (8.11%)	0 (0%)	
I	2 (3.0%)	2 (5.41%)	0 (0%)	
II	13 (19.7%)	11 (29.73%)	2 (6.90%)	
III	18 (27.3%)	8 (21.62%)	10 (34.48%)	
IV	30 (45.5%)	13 (35.14%)	17 (58.62%)	
Aneurysm site, *n* (%)				0.48
Anterior circulation				
ICA	22 (33.3%)	14 (37.84%)	8 (27.59%)	
ACA	3 (4.5%)	1 (2.70%)	2 (6.90%)	
AcomA	25 (37.9%)	12 (32.43%)	13 (44.83%)	
MCA	5 (7.6%)	3 (8.11%)	2 (6.90%)	
Posterior circulation				
PCA	2 (3.0%)	1 (2.70%)	1 (3.45%)	
BA	4 (6.1%)	4 (10.81%)	0 (0%)	
VA	5 (7.6%)	2 (5.41%)	3 (10.34%)	

WFNSS, World Federation of Neurological Societies Scale; mFisher, modified Fisher; ICA, internal carotid artery; ACA, anterior cerebral artery; AcomA, anterior communicating artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; BA, basilar artery; VA, vertebral artery.

TABLE 2 | Comparison of PBV on the bleeding side hemisphere and the non-bleeding side hemisphere.

	PBV* on bleeding side, ($\bar{x}$ ± SD)	PBV* on non-bleeding side, ($\bar{x}$ ± SD)	*P*-value
Frontal lobe	30.70 ± 8.13	30.68 ± 6.89	0.98
Parietal lobe	35.14 ± 9.71	33.17 ± 8.94	0.01
Occipital lobe	34.12 ± 7.92	32.82 ± 8.53	0.16
Basal ganglia	30.42 ± 7.67	30.08 ± 7.85	0.54
Cerebral hemisphere	32.59 ± 7.36	31.70 ± 7.04	0.02

**, PBV values were expressed in units of ml/1,000 ml.*
PBV, parenchymal blood volume.

TABLE 3 | Comparison of whole-brain PBV with clinical features and outcomes.

	Whole brain PBV * ($\bar{x}$± SD)	*P*-value
Hunt-Hess		<0.005
I-II	28.07 ± 5.33	
III	33.74 ± 5.07	
IV-V	35.20 ± 7.37	
WFNSS		<0.005
I-II	28.07 ± 5.33	
III	33.74 ± 5.07	
IV-V	35.20 ± 7.37	
mFisher		0.60
0	28.25 ± 7.49	
I	29.31 ± 2.39	
II	30.69 ± 5.19	
III	33.82 ± 6.82	
IV	32.35 ± 7.98	
Aneurysm site		0.82
Anterior circulation	32.24 ± 7.25	
Posterior circulation	31.69 ± 6.12	
Outcome		<0.005
Favorable	29.78 ± 5.54	
Poor	35.17 ± 7.66	

** PBV values were expressed in units of ml/1,000 ml.*
WFNSS, World Federation of Neurological Societies Scale; mFisher, modified Fisher. PBV, parenchymal blood volume.

Multivariate logistic regression results showed that only the blood volume of the parietal lobe on the bleeding side resulted as the independent risk factor predicting the functional outcome in patients at discharge (OR = 1.10, 95%CI: 1.00–1.20, $p = 0.04$) (**Table 4**).

DISCUSSION

As aforementioned, EBI plays a critical role in brain dysfunction, leading to the subsequent vasospasm, delayed neurological dysfunction, and mortality and disability. Research on early brain injury involves endothelial damage, changes in vascular smooth muscle contractility, vascular reactivity, and neuroinflammation, such as interleukin 6 (IL-6); a key component in the development of vasospasm, is related to the blood-brain barrier destruction. The aforementioned pathophysiological changes may lead to damage to the integrity of the neurovascular unit and result in impaired vascular autoregulation (34). To prevent further deterioration in patients with aneurysmal SAH, in addition to the general clinical evaluation, such as frequent neurological assessment and monitoring approaches, including cerebral microdialysis (CMD), cerebral EEG, and transcranial Doppler (TCD), to detect suspicious signs, prompt outcome prediction will better facilitate follow-up treatment and care delivery planning and balance medical resources to patients in greater need.

TABLE 4 | Multivariate logistic regression analysis (forward) of factors associated with outcome at discharge.

Characteristics	Mono-variate regression		Multi-variate regression	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age	1.08 (1.02–1.14)	0.01	1.11 (1.03–1.19)	0.01
Hunt-Hess	3.33 (1.85–2.99)	0.00	–	0.74
WFNSS	2.27 (1.55–3.31)	0.00	2.17 (1.38–3.43)	<0.005
mFisher	2.44 (1.31–4.54)	0.005	–	0.13
Site	0.69 (0.18–2.61)	0.58	–	–
Bleeding side $PBV_{parietal\ lobe}$	1.13 (1.05–1.22)	0.00	1.10 (1.00–1.20)	0.04
Bleeding side $PBV_{hemisphere}$	1.15 (1.05–1.27)	0.00	–	0.97
$PBV_{whoe\ brain}$		0.00	–	0.52

WFNSS, World Federation of Neurological Societies Scale; mFisher, modified Fisher; PBV, parenchymal blood volume.

In brain imaging after aneurysmal SAH, MRP has high sensitivity in depicting brain abnormalities, which makes it a good candidate for identifying early signs of vasospasm and ischemia in patients with aneurysmal SAH; yet, it is less commonly used than CTP in clinical practice due to the technical difficulty and examination accessibility (35). CTP was found to be reliable in vasospasm and DCI prediction and detection after aneurysmal SAH, and the CBF and MTT obtained were analyzed and suggested to be diagnostic thresholds (36–39). The measurements of MTT and TTP obtained from early CT perfusion were also demonstrated to be correlated with early clinical outcomes (40). Neuro PBV maps obtained from CBCT are a technique to measure cerebral blood volume throughout the brain to characterize its perfusion status (23). The reliability of PBV maps was demonstrated by the good correlation between PBV and conventional CT perfusion through both qualitative and quantitative comparative studies (29, 33, 41). By extending the imaging capabilities of the angio-suite, the PBV technique has been used in the assessment of ischemic cerebrovascular diseases and brain tumors in the brain during the procedure in the angio-suite for better patient management, and has gained significant value in clinical practice in recent years (24–28, 42) but not much value in SAH yet. Our study demonstrated PBV's feasibility in assessing the perfusion status in aneurysmal SAH, as well as the convenience of one-stop imaging evaluation. The major finding of our study was that the cerebral blood volume given by PBV maps in the early stage of aneurysmal SAH was significantly correlated with the initial severity of hemorrhage and the short-term prognosis of patients, which may predict early clinical outcome and aid in treatment planning.

All patients in this study received a PBV examination within 48 h after hemorrhage, during which time the incidence of ultra-early vasospasm was low (43), to explore the relationship between PBV and severity of EBI. Cerebral angiography performed after the PBV examination excluded the patients who had acute cerebral vasospasm or moderate to severe stenosis. Both the FDCT-derived PBV and conventional CTP are acquired based on the bolus detection of contrast agent under x-ray; it is challenging to distinguish between the contrast extravasation and the hematoma (44). Therefore, patients with a large local hematoma were excluded from our study. In addition, we selected ROIs that did not include hematoma to avoid large bias and only reflect the cerebral parenchymal blood volume. Our study showed that the blood volume of the selected areas on the bleeding side was higher than those on the non-bleeding side, especially in the parietal lobe and the cerebral hemisphere where significant differences were observed. These results are in concordance with the cerebral pathological changes after aneurysmal SAH. CBF could maintain stability in patients with intact autonomic regulation (45–47), but increased intracranial pressure (ICP) and decreased CBF after aneurysmal SAH lead to congestive changes in brain tissue manifested by dilated cerebral arterioles and increased CBV in patients with impaired autonomic regulation (11, 48, 49). The blood supply of the parietal ROIs that we selected was covered by the middle cerebral artery, which responded immediately after hemorrhage and manifested as cerebral congestion, resulting in increased PBV in the parietal ROIs. The association between CTP and aneurysmal SAH has been investigated previously, and our findings about PBV in this study show similar trends. PBV map and CTP-CBV/MRP-CBV have good consistency in terms of both visual comparison of perfusion pseudo-color maps and the quantitative analysis of ROI (26, 29, 30, 50, 51). In addition to PBV's application in AIS evaluation (24–26, 28) and initial practice in the prediction of DCI after aneurysmal SAH (23, 30), our study broadens the clinical application of PBV in stroke management.

In this study, significant differences were found between the PBV of different Hunt-Hess grades and WFNSS grades, which implies that the more severe the brain tissue congestion in the early stage of aneurysmal SAH, the higher the Hunt-Hess grade and the WFNSS grade. The PBV of the poor outcome group was significantly higher than that of the favorable outcome group, and the logistic regression model revealed that the PBV was an independent risk factor that could predict a patient's short-term outcome. The Hunt-Hess grade, the WFNSS grade, and the mFisher grade are routinely used as the basis for patient triage and outcome predictors but are given based on subjective judgment. On the contrary, cerebral PBV is a numeric value obtained by standard procedures. Our results may indicate that PBV has the potential to act as an objective screening method to predict outcomes in aneurysmal SAH. Patients with elevated PBV may indicate impaired autonomic regulation of the brain and subsequent treatment (e.g., optimal- cerebral perfusion pressure (CPP) targeted therapy guided by intracranial pressure (ICP) monitoring) can be applied immediately to maintain a reasonable CPP and a stable CBF to avoid cerebral congestion or ischemia. Future studies with a larger patient population and long-term outcomes will be conducted to explore the diagnostic threshold for PBV so as to make more objective and accurate predictions, and guide clinical interventions in a timely manner (52). During the COVID-19 pandemic, not only was the coronavirus likely to worsen hypertension and make aneurysms more prone to rupture, but intensive care unit (ICU) resources were more strained, leaving patients more vulnerable (53). PBV may help in

the future to early identify SAH patients with severe brain injury and a possible poor prognosis to better allocate medical resources to those most in need.

Compared with CTP and MRP, PBV has the following advantages: (1) PBV can be performed in the angio-suite when there is an endovascular surgery for ruptured aneurysms. The patients are exempted from additional waiting time. More importantly, a comprehensive analysis of cerebral perfusion and angiography could provide more clues for identifying abnormal cerebral perfusion caused by acute vasospasm and vascular abnormalities such as vascular stenosis; (2) The whole-brain volume reconstruction of PBV maps could visualize any slice of cerebral blood volume imaging on transversal, sagittal, and coronary views; (3) PBV realizes the imaging evaluation of patients with aneurysmal SAH together with other DSA techniques, such as 2-D angiography and color-coding blood flow analysis in the same angio-suite, which is the so-called one-stop imaging service in the angio-suite (54).

However, PBV only provides cerebral blood volume values at present but lacks perfusion parameters of CBF, MTT, and TTP. The evaluation of patients who have no obvious CBV abnormalities in the early stage, with only prolonged MTT and slightly decreased CBF, may be inaccurate (48). Improved PBV technology that can calculate more perfusion parameters in the future may help in a more comprehensive and accurate evaluation of the brain perfusion status (55). PBV acquisition currently still requires manual triggering in the fill run. The ideal time point for data collection is when the contrast agent reaches a steady-state filling in the brain capillary bed, that is, the concentration of the contrast agent in the artery = the concentration of the contrast agent in the tissue = the concentration of the contrast agent in the vein. However, manual triggering requires skilled operation and may result in inappropriate acquisition time, i.e., too early or too late when the contrast agent is not maintained in a steady-state equilibrium in the brain tissue. The PBV value component contains a part of CBF weight in this condition (23, 56, 57).

This study has several limitations: (1) This was a preliminary study with a relatively small sample size; (2) for ethical reasons, PBV examination was lacking in normal patients, which meant that the control group was not available; and (3) there was no discrimination between anterior and posterior circulation aneurysms. The accuracy of PBV measurement of the cerebellum and the brainstem may be affected due to the imaging limitations caused by the posterior fossa (58, 59). This study mainly focused on the feasibility of using PBV for cerebral perfusion status evaluation after aneurysmal subarachnoid hemorrhage. More systematic comparative studies of aneurysms in the anterior and posterior circulations need to be carried out.

CONCLUSIONS

Our results demonstrated that the cerebral blood volume measured by PBV maps at an early stage in aneurysmal SAH is significantly correlated with the initial severity of hemorrhage and the short-term prognosis of patients. The C-arm FDCT PBV technique enables a one-stop imaging evaluation and may be a reliable alternative to CTP and MRP in clinical assessment and in predicting aneurysmal SAH outcomes.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Research Ethics Committee of Nanjing Jinling Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Study concepts and study design: LW and XZha. Data acquisition: LW, QW, and XZho. Quality control of data and algorithms and manuscript preparation: LW and LZ. Statistical analysis and interpretation: LW, LZ, and QW. Manuscript editing: LW. Manuscript review: XZha. All authors contributed to the drafting of this article.

FUNDING

We declare that the present research was supported by Jiangsu Planned Projects for post-doctoral Research Funds (No. 2019k281), Jiangsu Natural Science Foundation (No. BK20191231) and Jiangsu Natural Science Foundation (No. SBK2019022915).

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers | Frontiers in Neurology

TYPE Mini Review
PUBLISHED 12 September 2022
DOI 10.3389/fneur.2022.977307

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Endovascular and Interventional Neurology,
a section of the journal
Frontiers in Neurology

RECEIVED 24 June 2022
ACCEPTED 25 August 2022
PUBLISHED 12 September 2022

CITATION
Santana D, Mosteiro A, Pedrosa L, Llull L, Torné R and Amaro S (2022) Clinical relevance of glucose metrics during the early brain injury period after aneurysmal subarachnoid hemorrhage: An opportunity for continuous glucose monitoring. *Front. Neurol.* 13:977307. doi: 10.3389/fneur.2022.977307

Clinical relevance of glucose metrics during the early brain injury period after aneurysmal subarachnoid hemorrhage: An opportunity for continuous glucose monitoring

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Hyperglycaemia, hypoglycaemia and higher glucose variability during the Early Brain Injury (EBI) period of aneurysmal subarachnoid hemorrhage (aSAH) have been associated with poor clinical outcome. However, it is unclear whether these associations are due to direct glucose-driven injury or if hyperglycaemia simply acts as a marker of initial severity. Actually, strict glucose control with intensive insulin therapy has not been demonstrated as an effective strategy for improving clinical outcomes after aSAH. Currently published studies describing an association between hyperglycaemia and prognosis in aSAH patients have been based on isolated glucose measurements and did not incorporate comprehensive dynamic evaluations, such as those derived from subcutaneous continuous glucose monitoring devices (CMG). Arguably, a more accurate knowledge on glycaemic patterns during the acute phase of aSAH could increase our understanding of the relevance of glycaemia as a prognostic factor in this disease as well as to underpin its contribution to secondary focal and diffuse brain injury. Herein, we have summarized the available evidence on the diagnostic and prognostic relevance of glucose metrics during the acute phase of cerebrovascular diseases, focusing in the EBI period after aSAH. Overall, obtaining a more precise scope of acute longitudinal glucose profiles could eventually be useful for improving glucose management protocols in the setting of acute aSAH and to advance toward a more personalized management of aSAH patients during the EBI phase.

KEYWORDS

subarachnoid hemorrhage, early brain injury, continuous glucose monitoring, stress hyperglycemia, glycemic variability, glucose profile

Introduction

Hyperglycaemia occurs in about three out of four aSAH patients within the first 72 h after the initial bleeding and it has been associated with poor clinical outcomes and secondary brain injury (1–7). However, it remains to be clarified whether these observed associations are due to direct deleterious effects induced by high blood sugar or if hperglycaemia is simply a marker of stroke severity. Although hyperglycemia has been related to worse outcome in several pathologies, there is conflicting evidence about the benefits of intensive glucose management for improving clinical outcomes in different critical settings (8, 9). Thus, the potential clinical benefit of strict control with intensive insulin therapy has not yet been validated by clinical trials (7, 10–13). Of note, intensive management of blood glucose may result in hypoglycaemia, and both hyperglycaemia and hypoglycaemia have been associated with higher risk of complications during the acute phase of aSAH and with poorer clinical recovery at long-term. Hyperglycaemia is, in part, a consequence of an acute stress response to brain injury and may enhance neuroinflammatory mechanisms and increase the risk of ischemic complications such as delayed cerebral ischemia (DCI) (5–7). Conversely, hypoglycaemia is also dangerous for the brain, which relies on glucose for maintaining its function, and low glucose levels may eventually increase secondary brain injury through a myriad of mechanisms that include a poorer tissue tolerance to ischemia (5–7). Besides, acute fluctuations in serum glucose concentrations are common after aSAH and may also result detrimental (1–7, 14–16). In this review, we will summarize the available evidence on the diagnostic and relevance of glucose metrics during the acute phase of cerebrovascular diseases, focusing in the EBI period after aSAH.

Glycaemic status in acute cerebrovascular illnesses: How to tackle the problem

Glycaemic dysregulation decisively affects vital and functional prognosis of patients across several cerebrovascular diseases, although it is still unclear how to effectively address the glycaemic status in the acute phase of critical diseases such as aSAH. Traditionally, glycaemic evaluation has relied on static parameters, like glycaemia on admission or premorbid glycaemic status including known-diabetes or glycated hemoglobin (HbA1c) on admission. Nonetheless, glycaemia is a rapidly changing parameter due to both disease evolution and acute management-related factors that are only partially understood. Therefore, static markers may be inadequate to address the true relevance of glycaemic status and to guide insulin therapy in the acute setting. To overcome this limitation, several studies addressed glycaemia as a dynamic variable by means of evaluating the glycaemic variability (GV) (17, 18). In this context, subcutaneous Continuous Glucose Monitoring (CGM) devices have emerged as a potential substitute to point of care standards in the inpatient setting. In brief, CGM devices are usually placed on the thigh, abdomen or arm, and measure interstitial fluid glucose generally through an oxidase-peroxidase reaction. That information is sent to an external device, then allowing a remote, non-invasive, high temporal resolution evaluation of the glycaemic status. Common technical limitations of CGM in an ICU setting include biofilm formation, need for calibration, measurement lag and the interaction of drugs such as acetaminophen or vasopressors (19, 20). Initial studies evaluating the feasibility of CGM in the ICU setting have mainly focused on the accuracy of the technique, before assessing its ability to guide treatments. In general, and in spite of the technical limitations cited above, the device accuracy seems to be acceptable and reproducible across different series and acute clinical settings, with no major safety issues. From a logistic and economic point of view, some reports indicate that CGM devices might significantly reduce nurse workload regarding glycaemic control and might be cost-effective (21, 22).

The exhaustive information obtained through CGM includes static measures such as mean, maximum and minimum glucose levels, the amount of time spent above or below a predefined threshold, and also several dynamic features accounting for GV. CGM also allows the identification of different longitudinal glucose profiles, as well as performing complex analyses of glucose homeostasis, which would be not feasible with conventional testing. The main advantages of CGM, compared to conventional finger prick testing, are the ability to comprehensively analyse a multitude of parameters and to obtain their longitudinal trajectory profiles. Reports on CGM in acute cerebrovascular diseases showed similar-to-better detection of dysglycaemic events, mainly hypoglycaemia, compared to the standard of care. Interestingly, some of these events show circadian variability and nocturnal preference (23, 24), being easily overlooked with the conventional scheduled capillary glucose measurements.

However, the information derived from CGM devices should be interpreted carefully, since definitions and thresholds of the novel glycaemic parameters could be complex and heterogeneous. Beyond the extraction of the aforementioned predefined key metrics, the comprehensive analysis of CGM-derived repeated measurements may require sophisticated analytic tools and pre-planned analytical strategies (19, 20). In addition, evidence regarding which subsets of patients would benefit from wearing a CGM device is still scarce (19).

The ability of CGM to guide intensive insulin treatments (IIT) is also a matter of debate. Although the use of CGM has spread in the outpatient setting for certain indications, its utility in the inpatient setting remains to be demonstrated. Thus, interventional clinical trials based on CGM are scarce in

comparison with accuracy and safety studies. A recent report in a cardiac ICU demonstrated good patient and caregivers' acceptance, accuracy and reliability of subcutaneous CGM measurements (25). Indeed, CGM could be of potential great value in the management of acute illnesses, especially in patients at risk for high GV and hypoglycaemia, including those affected by vascular brain injury (19). A retrospective analysis of two randomized controlled trials including critically ill patients that compared CGM-driven IIT vs. conventional arterial point of care (POC)-driven IIT showed that CGM driven-IIT did not result in a significantly reduced GV. However, glucose complexity measures calculated with real time CGM data were predictive of the risk of mortality (26). In one of those trials, real-time CGM-driven IIT was associated with a reduced risk of hypoglycaemic events, an observation that was also replicated in a similarly designed trial including postcardiac surgery patients (27, 28). In the same line, a recent trial comparing insulin dosing driven by CGM measurements vs. standard POC glucose testing in a cohort of hospitalized patients receiving IIT or bolus basal therapy showed earlier hypoglycaemia detection in the CGM group (29).

In summary, CGM technology seems safe, accurate and might be cost-effective in the acute inpatient setting, although its clinical value for guiding IIT or for prognostic purposes in patients who need tight glycaemic control, as those affected by acute brain lesions, remains to be demonstrated. Importantly, the benefit of strict glycaemic control with IIT for improving clinical outcomes in aSAH remains to be validated in clinical trials before an eventual implementation of CGM for guiding IIT (7, 10–13).

Diagnostic and prognostic relevance of static and dynamic glucose metrics in the acute phase of aSAH

Patients with aSAH may suffer focal and diffuse brain lesions in addition to the initial bleeding, a fact that dramatically impacts the functional and cognitive outcomes at long term. According to the moment of appearance, within or after the first 72 h from the initial bleeding, these brain lesions are classified as part of EBI or DCI, respectively (30–33). Traditionally, DCI secondary to vasospasm has been considered one of the main complications related to poor prognosis in this disease, although therapeutic approaches aimed to control angiographic vasospasm have not shown reliable clinical benefits (33, 34). On the other hand, the severity of EBI, both *via* acute ischemic lesions or microstructural diffuse lesions, is associated with an increased risk of systemic complications and with poorer clinical, cognitive and affective outcomes at long-term (35–37). There is growing evidence of the role that physiopathological changes play in the promotion of EBI after aSAH. These mechanisms include loss of cerebral autoregulation, microthrombosis, enhanced exposure to inflammation and oxidative stress, blood brain barrier (BBB) disruption and apoptotic cell death, among others (38–43).

Hyperglycaemia has been associated with a prothrombotic state, increased neuroinflammation, oxidative stress and BBB disruption in several clinical and preclinical models of central nervous system diseases. A plausible underlying mechanism is the overproduction of mitochondrial reactive oxygen species, which occurs preferentially in tissues that are insulin-independent like the brain (44–49). In experimental SAH, hyperglycaemia promotes neuronal apoptosis and is associated to higher incidence of vasospasm (43, 50). In the vulnerable brain, hyperglycaemia also promotes anaerobic glycolysis leading to the accumulation of lactate, a process thought to contribute to increased brain injury (6, 51–53).

From a clinical standpoint, dysglycaemia is a major prognostic factor in both early and late phases of spontaneous aSAH, as summarized in Table 1. First, hyperglycaemia has been associated with worse clinical and radiological presentation, as well as with higher in-hospital mortality, higher rates of neurological and systemic complications, and ultimately worse short-term and long-term functional outcomes (3, 5, 7, 14, 16, 54–62, 64–66). On the other hand, hypoglycaemia has been strongly linked to in-hospital mortality and incidence of vasospasm (55, 59, 61–63). Otherwise, poor premorbid metabolic control estimated by HbA1c upon admission does not seem to consistently correlate with the acute neurological status nor with DCI or neurological outcome at long-term (64, 65). Some authors have proposed the use of ratios to increase the predictive value of admission blood glucose levels. In this line, the glucose-potassium and glucose-phosphate ratios on admission proved to be a significant predictor of vasospasm, rebleeding, along with acute and mid-term functional outcomes (58, 60, 66, 67).

Even when hyperglycaemia on admission is a very sensible biomarker, it has been suggested that GV is a more reliable tool to predict outcomes (3, 14–16, 68, 69). Several formulas have been proposed to express the GV, yet they usually rely on comparison of low temporal resolution assessments of capillary glucose. A remarkable observation in terms of GV implications is the differential behavior between diabetic and non-diabetic patients during the acute phase of aSAH. Prior studies have suggested that the association between GV and outcome occurs in non-diabetic and well-controlled diabetic patients, but not in those with poorly controlled diabetes (69). Therefore, tolerance to high or low glucose levels may vary according to the premorbid glycaemic status.

Importantly, blood glucose levels might not always reflect those present in the brain interstitium as assessed with mycrodyalisis catheters (70, 71). In acute aSAH, glucose transport through the BBB is impaired, causing that even normal levels of blood glucose result relatively insufficient to supply

TABLE 1 Main studies assessing the impact of glucose and brain metabolism in prognosis and complications after spontaneous SAH.

Author	Study type	Population	Assessment	Results
Barletta et al. (14)	Retrospective	SAH HH >2 in ICU $n = 42$	Mean BG, GV, hypoG	↑GV: ↑incidence of brain infarction ↓GV: No difference in infarction between those with high and low mean BG
Beseoglu et al. (64)	Prospective observational	Non-diabetic aSAH $n = 78$	Admission BG and HbA1c	BG: Correlation with initial neurological status and mF. No correlation with DCI
Eagles et al. (7)	Retrospective	Non-diabetic aSAH $n = 389$	MaxG	MaxG <9, 2 mmol/L correlated with a decreased risk of unfavorable outcome
Helbok et al. (51)	Prospective observational	Poor-grade aSAH $n = 39$	MD glucose, PbtO2, and cerebral perfusion	Admission GCE: ↓brain pyruvate and glucose Non-GCE: ↑brain glucose up to day 7
Jung et al. (58)	Prospective observational	aSAH $n = 553$ cases 553 controls	Admission BG, K^+	BG: 98.4% hyperG on admission K^+: 26.0% hypoK^+, 0.5% hyperK^+ Severe group: ↑BG and GPR Non-severe group: ↑K^+
Kruyt et al. (5)	Meta-analysis	aSAH 17 studies ($n = 3,373$) for mean BG 8 studies ($n = 2,164$) for outcome	Weighted mean admission BG	HyperG on admission: increased risk for poor outcome compared with patients without hyperG
Kurtz et al. (15)	Retrospective	aSAH GCS <9 $n = 28$	ICP, PbtO2, MD, GV	↑GV: ↑risk of metabolic distress and hospital mortality
Liu et al. (59)	Retrospective	aSAH in ICU $n = 1,298$	Admission BG	U-shaped relationship between admission BG and 30-days all-cause mortality. Consistent at 90 days
Matano et al. (66)	Retrospective	Surgical aSAH $n = 333$	BG every 4 h, K^+	GPR, BG and K^+ correlated with DCI GPR correlated with VSp and poor outcome
McGirt et al. (3)	Retrospective	Surgical aSAH $n = 97$	BG every 6 h	Persistent hyperG: worse outcome at 2 weeks and 10 months Corrected admission hyperG: No correlation Mean daily BG: ↑40% poor outcome per 10mg/dL of increase
McIntyre et al. (61)	Retrospective	aSAH $n = 217$	Admission and hospitalization mean BG, MinG, MaxG, GV, DM history, HbA1c, BMI, insulin use	↑mean hospitalization BG: ↑mortality risk, mortality and complications predictor MinG: correlation with VSp MaxG: correlation with complications Admission BG >140 mg/dL: ↑ mortality DM history, BMI, HbA1c: No correlations
Naidech et al. (55)	Retrospective	aSAH $n = 172$	Mean BG, MaxG, MinG, GV	↑WFNS: ↑maxG, ↑mean BG, ↑GV, ↓inG Brain infarction: ↓minG Symptomatic VSp: ↓minG Worse outcome correlated to ↑admission. BG, ↑maxG, ↑mean BG, ↑maxG, ↓minG
Okazaki et al. (16)	Retrospective	aSAH in ICU $n = 122$	BG every 6 h, GV	↑GV, ↓minG: correlated with poor outcome
Pappacena et al. (57)	Retrospective	Non-diabetic aSAH. ($n = 6,098$) or TBI ($n = 11,812$) in ICU	MaxG, minG, mean BG, GV	↓MaxG, ↓MinG, ↓ mean BG, ↓GV in aSAH and TBI compared to overall ICU population Correlations between dysglycemia and mortality were stronger in aSAH/TBI than in general ICU population

(Continued)

TABLE 1 (Continued)

Author	Study type	Population	Assessment	Results
Sadan et al. (69)	Retrospective	aSAH in ICU $n = 2,451$	BG, GV	↓GV correlated with survival in non-diabetic and well-controlled diabetic aSAH patients
Schlenk et al. (63)	Prospective non-randomized	aSAH $n = 28$	BG, MD glucose	MD low and high-glucose episodes occurred independently of BG
Sun et al. (65)	Retrospective	aSAH $n = 119$	Admission glycemic gap (aGG)	↑ aGG predicted mortality and poor outcome better than admission BG, and correlated with DCI and EVD placement
Thiele et al. (62)	Retrospective (impact study)	aSAH $n = 834$	Admission and average BG. Strict glucose control protocol (GCP)	↑verage BG correlated with ↑risk of death ↑admission BG showed no correlations GCP initiation: No effect on in-hospital mortality. ↑hypoG. ↑ VSp
van Donkelaar et al. (56)	Retrospective	aSAH in ICU $n = 285$	BG and lactate first 24 h	↑BG correlated with DCI ↑lactate correlated with poor outcome
Wang et al. (60)	Retrospective	Non-diabetic aSAH $n = 744$	Admission BG and GPR	↑GPR correlated with clinical and radiological severity and predicted rebleeding and poor outcome
Zetterling et al. (71)	Retrospective	aSAH with EVD $n = 19$	BG every 3 h. MD glucose. MD/BG ratios	Weak positive correlation between BG and MD glucose. Insulin therapy correlated with ↓MD although BG remained normal
Zhang et al. (67)	Retrospective	aSAH $n = 198$	Admission GPR	Positive correlation between GPR and WFNS ↑GPR in patients with poor outcome

aSAH: aneurysmal Subarachnoid Hemorrhage; HH, Hunt and Hess scale; BG, Blood Glucose; GV, Glucose variability; HypoG, Hypoglycemia; mF, Modified Fisher scale; DCI, Delayed Cerebral Ischemia; MaxG, Maximum glucose; MD, Microdyalisis; PbtO2, Brain tissue Oxygen tension; GCE, Global Cerebral Edema; HypoK, Hypokalemia; HyperK, Hyperkalemia; HyperG, Hyperglycemia; GPR, Glucose/Potassium Ratio; GCS, Glasgow Coma Scale; ICP, Intracranial Pressure; MinG, Minimum Glucose; VSp, Vasospasm; DM, Diabetes Mellitus; BMI, Body Mass Index; WFNS, World Federation of Neurosurgical Societies scale; TBI, Traumatic Brain Injury; EVD, External Ventricular Drain.

the raised brain metabolic demand that occurs during the EBI period (71). This phenomenon poses patients with aSAH at a vulnerable state, where glycaemic fluctuations may provoke brain metabolic distress and secondary injury. Remarkably, systemic GV even within normal limits of blood glucose levels has also been associated with the incidence of cerebral metabolic distress, evaluated though multimodal monitoring with cerebral microdialysis probes (15, 51). Henceforth, GV instead of absolute glucose levels might better reflect the clinical course of severe aSAH, and eventually guide glycaemic-control interventions.

To our knowledge no studies regarding the prognostic relevance of glucose temporal profiles have used GCM devices in the specific setting of aSAH. Indeed, there is no sufficient evidence to conclude that longitudinal evaluation of glycaemic patterns have a greater prognostic value during the EBI period of aSAH. The vast majority of published data on hyperglycaemia and prognosis in aSAH patients are based on scheduled capillary glucose measurements as implemented in standard clinical practice (e.g., capillary glucose determinations every 6 h within the first days after bleeding) and have not considered including comprehensive dynamic evaluations, such as those derived from CGM devices. Arguably, using CGM to obtain accurate glycaemic profiles during the acute phase of aSAH could help define the relevance of glycaemia as a prognostic factor in this disease, as well as underpin its contribution to secondary focal and diffuse brain injury.

Diagnostic and prognostic yield of glucose monitoring in acute cerebrovascular diseases

Studies focused on hyperacute glucose monitoring in cerebrovascular diseases have included mainly patients affected by acute ischemic stroke (AIS). In this setting, both admission and acute-phase hyperglycaemia have been associated with mid-term and long-term morbidity and mortality following a J-shaped fashion, as well as with higher incidence of infarct growth, ischemic recurrence risk and post-stroke cognitive impairment (72–76). After alteplase infusion, hyperglycaemia correlates with worse recanalization status, higher odds of symptomatic haemorrhagic transformation (sICH) and poorer clinical recovery (77–80). Higher GV after alteplase administration has also been associated with higher concentrations of circulating markers of inflammation and with worse clinical outcomes (81). In the same line, after mechanical thrombectomy, glycaemic disarrangements have been associated

TABLE 2 Studies assessing potential clinical impact of CGM in cerebrovascular acute disease management.

Author	CGM manufacturer	Population	Outcome	Findings
Ribo et al. (89)	Minimed, medtronic	MCA stroke receiving IV alteplase ($n = 47$)	Infarct growth. Short term clinical course	Hyperglycemia during OT associated with poorer outcome and greater infarct growth in DWI
Shimoyama et al. (90)	Minimed, medtronic	ICA/MCA stroke ($n = 78$)	Infarct growth	Mean glucose & AUC >140 associated with infarct growth at 24 h and 72 h
Wada et al. (91)	iPro 2, medtronic	AIS ($n = 58$) and AHS ($n = 42$)	mRs ≥3 at 3 months	Mean glucose, AUC 8 & distribution time >8 were linked to mRs ≥ 3
Nukui et al. (23)	Freestyle libre pro, abbott	AIS within 7 days ($n = 39$)	Hyper and hypoglycemia detection	Glucose events after AIS are frequent and show circadian variability
Palaiodimou et al. (24)	iPro 2, medtronic	AIS ($n = 48$) and AHS ($n = 14$)	Clinical outcome at 3 months. Hypoglycemia detection	Higher MAG relates to lower likelihood of neurological improvement. Hypoglycaemia is better detected by CGM and is mainly nocturnal

Studies limited to accuracy and feasibility of CGM were excluded. Of note, up to date there are no trials regarding CGM in the setting of aSAH. MCA, Middle Cerebral Artery; OT, Occlusion Time; DWI, Diffusion-Weighted Imaging; ICA, Internal Carotid Artery; AUC, Area Under the Curve; AIS, Acute Ischemic Stroke; AHS, Acute Haemorrhagic Stroke; mRs, Modified Rankin Scale; MAG, Mean Absolute Glucose.

with worse outcomes, higher frequency of sICH and higher risk of death, although no link was found with recanalization rates (82–85). In intracerebral hemorrhage (ICH), hyperglycaemia at admission has been related to worse functional outcomes and death, in both diabetic and non-diabetic populations (86, 87). Reassuringly, a recent meta-analysis that evaluated the prognostic relevance of GV in both AIS and ICH showed a significant association between lower GV and reduced mortality at 30 and 90 days after stroke (88).

Nonetheless, studies using CGM in stroke are still scarce and have been based in modest population sizes. Disglycaemia measured by CGM is frequent after acute cerebrovascular events and has been linked to infarct growth in AIS (89, 90) and with poor prognosis after AIS and ICH (91), as shown in Table 2. It is noteworthy that, in these populations, CGM devices significantly improved hypoglycemia detection compared to standard clinical practice, thus opening a window of opportunity for CGM in patients that require aggressive glycaemic control (23, 24). However, to date, intensive glucose lowering in the acute phase of AIS has not reliably proven a clinical benefit, pointing the lack of consensus on hyperglycaemia definition or blood glucose targets (92, 93).

Conclusions and future directions

Hyperglycaemia, hypoglycemia and glucose variability during the acute phase of aSAH have been associated with an increased risk of in hospital complications and with poor long-term functional recovery. However, it is unclear whether these associations are due to direct deleterious effects induced by glucose dysregulation or if hyperglycaemia is an epiphenomenon related to the initial bleeding severity. In addition, it remains inconclusive whether there are specific longitudinal glycaemic profiles during the EBI period with special prognostic implications and/or more prone to lead to secondary brain injury. Arguably, the use of comprehensive dynamic evaluations, such as those derived from CGM devices, could aid to obtain a more precise understanding of such a highly dynamic process that is conditioned by both systemic complications and specific therapeutic approaches. A more accurate knowledge on glycaemic patterns during the acute phase of aSAH could increase our understanding of the relevance of glycaemia as a prognostic factor in this disease and to underpin its contribution to secondary focal and diffuse brain injury. In this context, the evaluation of biomarkers related with brain microvascular, metabolic and microstructural integrity using quantitative advanced MRI along with the quantification of circulating and cerebrospinal fluid (CSF) molecules related with brain injury could be highly informative for identifying glucose profiles associated with higher brain damage after aSAH. More research is needed to understand the most appropriate and informative timing for glucose monitoring, and how to combine glucose metrics with surrogate markers of acute brain injury. Eventually this information may lead to improve glucose management protocols in the setting of acute aSAH, to optimize the design of clinical trials aimed to modulate glucose levels and to advance toward a more personalized management of aSAH sufferers during the EBI period.

Author contributions

DS, AM, LP, LL, RT, and SA participated in writing the manuscript and editing critical parts of this review. LL,

RT, and SA gave the final approval for this submission. All authors contributed to the article and approved the submitted version.

Funding

We thank the Spanish Ministry of Economy and Competitiveness for the grant given to SA and RT [project PI19/00936 funded by Instituto de Salud Carlos III and co-funded by the European Regional Development Fund (ERDF)], the Fundació la Marató de TV3 for the grant given to SA (grant number 17/C/2017). DS is supported by a grant from Hospital Clinic de Barcelona (Contracte Clínic de Recerca Emili Letang-Josep Font).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers | Frontiers in Neurology

TYPE Mini Review
PUBLISHED 21 September 2022
DOI 10.3389/fneur.2022.1000454

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Endovascular and Interventional Neurology, a section of the journal Frontiers in Neurology

RECEIVED 22 July 2022
ACCEPTED 30 August 2022
PUBLISHED 21 September 2022

CITATION
Andersen CR, English SW and Delaney A (2022) Made to measure—Selecting outcomes in aneurysmal subarachnoid hemorrhage research. *Front. Neurol.* 13:1000454. doi: 10.3389/fneur.2022.1000454

Made to measure—Selecting outcomes in aneurysmal subarachnoid hemorrhage research

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There has been limited new high-level evidence generated to guide aneurysmal subarachnoid hemorrhage (aSAH) management in the past decade. The choice of outcome measures used in aSAH clinical trials may be one of the factors hindering progress. In this narrative review we consider the current process for determining "what" to measure in aSAH and identify some of the shortcomings of these approaches. A consideration of the unique clinical course of aSAH is then discussed and how this impacts on selecting the best timepoints to assess change in the chosen constructs. We also review the how to critically appraise different measurement instruments and some of the issues with how these are applied in the context of aSAH. We conclude with current initiatives to improve outcome selection in aSAH and future directions in the research agenda.

KEYWORDS

subarachnoid hemorrhage, outcome assessment (health care), core outcome set (COS), measurement instruments, patient reported outcome measures, stroke

Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is a devastating type of stroke that is caused by the rupture of an abnormal intracranial artery. It is associated with a high degree of mortality and a majority of survivors are left with long-term morbidity (1, 2). Despite the burden this condition places on patients, their families and society more generally, there is limited high-level evidence to guide treatment (3, 4). As such aSAH is, and will remain, an area of significant research interest. Ensuring that this research is efficient and well-designed to meet the needs of patients and health care providers is crucial.

One area of research design that is often overlooked is the selection of outcome measures. Getting the outcome measure selection right is fundamental for ensuring that the inferences that we draw from clinical research are valid and patient focused. Using a poorly chosen primary outcome measure might miss a clinical important benefit, or a surrogate outcome may suggest benefit of an intervention when there is none, or worse harm. Research is littered with examples of both (5, 6).

Choice of the outcome domain of interest by researchers is guided by the stage of research, population of interest, intervention being studied, and the comparator chosen. Researchers should consider the domains or outcomes that are most relevant to the research question and when is the most relevant timepoint/s for assessing this outcome (see Figure 1). They should then review the available instruments to determine which is best able to detect clinically meaningful change in this domain (7). Central to this process should be the end users of clinical research, patients and caregivers, policy makers, and the health care professionals that provide care.

What to measure: Choosing the right domains

Outcome domains are defined as the aspects of a medical condition that are important to patients, researchers, and health care providers and may be used to measure or assess the effects of interventions. Conceptually, outcome domains can be considered across a continuum of increasing complexity from pathophysiological variables such as blood tests or imaging results, through individual symptoms, then assessments of body function or activities, to patient perceptions of health and overall measures of quality of life (QoL) (8). Other commonly used taxonomies such as those developed by the OMERACT investigators also include domains such as survival and resource use (see Figure 2) (9, 10). As outcome domains progress along the continuum from pathophysiological through to overall measures of QoL they generally increase in authority and their ability influence clinical practice.

In aSAH, the different outcome domains chosen by researchers have varied significantly and been inconsistent across studies. In a review of 129 randomized controlled trials (RCTs) over a 20 year period survival is the most commonly reported outcome domain although it is only used as a primary outcome in 4% of studies (11). A measure of general patient function is also reported in more than half of the included studies, one in five used a functional measure as the primary outcome. Measures of how a patient feels, functions, or survives were used as a primary outcome in less than half of the studies, although those with higher numbers of participants were more likely to choose clinically meaningful outcome measures. Surrogate outcomes such as radiological vasospasm or transcranial doppler findings are much more likely to be reported and used as a primary outcome than measures of cognition or QoL. Patient reported QoL was only reported in 8.5% of included studies and its use as a primary outcome was only reported in one study.

Although pathophysiological domains are often easier to measure and demonstrate a statistically significant difference they should be interpreted with caution. Radiological vasospasm provides an important insight to this in aSAH research. After mortality and functional outcomes, angiographic vasospasm (as demonstrated with an imaging modality such as transcranial doppler or angiography) is the third most reported domain in aSAH RCTs with 8% of studies also choosing this as a primary outcome measure (11). Angiographic vasospasm seems a reasonable candidate for a pathophysiological outcome domain. It has both a biologically plausible mechanism for causing cerebral infarction and there is a strong association between the presence of angiographic vasospasm and poor outcomes. Notably however, the results of the well-designed CONSCIOUS-1 and CONSCIOUS-2 studies showed the use of clazosentan resulted in a dose-dependent reduction in angiographic vasospasm but did not show an improvement in clinically meaningful outcomes (12–14). Angiographic vasospasm therefore has biological plausibility and a strong

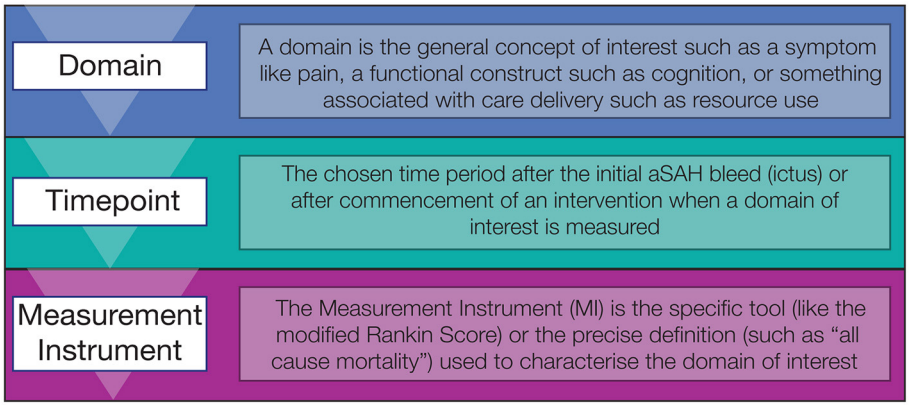

FIGURE 1
Three step process for selecting outcome measures in aSAH, starting with the domain of interest, the timepoint and then measurement instrument.

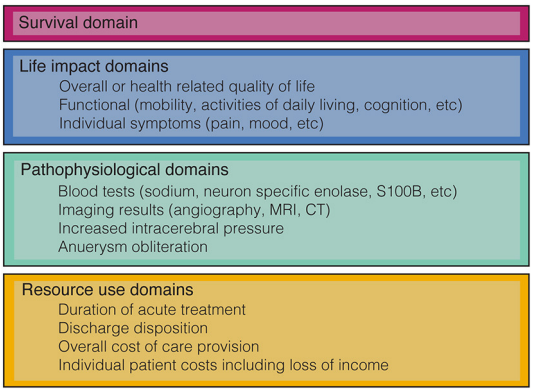

FIGURE 2
Classification of some of the common outcome domains used in aSAH research based on the OMERACT filter 2.0 (10).

association, but the best available evidence does not demonstrate that reducing vasospasm leads to an improvement in a more complex outcome describing how a patient feels, functions, or survives and therefore it should be used in research with caution (15, 16).

Another potential issue in aSAH research is the selection of outcome domains by researchers that do not meet the needs of the main end users of the research: patients and health care professionals. Multiple studies in the medical literature have shown that there is often a mismatch between the domains selected by researchers and those that are prioritized by end users (5, 17, 18). A recent systematic review did not identify any articles that described what domains aSAH patient or family prioritize in clinical research (19). It did however identify six categories of outcome domains that respondents felt helped or hindered their recovery including cognitive, physical, emotional, psychological, social, and emotional domains. Most of these domains are not well–reported in aSAH RCTs (11). The lack of understanding with respect to what outcome domains key stakeholder prioritize and likely mismatch remains an ongoing issue in aSAH research.

When to measure: Choosing the right timepoints

When the specific domains of interest have been established, it is important to determine the optimal time point for measurement. Ideally, researchers should be guided by temporal analysis of the domain of interest, estimating the earliest time point where there is minimal further change attributable to the intervention being evaluated. Decisions regarding optimal timepoints will also be influenced by the logistical challenges of conducting trial research. The longer the interval for assessment the higher the risks of loss to follow up and generally the higher the costs of conducting the research. There is also a concern that potentially beneficial treatments are delayed from being available if the time to outcome assessment is extended.

Unlike many remitting-relapsing conditions such as rheumatoid arthritis, aSAH follows a characteristic time course from ictus. This makes the decision of timepoints also relevant in terms of the disease trajectory as well as the timing of the intervention. Patients often have a hyper-acute phase of early brain injury in the first 24–48 h followed delayed brain injury in the subsequent weeks due to complications such as delayed cerebral ischemia, hospital acquired infection, hydrocephalus and rebleeding (20, 21). In the weeks after ictus some pathophysiological outcome domains such as cerebral infarction will become settled with minimal further change expected in the subsequent months (22). Some outcome domains such as resource use may be determined at landmark events such as intensive care or hospital discharge. More complex outcomes such as function and QoL measures generally remain dynamic for months after the initial ictus. The researchers of the landmark International Subarachnoid Aneurysm Trial used a functional domain (including survival) at 12 months from ictus as the primary outcome, but as there was potential change attributable the interventions over a longer period of time, continued to report timepoints years after the intervention in subsequent publications (23, 24).

Current selection of timepoints in aSAH RCTs is highly variable even within commonly reported domains. Within functional domains, the two most reported scores are reported at as early as 10 days post ictus up to many years post ictus. The most common timepoint for functional domains and survival is 3 months, with 6 and 12 months also frequently reported (11). This variability can make comparing different studies more challenging and may lead to research waste.

How to measure: Choosing the right measurement instruments

Once the domain and timepoints have been determined, researchers need to find the best measurement instrument (MI) to operationalize the construct of interest. An ideal MI should be reliable, valid, responsive and interpretable (25). A reliable MI should give consistent results every time it is used. It should have minimal sources of variation beyond the intervention of interest and should attempt to estimate these sources of variation (the measurement error) so they can be standardized (26). Validity relates to the MI accurately measuring the construct of interest. Responsiveness is the ability of the MI to detect a change in the domain of interest. Interpretability of a MI such as mortality at 3 months is straightforward but this may not necessarily be the case with more complex MI such as a patient reported QoL scale. A patient reported questionnaire will need to ensure users

understand how the scores are distributed and what a minimally important clinical difference might be to address interpretability.

There is a wide range of pathophysiological domains that are reported in aSAH with radiological vasospasm, cerebral infarction and delayed cerebral ischemia the most commonly reported in RCTs (11). The MIs and definitions for these domains are however highly variable. With respect to radiological vasospasm, studies have used transcranial doppler of the middle cerebral artery and compared mean thresholds or a Lindegaard ratio (27) or alternatively have used digital subtraction angiography, or CT angiography (28–30). Whilst there are advantages and disadvantages to each of these methods it is unclear which is the best way to measure radiological vasospasm. DCI has also been defined in many ways including delayed neurological deterioration, symptomatic vasospasm and clinical vasospasm (31–33). This heterogeneity limits our ability to interpret and draw inferences with respect to the true impact of an intervention and compare results between studies (34).

Measuring resource use is usually done in terms of time increments (duration of hospital admission, length of therapy) or in financial cost. Some of this data such as length of stay or number of procedures are more easily recorded or able to be extracted from administrative data including the electronic patient record. Length of hospital stay is the most commonly reported resource use measure in aSAH but non–clinical factors such as insurance status and local institutional policies introduce significant variability that may reduce reliability (11, 35). Measuring the time spent at home in the 90 days post ictus is a novel measure of disposition that may also be a reasonable surrogate for functional outcomes (36). Combining administrative information with patient-reported questionnaires could identify more nuanced data relevant to patients such as reduction in income and other costs that are more difficult to measure and may improve validity by providing a more accurate measure of resource use (37).

Function can be conceptualized through specific body functions (such as cognition or dexterity), through activities (such as mobility and self-care) and participation (such as engagement in work or social life) (38). Despite a pattern of neurological sequelae that is distinct to other forms of neurological conditions there are no functional MI that have been developed specifically for aSAH in common use. The modified Rankin score (mRS) and the Glasgow Outcome Scale (GOS) were developed for stroke patients and brain injury patients respectively (39–41). These functional scores assess activity and are frequently reported and used as a primary outcome in aSAH research. Assessment specific neurological functioning such as the Finger Tapping Test (dexterity), Verbal Fluency Test (language), Trail Marking Test (executive function) and Weschler Adult Intelligence Scale (cognition) have been used in only limited settings (42–45).

The modified Rankin score (mRS) is an ordinal scale of increasing disability that was developed for use in stroke patients. In recent times the mRS has become the most used functional outcome MI in aSAH research (11). Whilst the validity and reliability of the mRS is well–studied in stroke patients it's measurement properties with respect to aSAH are less well–studied (46, 47). There is evidence that the method of mRS acquisition in aSAH could introduce variance and therefore reduce the reliability (48). It is also somewhat limited and many important body function characteristics such as cognition are not captured. This limitation implies a ceiling to the mRS, whereby many patients that may have a good assessment based on self-care but still have significant impairment related to other body functions is not captured (49, 50). In large international trials the mRS as a primary endpoint has demonstrated a clinical important difference in functional outcome although a more comprehensive scale without the associated ceiling effects may be more responsive and allow smaller sample sizes (24).

Many functional scales such as the mRS and GOS are dichotomized into "good" and "poor" outcomes which improves its interpretability but how this is done is not consistent (11). Ideally researchers should consider the distribution of mRS outcomes, but this may not be known prior to study commencement. Work by the SAHIT investigators has shown that in some trials up to 75% of patients are classified as a "good" outcome reducing the power of this MI (49). In stroke research there has been a push to use the full ordinal scale when employing the mRS to improve the statistical power and identify change across the whole ordinal range despite the perceived reduction in interpretability (51, 52).

As outcome domains become more complex it becomes increasingly crucial that the MI is assessed from the patient's perspective to ensure that the assessment of health status is accurate (53). Patient reported outcome measures (PROMs) are when a patient or caregiver directly reports symptoms, function or an assessment of quality of life (54, 55). There is currently only limited application of PROMs in aSAH research with these MI reported in <10% of recent RCTs (11). The PROMs used in recent RCTs are primarily generic measures of QoL including the Short Form 36 Health Survey and the EQ5D Score (56, 57). Some neurological PROMS have been assessed in the context of aSAH patients such as the Stroke-Specific Quality of Life Scale, the Neuro-QoL and Quality of Life after Brain Injury Overall Scale (58–62). More recently there have emerged several aSAH specific PROMs with the subarachnoid hemorrhage specific outcome tool (SAHOT) and the Screening for Symptoms in Aneurysmal Subarachnoid Hemorrhage (SOS-SAH) questionnaire (63, 64). Assessment for a PROMs reliability, validity, responsiveness, and interpretability is challenging and more work needs to be done to further evaluate these instruments. Notably a recent systematic review of PROMs (published prior to the SOS-SAH) concluded that there is currently an insufficient evidence base for selecting an appropriate PROM in aSAH (65).

Moving forward

Moving forward there are multiple ways in which to improve outcome selection in aSAH research. One of the most important reforms is to ensure that there is patient and care giver involvement through all stages of the research process. This will help address any potential mismatch between the outcomes chosen by researchers and those prioritized by patients and health care providers. Patient involvement in outcomes research has been shown to widen the research agenda and led to the use of more patient relevant outcomes in clinical trials (66).

Pathophysiological outcomes remain important especially in early phase research and pilot studies. It is recommended that researchers move away from targeting pathophysiological outcomes such as radiological vasospasm and use alternative domains such as delayed cerebral ischemia and radiological evidence of cerebral infarction. These domains are likely to offer more robust insights to intervention efficacy (67, 68). Definitive research should continue to only use primary outcomes domains that represent how a patient feels, functions, or survives.

Choosing timepoints that can be standardized in the context of aSAH remains a challenge. Ideally, analysis of large databases and trial data repositories such as the SAHIT will allow better understanding of the trajectories of different outcome domains and help researchers identify ideal timepoints. Key stakeholders including patients and health care providers should also be consulted. In the interim it is recommended that researchers follow current expert consensus to use 3 months after ictus for most outcomes with a clear ceiling effect and longer time periods where there may be ongoing change such as rebleeding or recanalization (69).

Several notable standardization initiatives in aSAH research have improved the selection and use of outcome measures. The work by an international panel of experts over a decade ago proposed standardized definitions for DCI and cerebral infarction and this has helped address variable reporting of these instruments in aSAH research (34). More recently there has been important work by the National Institute of Neurological Diseases and Stroke Common Data Elements (NINDS-CDE) (70). This work classified over 50 MI into core, supplemental-highly recommended, supplemental, and exploratory. It also provided detailed case report forms to improve consistency of reporting. The mRS and the Montreal Cognitive Assessment were highly recommended supplemental MI, with the GOS, GOS-Extended, and Death as supplemental and all other outcomes classified as exploratory. The expert panel did not identify any core outcomes however (69).

When a domain and timepoint has been identified, it is recommended that researchers evaluate potential MI for reliability, validity, responsiveness, and interpretability. The Consensus-based Standards for the Selection of health Measurement INstruments (COSMIN) provides detailed advice and tools that use these criteria to determine the most appropriate MI (71). With respect to PROMs some of this work has been completed and may only need updating to account for the recently developed PROMs (65).

Ideally, MIs that assess domains for symptoms, functional domains and overall quality of life should be developed for specifically for an aSAH cohort with aSAH patient involvement given the unique sequalae and clinical course of the disease. The two recently developed aSAH PROMs are a promising start but require further testing and evaluation (63, 64). There is a need for aSAH specific functional measures that do not have the ceiling effects of current scales and include important domains such as cognition. We are not aware of any new functional measures being developed however and it is likely that mRS and GOS will continue as the most commonly applied functional MI. As such it is recommended that analysis using the full ordinal scale is considered even when this occurs at the cost of some interpretability. If it is decided to progress with dichotomization then researchers should estimate the expected distribution of scores when determining "good" vs. "bad" or default to the recommendations of the NINDS-CDE (69).

Working with patients, health care providers and researchers we should identify domains that are most relevant to improving health care delivery. Work to develop consensus for a set of core outcome domains for aSAH is currently under way (72). This international collaboration of patients, researchers and health care providers will determine a limited set of outcome domains across the four main categories in Figure 2, timepoints and the measurement instruments to create a core outcome set (COS). COS reduce research waste, improve consistency, and enable better comparison between studies.

Conclusion

Selection of appropriate MI is a critical step in the design of robust clinical research. In this article we have characterized this process as considering three main components, what to measure, when to measure, and how to measure. Significant improvements have been made in this area with respect to standardization and the development of aSAH specific MI, but there remains a need for simplified aSAH specific functional measures. Efforts to reduce the potential mismatch between the outcomes selected by researchers and the users of the research (patients and health care providers) is crucial. The development of a COS in aSAH should help to address any mismatch and will be another significant step forward in improving research efficiency and generating more high-level research in this devastating condition.

Author contributions

CA conceived the review and wrote the initial draft of the manuscript. AD and SE provided significant edits and assistance with restructuring the subsequent drafts. All authors read and approved the final version.

Funding

This work was supported by the Ottawa Hospital Academic Medical Organization Innovation Fund Grant provided to improve outcome measurement in subarachnoid hemorrhage.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers | Frontiers in Neurology

TYPE Original Research
PUBLISHED 24 October 2022
DOI 10.3389/fneur.2022.1014501

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Endovascular and Interventional Neurology, a section of the journal Frontiers in Neurology

RECEIVED 08 August 2022
ACCEPTED 10 October 2022
PUBLISHED 24 October 2022

CITATION
Wang L, Zhang Q, Zhang G, Zhang W, Chen W, Hou F, Zheng Z, Guo Y, Chen Z, Wang Y, Hernesniemi J, Andrade-Barazarte H, Li X, Li T, Feng G and Gu J (2022) Risk factors and predictive models of poor prognosis and delayed cerebral ischemia in aneurysmal subarachnoid hemorrhage complicated with hydrocephalus. *Front. Neurol.* 13:1014501. doi: 10.3389/fneur.2022.1014501

Risk factors and predictive models of poor prognosis and delayed cerebral ischemia in aneurysmal subarachnoid hemorrhage complicated with hydrocephalus

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Objective: To evaluate the correlation of serum biological markers and related scales to the occurrence of delayed cerebral ischemia and clinical prognosis in patients with aneurysmal subarachnoid hemorrhage (aSAH) complicated with acute hydrocephalus before admission.

Methods: The clinical data of 227 patients with pre-admission aSAH complicated with acute hydrocephalus admitted to Henan Provincial People's Hospital from April 2017 to December 2020 were retrospectively analyzed. Patients were grouped according to the presence or absence of delayed cerebral ischemia (DCI) after surgery and the prognosis at 6 months after discharge. Univariate and multivariable logistic regression analysis were performed to analyze the relationship between serum biological indicators combined with aneurysm related clinical score scale and the occurrence and prognosis of delayed cerebral ischemia. ROC curves and nomogram were drawn.

Results: Multivariable Logistic regression analysis showed that high Hunt-Hess grade and surgical clipping were independent risk factors for postoperative DCI ($P < 0.05$). Older age, higher Hunt-Hess grade, higher CRP and neutrophil levels were independent risk factors for poor prognosis at 6 months after surgery ($P < 0.05$). ROC curve analysis showed that the area under the curve (AUC) of Hunt-Hess grade and surgical method for predicting DCI in patients with aSAH combined with hydrocephalus after surgery were 0.665 and 0.593. The combined AUC of Hunt-Hess grade and surgical method was 0.685, the sensitivity was 64.9%, and the specificity was 64.7%. The AUC of CRP, neutrophil, age and Hunt-Hess grade for predicting poor prognosis in patients with aSAH combined with hydrocephalus at 6 months after surgery were 0.804,

0.735, 0.596, 0.757, respectively. The combined AUC of CRP, neutrophil, age, Hunt-Hess grade was 0.879, the sensitivity was 79%, and the specificity was 84.5%. According to the correction curve, the predicted probability of the nomogram is basically consistent with the actual probability.

Conclusion: Hunt-Hess grade and surgical method are independent predictors of postoperative DCI in patients with aSAH complicated with hydrocephalus. "CRP," "neutrophil," "age" and "Hunt-Hess grade" at admission are independent predictors of clinical prognosis in patients with aSAH complicated with hydrocephalus. The combination of the above indicators has high predictive value.

KEYWORDS

aneurysmal subarachnoid hemorrhage (aSAH), hydrocephalus, inflammation, Hunt-Hess grade, delayed cerebral ischemia (DCI), prognosis, outcome, risk factor

Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is one of the most common neurological emergencies in clinical practice, accounting for about 5% of stroke patients (1, 2), with a mortality rate of 35%, and about one third of survivors are left with permanent disability (3, 4). Delayed cerebral ischemia is one of the main causes of high mortality and morbidity (5). DCI is a clinical imaging syndrome that includes focal ischemia and/or cognitive impairment on CT/MRI and/or cerebral infarction (6).

Hydrocephalus is a common serious complication of aSAH, and about 20 to 30% of aSAH patients will develop acute hydrocephalus due to obstruction of cerebrospinal fluid circulation or abnormal absorption (7–9). Acute hydrocephalus will not only aggravate the early neurological impairment of patients with aSAH, further aggravate the clinical condition, but also impair the neurological function of patients in the recovery period after aSAH surgery (10). Although patients with aSAH with acute hydrocephalus can be treated with surgery or lumbar cisternae drainage, these patients represent a subgroup of patients with more advanced aSAH. Therefore, for patients with aSAH complicated with hydrocephalus on admission, searching for biomarkers that can predict the prognosis of the patients is conducive to early formulation of a reasonable treatment plan, so as to improve the prognosis and reduce the mortality of the patients.

In recent years, more and more attention has been paid to the determination of various biomarkers in blood. Studies have shown that Inflammatory markers, blood cell markers, blood glucose markers, blood lipid markers, and aneurysmal-related clinical scoring scales (such as Hunt-Hess scale, modified Fisher scale, and WFNS scale) have high clinical reference value in predicting the clinical prognosis of patients without hydrocephalus and aSAH at admission (11–16). However, no studies have shown the prognostic value of clinical blood indicators or other related indicators in patients with aSAH complicated with acute hydrocephaluson admission.

The purpose of this study was to retrospectively analyze the clinical data of aSAH patients with acute hydrocephalus at admission and the prognostic results at 6 months after surgery, and to explore the predictive value of blood biomarkers and aneurysmal-related clinical score scale for the presence of DCI and different prognosis in aSAH patients with acute hydrocephalus after surgery. It provides sufficient theoretical basis for early clinical intervention and improvement of prognosis of aSAH patients.

Abbreviations: aSAH, aneurysmal arachnoid hemorrhage; AUC, areas under curve; CPe, choroid plexus epithelium; CRP, C-reactive protein; CSF, cerebrospinal fluid; CT, Computed tomography; CTA, CT angiography; DCI, delayed cerebral ischemia; DSA, digital subtraction angiography; IL-1, interleukin 1; IL-6, interleukin 6; IVH, intraventricular hemorrhage; mRS, modified Rankin scale; PHH, post-haemorrhagic hydrocephalus; ROC, receiver operating characteristic; TLR4, Toll-like receptor 4; TNF-α, tumor necrosis factor α.

Materials and methods

General information

A total of 227 patients with aSAH complicated with hydrocephalus admitted to Henan Provincial People's Hospital from April 2017 to December 2020 were retrospectively

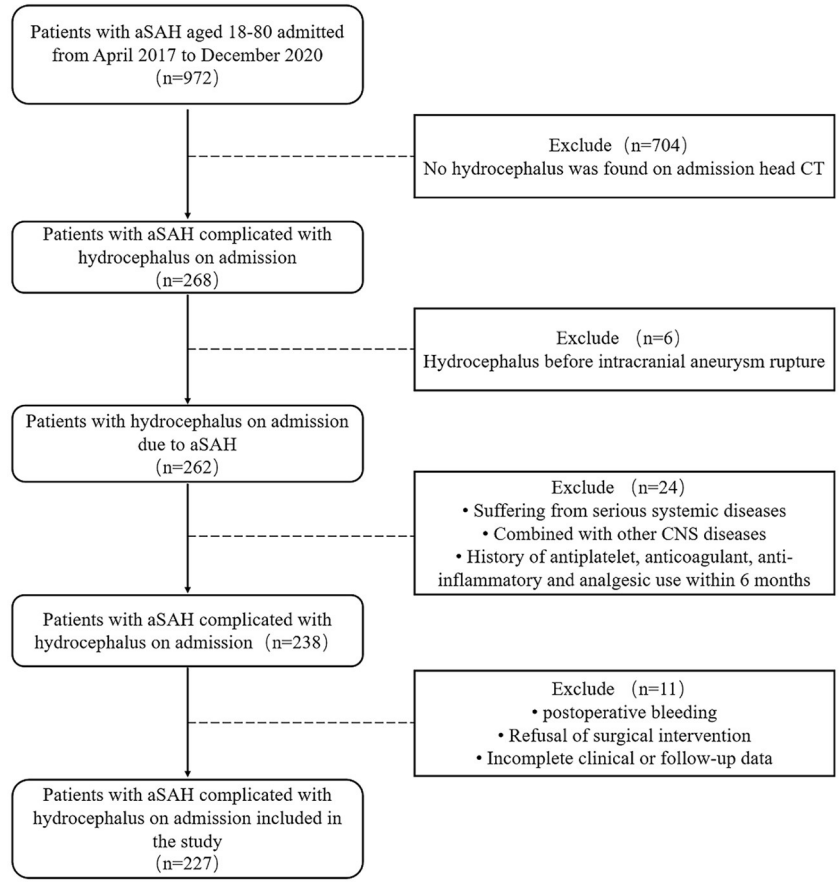

FIGURE 1
Flow chart of patient selection.

enrolled. One hundred and fifty were females and 77 were males.

The inclusion criteria were as follows: (1) aSAH confirmed by head CT or CT angiography (CTA) or DSA; (2) Hydrocephalus was found by head CT examination on the day of admission; (3) Intervention or craniotomy clipping treatment within 10 days after admission; (4) 18–80 years old; 5. Complete admission and venous blood collection within 24 h after onset; (6) Come to our hospital for review 6 months after operation; (7) No new neurological diseases occurred 6 months after discharge; (8) CT findings of new infarction in DCI patients are not related to surgery.

The exclusion criteria were as follows: (1) non-aneurysmal subarachnoid hemorrhage, such as moyamoya disease, arteriovenous malformations, etc.; (2) History of hydrocephalus; (3) Sequelae of previous neurological diseases; (4) Suffering from serious systemic diseases, such as heart, liver, renal insufficiency, and blood system diseases; (5) Complicated with other intracranial diseases, such as intracranial infection and intracranial artery stenosis; (6) A history of taking aspirin, non-steroidal drugs, anti-inflammatory and analgesic drugs 6 months before admission; (7) Pregnant or lactating women; (8) Incomplete clinical data.

Methods

The basic clinical data of the patients were collected, including age, gender, smoking history, drinking history, underlying diseases (hypertension, coronary heart disease, diabetes mellitus, cerebral infarction), Hunt-Hess grade on admission, imaging examination data, aneurysm location record, modified Fisher grade, etc. Hematological indexes (inflammatory indexes, blood cell indexes, blood lipid indexes) were recorded within 24 h after admission. The patients were divided into DCI group and non-DCI group according to

whether DCI occurred after operation. The patients were divided into good prognosis group (mRS $\leq$2) and poor prognosis group (mRS >2) by modified Rankin score (mRS) according to the condition at 6 months after operation.

Statistical analysis

SPSS 25.0 statistical software was used for data processing. Measurement data conforming to normal distribution were expressed as ($\overline{x} \pm s$), and comparison between groups was performed by *t*-test. Measurement data that did not conform to normal distribution were also expressed as ($\overline{x} \pm s$), and comparison between groups was performed by Mann-Whitney U-test. Statistical data were expressed as percentage (%), and comparison between groups was performed by $\chi 2$ test. Factors that might predict prognosis were used as independent variables in univariate analysis. On the basis of univariate analysis, indicators with $P < 0.05$ were included in multivariable Logistic regression analysis to generate independent risk factors. Receiver Operating characteristic curve (ROC) was established to determine the AUC, sensitivity, specificity and cutoff values of the final prognostic indicators. ROC curve was drawn by combining the significant indexes in multivariable analysis. Based on the results of multivariable logistic regression, the Nomogram was drawn using R4.2 software for meaningful indicators, and 1,000 Bootstrap samples were corrected to measure the predictive ability of Nomogram and reduce overfitting bias. In this study, $P < 0.05$ was defined as statistically significant.

Results

A total of 227 patients with aSAH complicated with hydrocephalus were enrolled (Figure 1). According to the occurrence of postoperative DCI, they were divided into DCI group (74 cases) and non-DCI group (153 cases). There were 44 females and 30 males in DCI group, with an average age of (65.16 ± 9.85) years. There were 106 females and 47 males in the non-DCI group, with an average age of (63.36 ± 11.38) years. In DCI group, 55 ruptured aneurysms were located in anterior circulation and 19 ruptured aneurysms were located in posterior circulation. Thirty seven cases received interventional therapy and 37 cases received clipping therapy. In the non-DCI group, 94 ruptured aneurysms were located in the anterior circulation and 59 in the posterior circulation. One hundred and five cases were treated with interventional therapy and 48 cases were treated with clipping therapy (Table 1).

According to mRS score at 6 months after surgery, the patients were divided into good prognosis group (103 cases) and poor prognosis group (124 cases). In the good prognosis group, there were 74 females and 29 males, with an average age of (61.96 ± 11.13) years. There were 76 females and 48 males in the poor prognosis group, with an average age of (65.60 ± 10.49) years. In the good prognosis group, 70 ruptured aneurysms were in the anterior circulation and 33 ruptured aneurysms were in the posterior circulation. Seventy one cases were treated with interventional therapy and 32 cases were treated with clipping therapy. In the poor outcome group, 79 ruptured aneurysms were in the anterior circulation and 45 were in the posterior circulation. Seventy one cases received interventional therapy and 53 cases received clipping therapy (Table 2).

Univariate analysis

There were no significant differences in DCI group with non-DCI in gender, age, smoking history, drinking history, diabetes, hypertension, cerebral infarction, coronary heart disease, aneurysm location, lymphocyte, monocyte, procalcitonin, hematocrit, red blood cell distribution width, average blood platelet volume, platelet count, large platelet volume, total cholesterol, triglyceride, high density lipoprotein, low density lipoprotein, apolipoprotein A1, apolipoprotein B100, fibrinogen and albumin levels ($P > 0.05$). The levels of Hunt-Hess grade, modified Fisher grade, CRP, white blood cells, neutrophil and D-dimer in DCI group were higher than those in non-DCI group ($P < 0.05$). The amount of surgical clipping in the DCI group was higher than that in the non-DCI group ($P < 0.05$). The level of eosinophil in DCI group was lower than that in non-DCI group ($P < 0.05$) (Table 1).

There were no significant differences in good prognosis group with poor prognosis in gender, smoking history, drinking history, diabetes, hypertension, cerebral infarction, coronary heart disease, surgical procedure, aneurysm location, monocyte, procalcitonin, hematocrit, red blood cell distribution width, average blood platelet volume, platelet count, large platelet volume, total cholesterol, triglyceride, high density lipoprotein, low density lipoprotein, apolipoprotein A1, apolipoprotein B100, fibrinogen and albumin levels ($P > 0.05$). The age, Hunt-Hess grade, modified Fisher grade, CRP, leukocyte, neutrophil, lymphocyte, eosinophil and D-dimer levels in the poor prognosis group were higher than those in the good prognosis group, with statistical significance ($P < 0.05$) (Table 2).

Multivariable logistic regression analysis

According to the results of univariate analysis, the occurrence of DCI was taken as the dependent variable. Hunt-Hess grade, modified Fisher grade, surgical approach (intervention, clipping), CRP, leukocytes, neutrophils, eosinophils, and D-dimer levels were used as independent variables. Logistic regression model analysis showed that "Hunt-Hess grade was high" (OR = 1.900, 95%Cl: 1.359–2.657)

TABLE 1 Univariate analysis (Based on DCI group, non-DCI group).

Characteristics	Non-DCI ($n = 153$)	DCI ($n = 74$)	P-value
Gender			$P = 0.143$
Female	106 (69.28%)	44 (59.46%)	
Male	47 (30.72%)	30 (40.54%)	
Age (years)	63.36 ± 11.38	65.16 ± 9.85	$P = 0.277$
Smoking history	23 (15.03%)	17 (22.97%)	$P = 0.141$
Drinking history	21 (13.73%)	8 (10.81%)	$P = 0.537$
Diabetes	15 (9.80%)	5 (6.76%)	$P = 0.448$
Hypertension	96 (62.75%)	48 (64.86%)	$P = 0.756$
Cerebral infarction	19 (12.42%)	12 (16.22%)	$P = 0.411$
Coronary heart disease	15 (9.80%)	14 (18.92%)	$P = 0.054$
Modified Fisher grade			$P = 0.005$
Grade I	13 (8.50%)	2 (2.70%)	
Grade II	81 (52.94%)	30 (40.54%)	
Grade III	26 (16.99%)	16 (21.62%)	
Grade IV	33 (21.57%)	26 (35.14%)	
Hunt and Hess grade			$P = 0.000$
Grade I	1 (0.65%)	0	
Grade II	55 (35.95%)	8 (10.81%)	
Grade III	62 (40.52%)	35 (47.30%)	
Grade IV	27 (17.65%)	21 (28.38%)	
Grade V	8 (5.23%)	10 (13.51%)	
Surgical method			$P = 0.007$
Interventional	105 (68.63%)	37 (50.00%)	
Clipping	48 (31.37%)	37 (50.00%)	
Location of aneurysm			$P = 0.055$
Anterior circulation	94 (61.44%)	55 (74.32%)	
Posterior circulation	59 (38.56%)	19 (25.68%)	
Laboratory results			
CRP (mg/L)	22.21 ± 33.19	33.67 ± 36.93	$P = 0.002$
WBC ($\times 10^9$/L)	10.99 ± 4.52	13.16 ± 4.50	$P = 0.001$
Neutrophil ($\times 10^9$/L)	9.24 ± 4.39	11.20 ± 4.00	$P = 0.000$
Lymphocyte ($\times 10^9$/L)	1.04 ± 0.50	1.01 ± 0.49	$P = 0.699$
Monocyte ($\times 10^9$/L)	0.67 ± 1.18	0.64 ± 0.34	$P = 0.178$
Eosinophil ($\times 10^9$/L)	0.05 ± 0.16	0.02 ± 0.06	$P = 0.027$
Procalcitonin (ng/mL)	0.21 ± 0.06	0.23 ± 0.06	$P = 0.094$
Hematocrit	0.37 ± 0.05	0.38 ± 0.37	$P = 0.098$
RDW-CV (%)	12.85 ± 1.18	13.05 ± 1.19	$P = 0.376$
MPV (fL)	10.32 ± 1.37	14.85 ± 36.82	$P = 0.113$
PLT ($\times 10^9$/L)	213.90 ± 65.75	214.84 ± 74.81	$P = 0.787$
P-LCR (%)	28.53 ± 9.64	29.93 ± 9.99	$P = 0.396$
D-Di (μg/ml)	3.63 ± 8.01	3.61 ± 3.84	$P = 0.002$
TC (mmol/L)	4.58 ± 1.07	4.44 ± 1.10	$P = 0.392$
TG (mmol/L)	1.74 ± 1.74	1.38 ± 0.80	$P = 0.380$
HDL (mmol/L)	1.24 ± 0.34	1.22 ± 0.33	$P = 0.720$
LDL (mmol/L)	2.60 ± 0.83	2.51 ± 0.81	$P = 0.438$
Apo A1 (g/L)	1.13 ± 0.29	1.06 ± 0.27	$P = 0.097$
Apo B100 (g/L)	0.85 ± 0.23	0.84 ± 0.24	$P = 0.783$
FBG (g/L)	3.76 ± 1.30	3.88 ± 1.13	$P = 0.289$
ALB (g/L)	38.27 ± 5.49	39.41 ± 5.00	$P = 0.197$

CRP, C reactive protein; WBC, white blood cell; RDW-CV, red blood cell distribution width-CV; MPV, mean platelet volume; PLT, platelet; P-LCR, platelet-large cell ratio; D-Di, D-Dimer; TC, total cholesterol; TG, triglyceride; HDL, high density lipoprotein; LDL, low density lipoprotein; Apo A1, apolipoprotein a1; Apo B100 = apolipoprotein B100; FBG, fibrinogen; ALB, albumin.

TABLE 2 Univariate analysis (Based on good prognosis group, poor prognosis group).

Characteristics	Good outcome (mRS 0–2, $n = 103$)	Poor outcome (mRS 3–6, $n = 124$)	*P*-value
Gender			$P = 0.094$
Female	74 (71.84%)	76 (61.29%)	
Male	29 (28.16%)	48 (38.71%)	
Age (years)	61.96 ± 11.13	65.60 ± 10.49	$P = 0.013$
Smoking history	16 (15.53%)	24 (19.35%)	$P = 0.452$
Drinking history	13 (12.62%)	16 (12.90%)	$P = 0.949$
Diabetes	10 (9.71%)	10 (8.06%)	$P = 0.663$
Hypertension	65 (63.11%)	79 (63.71%)	$P = 0.925$
Cerebral infarction	13 (12.62%)	19 (15.32%)	$P = 0.661$
Coronary heart disease	13 (12.62%)	16 (12.90%)	$P = 0.949$
Modified Fisher grade			$P = 0.000$
Grade I	12 (11.65%)	3 (2.42%)	
Grade II	64 (62.14%)	47 (37.90%)	
Grade III	16 (15.53%)	26 (20.97%)	
Grade IV	11 (10.68%)	48 (38.71)	
Hunt and Hess grade			$P = 0.000$
Grade I	1 (0.97%)	0	
Grade II	46 (44.66%)	17 (13.71%)	
Grade III	48 (46.60%)	49 (39.52%)	
Grade IV	7 (6.80%)	41 (33.06%)	
Grade V	1 (0.97%)	17 (13.71%)	
Surgical method			$P = 0.070$
Interventional	71 (68.93%)	71 (57.26%)	
Clipping	32 (31.07%)	53 (42.74%)	
Location of aneurysm			$P = 0.502$
Anterior circulation	70 (67.96%)	79 (63.71%)	
Posterior circulation	33 (32.04%)	45 (36.29%)	
Laboratory results			
CRP (mg/L)	9.85 ± 12.86	39.32 ± 41.11	$P = 0.000$
WBC ($\times 10^9$/L)	10.24 ± 3.69	12.90 ± 4.96	$P = 0.000$
Neutrophil ($\times 10^9$/L)	8.06 ± 3.19	11.38 ± 4.63	$P = 0.000$
lymphocyte ($\times 10^9$/L)	1.11 ± 0.49	0.96 ± 0.49	$P = 0.011$
Monocyte ($\times 10^9$/L)	0.73 ± 1.42	0.60 ± 0.34	$P = 0.960$
Eosinophil ($\times 10^9$/L)	0.05 ± 0.11	0.03 ± 0.16	$P = 0.001$
Procalcitonin (ng/mL)	0.22 ± 0.06	0.22 ± 0.07	$P = 0.664$
Hematocrit	0.37 ± 0.04	0.38 ± 0.05	$P = 0.624$
RDW-CV (%)	13.02 ± 1.23	12.83 ± 1.14	$P = 0.301$
MPV (fL)	10.38 ± 1.38	12.97 ± 28.47	$P = 0.483$
PLT ($\times 10^9$/L)	214.72 ± 60.60	213.78 ± 74.95	$P = 0.793$
P-LCR (%)	29.11 ± 10.60	28.91 ± 9.11	$P = 0.897$
D-Di (μg/ml)	1.93 ± 4.60	5.02 ± 8.13	$P = 0.000$
TC (mmol/L)	4.60 ± 0.99	4.47 ± 1.15	$P = 0.420$
TG (mmol/L)	1.66 ± 1.79	1.57 ± 1.21	$P = 0.418$
HDL (mmol/L)	1.27 ± 0.30	1.21 ± 0.35	$P = 0.158$
LDL (mmol/L)	2.61 ± 0.76	2.53 ± 0.86	$P = 0.496$
Apo A1 (g/L)	1.14 ± 0.21	1.08 ± 0.32	$P = 0.106$
Apo B100 (g/L)	0.84 ± 0.21	0.84 ± 0.24	$P = 0.935$
FBG (g/L)	3.67 ± 1.17	3.91 ± 1.30	$P = 0.165$
ALB (g/L)	38.99 ± 5.64	38.42 ± 5.06	$P = 0.504$

TABLE 3 Multivariable logistic analysis (Based on DCI group, non-DCI group).

Characteristics	OR	95% CI	*P*-value
Hunt-Hess grade	1.900	1.359–2.657	0.000
Surgical method			
Interventional	1		
Clipping	2.069	1.137–3.765	0.017
Modified Fisher grade			0.318
CRP			0.199
WBC			0.059
Neutrophil			0.234
Eosinophil			0.256
D-Di			0.777

OR, odds ratio; Cl, confidence interval.

TABLE 4 Multivariable logistic analysis (Based on good prognosis group, poor prognosis group).

Characteristics	OR	95% CI	*P*-value
Age	1.038	1.003–1.074	0.033
CRP	1.057	1.031–1.084	0.000
Neutrophil	1.212	1.076–1.365	0.002
Hunt-Hess grade	2.538	1.532–4.208	0.000
Modified Fisher grade			0.103
WBC			0.074
Lymphocyte			0.922
Eosinophil			0.777
D-Di			0.064

OR, odds ratio; Cl, confidence interval.

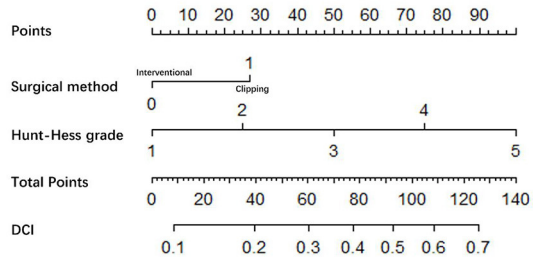

FIGURE 2
Nomogram (Based on DCI group, non-DCI group).

and "surgical clipping" (OR = 2.069, 95%Cl: 1.137–3.765) increased the risk of DCI compared with intervention. Hunt-Hess grade and surgical clipping were independent risk factors for postoperative DCI in patients with aSAH complicated with hydrocephalus ($P < 0.05$) (Table 3).

According to the results of univariate analysis, the prognosis at 6 months after surgery (good and poor) was used as the dependent variable. Age, Hunt-Hess grade, modified Fisher grade, CRP, leukocytes, neutrophils, lymphocytes, eosinophils and D-dimer were used as independent variables. Logistic regression model analysis showed that the independent risk factors for poor prognosis in patients with aSAH complicated with hydrocephalus at 6 months after surgery were "increased age" (OR = 1.038, 95%Cl: 1.003–1.074) and "increased CRP" (OR = 1.057, 95%Cl: 1.031–1.084), "increased neutrophils" (OR = 1.212, 95%Cl: 1.076–1.365) and "high Hunt-Hess grade" (OR = 2.538, 95%Cl: 1.532–4.208) ($P < 0.05$) (Table 4).

Nomogram

Significant logistic analysis indicators were used to construct Nomogram (Figures 2, 3). Nomogram can be used to assess the risk of DCI and poor prognosis in patients with aSAH complicated with acute hydrocephalus.

The probability of DCI was predicted according to the risk value corresponding to the total score, which was calculated according to the patient's "Hunt-Hess grade" and "surgical method." And the contribution of each factor to the overall risk of DCI was revealed (Figure 2).

The probability of poor prognosis was predicted according to the risk value corresponding to the total score, which was calculated according to the patient's "age," "CRP," "neutrophil" and "Hunt-Hess grade." And the contribution of each factor to the overall risk of poor prognosis was revealed. For example, for a "72-year-old" aSAH patient with acute hydrocephalus, "CRP = 25.47 mg/L," "neutrophil = 9.4×10^9/L," "Hunt-Hess grade 4," the probability of poor prognosis is 84%. According to the positions of each factor of the Nomogram, 15 points of "72 years old," 13 points of "CRP = 25.47 mg/L," 17 points of "neutrophil = 9.4×10^9/L," and 25 points of "Hunt-Hess

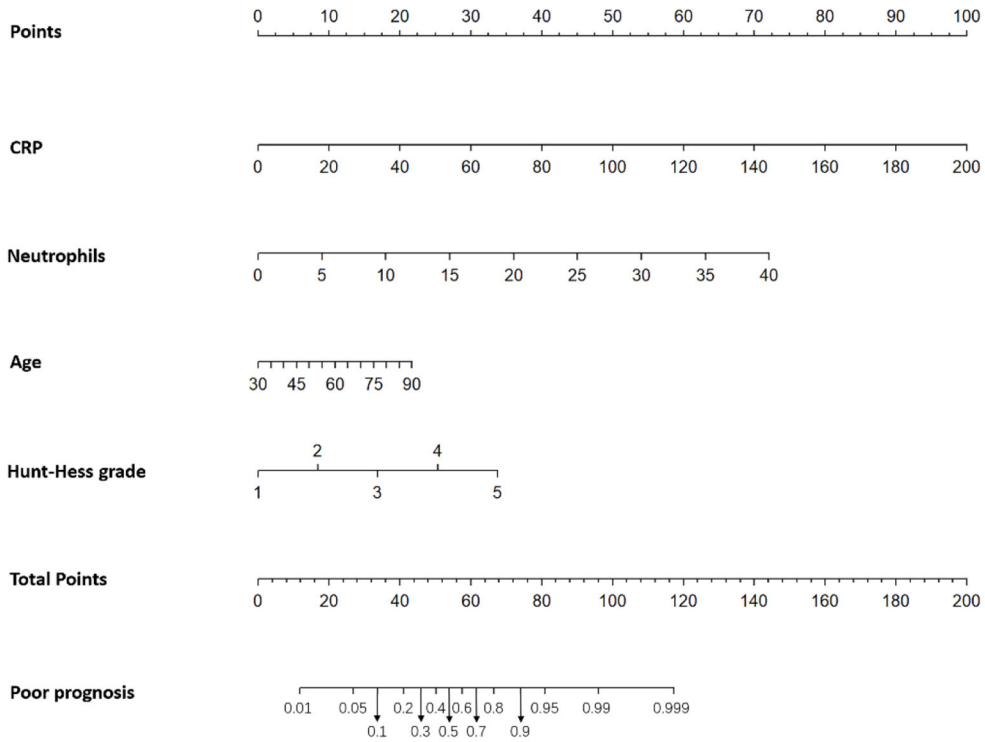

FIGURE 3
Nomogram (Based on good prognosis group, poor prognosis group).

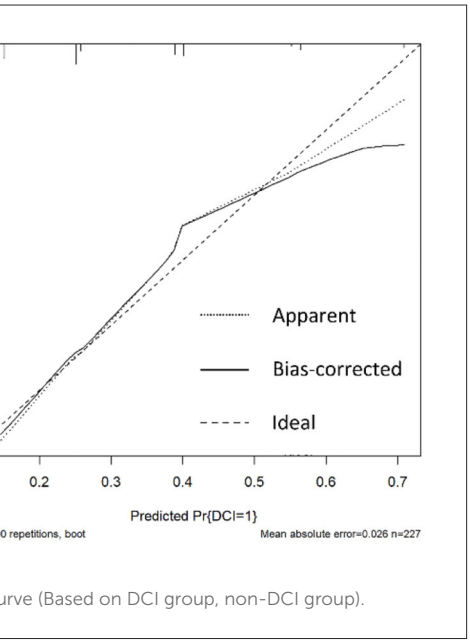

FIGURE 4
Calibration curve (Based on DCI group, non-DCI group).

grade 4" were calculated. Then the positions of each factor were summed to obtain a total score of 70. A score of 70 corresponds to an ∼84% probability of poor prognosis (Figure 3).

Verify the Nomogram: The calibration curve of the prediction model with 1,000 duplicate samples established by bootstrapping method has high accuracy (Figures 4, 5).

ROC curve analysis

The optimal cut-off values of "Hunt-Hess grade" was 2.5. The AUC of "Hunt-Hess grade" and "surgical method" were 0.665 and 0.593, respectively, in predicting the DCI of aSAH combined with hydrocephalus after surgery. The sensitivities were 89.2 and 50%, respectively. The specificity ware 36.6 and 68.6%, respectively. The AUC of " Hunt-Hess grade + surgical method" was 0.685, the sensitivity was 64.9%, and the specificity was 64.7% (Table 5 and Figure 6).

The optimal cut-off values of "age," "Hunt-Hess grade," "CRP" and "neutrophil" were 61.5, 3.5, 11.4, and 9.06, respectively, in predicting the poor prognosis of aSAH combined with hydrocephalus at 6 months after surgery. The AUC were 0.596, 0.757, 0.804, and 0.735, respectively. The sensitivities were 74.2, 46.8, 74.2, and 73.4%, respectively. The specificity ware 42.7, 92.2, 76.7, and 68%, respectively. The AUC of "age + Hunt-Hess grade + CRP + neutrophils" was 0.879, the sensitivity was 79%, and the specificity was 84.5% (Table 6 and Figure 7).

Discussion

Aneurysmal subarachnoid hemorrhage often causes hydrocephalus (17, 18), which can aggravate neurological impairment and seriously affect the prognosis of patients. Patients with aSAH complicated with acute hydrocephalus have a poor prognosis and high mortality, and even those who survive are often left with neurological damage or cognitive impairment (10). aSAH-associated hydrocephalus is thought to occur through the following mechanisms: (1) Blood products hinder the normal circulation of cerebrospinal fluid; (2) Excessive secretion of cerebrospinal fluid; (3) Cerebrospinal fluid reabsorption is reduced due to blood products affecting arachnoid granules (19–21). In addition, the subarachnoid inflammatory response to blood products may vary depending on the severity of the patient. From the perspective of the physiological mechanism of acute hydrocephalus after aSAH, the degree of inflammatory response of subarachnoid space to blood products determines the effect of cerebrospinal fluid obstruction and cerebrospinal fluid overproduction on acute hydrocephalus. Thus, this group of patients with early post-aSAH hydrocephalus, that is, acute hydrocephalus before aSAH admission, may represent a subgroup of patients with a stronger inflammatory response. Therefore, it is of great clinical significance to study the predictors of postoperative DCI and poor prognosis in patients with aSAH complicated with acute hydrocephalus, and to take targeted preventive measures as early as possible for high-risk patients with poor prognosis, which is helpful to improve the prognosis of patients.

Delayed cerebral ischemia

DCI will seriously affect the prognosis of aSAH patients (6). Consistent with previous studies, the presence of DCI in this study was associated with poor prognosis (14.56% of patients with good prognosis had DCI, and 47.58% of patients with poor prognosis had DCI, $P < 0.05$).

In recent years, with the continuous development of imaging equipment and minimally invasive techniques, and the use of drugs to prevent cerebral vasospasm, the incidence of DCI after intracranial aneurysm surgery has been reduced (4). However, the incidence of DCI after aneurysm clipping and interventional therapy remains controversial. Ding et al. (5) believed that there was no significant difference in the incidence of DCI between clipping and interventional therapy. Dorhout et al. (22)

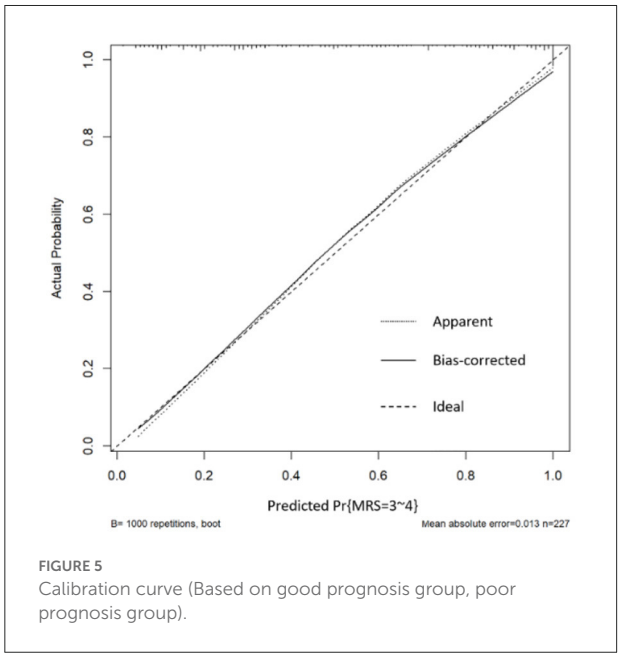

FIGURE 5
Calibration curve (Based on good prognosis group, poor prognosis group).

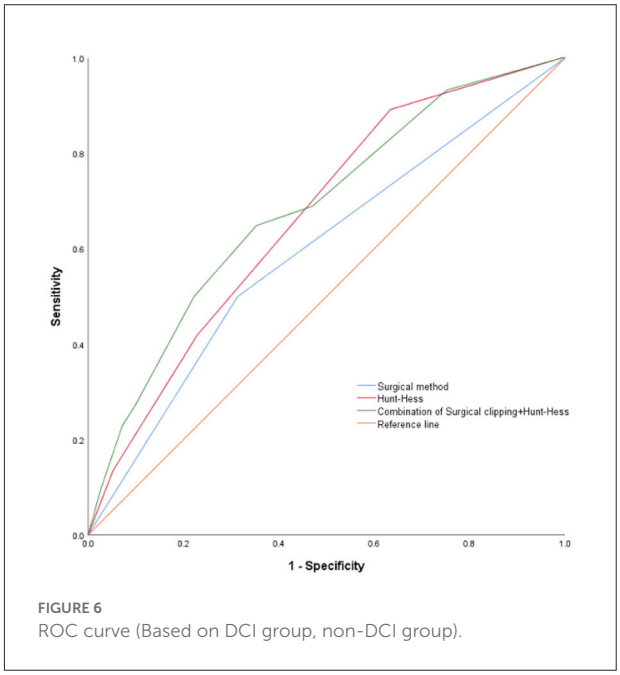

FIGURE 6
ROC curve (Based on DCI group, non-DCI group).

TABLE 5 The AUC, cut-off value, sensitivity, specificity from the ROC curve (Based on DCI group, non-DCI group).

Characteristics	AUC	95% CI	Cut-off	Sensitivity (%)	Specificity (%)
Hunt-Hess grade	0.665	0.592–0.737	2.5	89.2	36.6
Surgical method	0.593	0.513–0.673	-	50	68.6
Combination	0.685	0.611–0.758	-	64.9	64.7

TABLE 6 The AUC, cut-off value, sensitivity, specificity from the ROC curve (Based on good prognosis group, poor prognosis group).

Characteristics	AUC	95% CI	Cut-off	Sensitivity (%)	Specificity (%)
CRP	0.804	0.748–0.861	11.4	74.2	76.7
Neutrophil	0.735	0.670–0.800	9.06	73.4	68
Age	0.596	0.522–0.670	61.5	74.2	42.7
Hunt-Hess grade	0.757	0.695–0.819	3.5	46.8	92.2
Combination	0.879	0.835–0.923	-	79	84.5

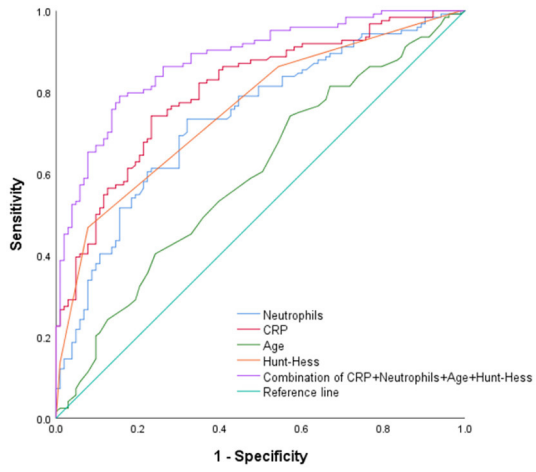

FIGURE 7
ROC curve (Based on good prognosis group, poor prognosis group).

believe that compared with interventional surgery, clipping is more likely to lead to DCI. Meta-analysis by Oliveira et al. (23) showed that there was no statistical difference in the incidence of postoperative DCI between the clipping group and the intervention group. Compared with interventional surgery, clipping surgery can remove the thrombus, but it also causes some damage to the vessel wall, thus increasing the incidence of DCI. This study confirmed that the incidence of DCI was higher with clipping than with intervention, which may be due to more severe brain injury with clipping than with intervention. Therefore, it is important to understand the differences of postoperative DCI between different surgical methods and effectively choose different surgical methods according to the patient's condition to reduce the incidence of postoperative DCI.

Inflammatory indicators

Inflammation runs through the whole process of aSAH injury mechanism. When aneurysms rupture, blood cells deposited in the subarachnoid space stimulate brain tissue and activate immune regulatory cells in the central nervous system, and a large number of inflammatory cells enter the subarachnoid space, rapidly causing an inflammatory response (24, 25). On the other hand, in patients with aSAH combined with hydrocephalus, cerebrospinal fluid circulation pathway is impaired and CSF secretion/absorption is unbalanced, which makes inflammatory cells accumulate in the subarachnoid space and further aggravate the inflammatory response (24, 26–28). Inflammatory reaction can activate the immune system to release inflammatory cells and inflammatory mediators, leading to the occurrence and development of cerebral vasospasm, aggravating the occurrence of brain injury, and affecting the prognosis of patients (25, 29).

Inflammatory signal transduction pathway plays an important role in early neuronal injury after SAH. Heme, oxygenated hemoglobin, methemoglobin, peroxidase-2, matricellular proteins, heat shock protein, fibrinogen and so on produced by erythrocyte degradation after aneurysm rupture can lead to the activation of early inflammatory signaling pathways (such as TLR4) in aSAH when large amounts of blood enter the subarachnoid space (28, 30). On the one hand, as innate immune cells (resident macrophages) of the central nervous system, microglia are one of the causes of brain damage in the nervous system after aSAH (31). When activated, microglia produce numerous proinflammatory cytokines, such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α), which trigger early neuroinflammatory responses and oxidative stress (32, 33). In addition, astrocytes play an important role in maintaining the integrity of blood-brain barrier and supporting neuronal activity (34) and can differentiate into both proinflammatory (TYPE A1) and anti-inflammatory (TYPE A2) types in response to different stimuli (35). The breakdown products of red blood cells contribute to the transformation of astrocytes into type A1, resulting in increased vascular permeability and impaired the integrity of blood-brain barrier. Under the dual factors of proinflammatory cytokines and increased of blood-brain barrier permeability, the inflammatory response is accelerated, leading to neuronal apoptosis (28).

As an inflammation related protein in the acute phase, C-reactive protein (CRP) is widely used as a marker of inflammation and tissue damage. CRP is produced by the liver.

When the body is injured or under the action of inflammatory factors, the liver will rapidly produce CRP and release it into the peripheral blood. The CRP in peripheral blood increased rapidly in a short time (36–38). In patients with aSAH complicated with acute hydrocephalus, a large number of pro-inflammatory cytokines are produced under the inflammatory signal transduction pathway, and the liver rapidly produces a large amount of CRP under the action of IL-1, IL-6 and other factors (39). Similarly, proinflammatory factors promote neutrophil increased recruitment and decreased apoptosis. Neutrophil can release a large number of inflammatory mediators to participate in inflammatory response and pathological nerve injury, resulting in brain edema, blood-brain barrier destruction and secondary brain injury, affecting the prognosis of patients (16, 40, 41).

In this study, it was found that the levels of serum CRP and neutrophil were higher in poor prognosis group 6 months after operation than in good prognosis group, and the increased levels of serum CRP and neutrophil were independent risk factors for poor prognosis 6 months after operation in patients with aSAH complicated with hydrocephalus. However, CRP and neutrophil are non-specific markers of inflammation that can be elevated in any tissue injury. Therefore, combined Hunt-Hess grade can improve its clinical value.

Hunt-Hess grade

Hunt-Hess grade is an important grade to evaluate the neurological injury and consciousness level of aSAH patients, which can be divided into I-V grade, which directly reflects the severity of the disease to a certain extent. In Hunt-Hess grade I to III patients, early surgery is generally considered necessary because of less bleeding and mild disease. Most patients have a good prognosis after aggressive emergency surgery. The clinical prognosis of Hunt-Hess grade IV–V intracranial aneurysms is poor regardless of surgery or conservative treatment. Most of these patients are treated conservatively, and further surgical treatment is needed after the condition is stable. Many studies have shown that the higher the Hunt-Hess grade in aSAH patients, the higher the risk of poor prognosis (42–44). This study found that the Hunt-Hess grade of patients with aSAH complicated with hydrocephalus at 6 months after surgery in the poor prognosis group was higher than that in the good prognosis group, and higher Hunt-Hess grade at admission was an independent risk factor for poor prognosis in patients with aSAH complicated with hydrocephalus at 6 months after surgery. However, the Hunt-Hess grading evaluation is greatly affected by the patient's own consciousness state and subjective factors of the surgeon, and the combination of biomarkers (such as CRP and neutrophils) can improve the accuracy of prognosis prediction.

Age

The prognosis of elderly aSAH patients with hydrocephalus is poor. The reason may be that the older the patient is, the worse the basic condition is. In addition, elderly patients are often accompanied by brain parenchyma atrophy, enlargement of the subarachnoid space, and aneurysm rupture of the subarachnoid space to accommodate more blood (45). In addition, the degree of meningeal fibrosis increases with age, resulting in impaired CSF circulation and reduced CSF absorption (18). In the case of aSAH, older people are more likely to develop hydrocephalus, and patients' neurons are more likely to be damaged. Age is an independent risk factor for poor prognosis in aSAH patients with acute hydrocephalus.

In this study, Surgical clipping and higher Hunt-Hess grade were independent risk factors for postoperative DCI in patients with aSAH complicated with acute hydrocephalus. Postoperative DCI is one of the high risk factors for poor prognosis in patients 6 months after surgery. The nomogram was established to assess the probability of postoperative DCI according to the patient 's Hunt-Hess grade at admission and the type of surgery used, thereby proactively taking preventive measures against DCI early. Older age, increased CRP and neutrophil levels, and higher Hunt-Hess grade were independent risk factors for adverse outcome 6 months after operation in patients with aSAH complicated with acute hydrocephalus. The Nomogram was established by combining "age," "CRP," "neutrophil" and "Hunt-Hess grade." The possibility of poor prognosis of patients can be evaluated within 24 h after admission, so that early measures can be taken to improve the prognosis of patients. The advantage of Nomogram as a multi-factor prediction tool is that it can provide quantifiable probabilities and reflect the contribution of each included factor to the prediction. The predicted probability of postoperative DCI and poor prognosis is compared with the actual probability in the calibration curve. The calibration curve showed that the predicted probability of postoperative DCI and poor prognosis was basically consistent with the actual probability. This suggests that nomogram has good clinical application value in this study and can assist in clinical decision making. For patients with high risk of postoperative DCI and poor prognosis, a high risk warning mechanism should be established, disease monitoring should be strengthened, surgical plan should be carefully selected, and intervention measures should be taken as early as possible to reduce the risk of adverse prognosis.

Conclusion

In conclusion, Hunt-Hess grade at admission and surgical clipping were independent predictors of postoperative DCI. The detection of CRP and neutrophil levels in aSAH patients

with hydrocephalus on admission combined with Hunt-Hess grading scale can identify high-risk groups with poor prognosis and provide early intervention. At the same time, it also helps clinicians to make precise treatment, reduce the disability rate and improve the quality of life as much as possible.

Limitation

The detection of serum CRP and neutrophil levels at admission and the Hunt-Hess grading assessment are simple, rapid and practical, and have great prognostic value for patients with aSAH complicated with acute hydrocephalus 6 months after surgery. However, this study had the following limitations: it was a retrospective, single-center study with a small sample size; In addition, serum samples were collected from all patients within 24 h after admission, but there was no dynamic observation of the changes of serum samples in multiple periods before surgery. For patients with aSAH complicated with acute hydrocephalus before admission, the occurrence of postoperative DCI is associated with poor prognosis. Therefore, in future studies, when these patients developed DCI after surgery, immediately take blood several times in time periods to dynamically observe the changes of indicators. Patients who developed DCI after surgery are studied to investigate the risk factors for poor prognosis 6 months after surgery. In addition, subsequent multicenter prospective clinical trials are needed to further verify these risk factor effect, and subsequent basic experiments are needed to explore its pathophysiological mechanism and understand its role in disease progression, so as to guide clinicians in the treatment and judgment of disease.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

Conceptualization and methodology: JG. Software and formal analysis, data analysis and interpretation, and writing—original draft: LW and QZ. Funding acquisition: ZC, JH, and HA-B. Resources: JG, FH, ZZ, YG, ZC, JH, HA-B, GF, and TL. Data curation: LW, QZ, GZ, and WZ. Writing—review and editing: LW, QZ, and JG. Supervision: WC, YW, and XL. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by Natural Science Foundation of Henan Province, [Grant numbers: 222300420412]; by the Senior Specialist Foreign Expert Project, [Grant numbers: G20190126006]; and by Department of Science and Technology of Henan Province.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers | Frontiers in Neurology

TYPE Original Research
PUBLISHED 25 November 2022
DOI 10.3389/fneur.2022.1068499

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Endovascular and Interventional Neurology, a section of the journal Frontiers in Neurology

RECEIVED 13 October 2022
ACCEPTED 03 November 2022
PUBLISHED 25 November 2022

CITATION
Andersen CR, Presseau J, Saigle V, Fitzgerald E, Lamanna M, Talbot P, Delaney A and English SW (2022) Prioritizing outcome measures after aneurysmal subarachnoid hemorrhage: A q-sort survey of patients, health care providers and researchers.
Front. Neurol. 13:1068499.
doi: 10.3389/fneur.2022.1068499

Prioritizing outcome measures after aneurysmal subarachnoid hemorrhage: A q-sort survey of patients, health care providers and researchers

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Objective: To understand which outcome measures patients and their families, health care providers, and researchers prioritize after aneurysmal subarachnoid hemorrhage (aSAH).

Methods: We conducted a cross-sectional q-sort survey with participants from three key stakeholder groups. Potential outcomes were identified from interviews and focus groups. Participants were purposively sampled to achieve diversity based on stakeholder group, geography, and profession. Respondents sorted 27 outcomes in a quasi-normally distributed grid (Q-Sort) from most to least important. Principal components analysis was used to determine similarities in the way participants sorted the outcome measures resulting in distinct groupings. Overall rankings were also reported.

Results: 112 participants were invited. 70 responded and 64 participants from 25 different countries completed a Q-sort. Balanced stakeholder representation was achieved. Five distinct patterns were identified based on survival, pathophysiological, psychological, resource use, and functional outcome measures. Quality of life as reported by the patient was the highest ranked outcome measure followed by independence and functional measures. Survival and biomedical outcomes were ranked in the middle and cost measures last.

Conclusions: In this diverse sample of key stakeholders, we characterized several distinct perspectives with respect to outcome measure selection in aSAH. We did not identify a clear pattern of opinion based on stakeholder group

or other participant characteristics. Patient-reported measure of quality of life was ranked the most important overall with function and independence also highly rated. These results will assist study design and inform efforts to improve outcome selection in aSAH research.

KEYWORDS

subarachnoid hemorrhage, core outcome set (COS), patient reported outcome measure (PROM), Q-method analysis, outcome assessment (health care), stroke

Introduction

Clinical trials define an "outcome" as a measurement or observation used to assess the effect of an intervention or process of care with respect to side effects (risks) and effectiveness (benefits) (1). Outcome selection is a complex task that requires consideration of multiple factors including the research question, target population, intervention, and comparator being studied. Also important are the measurement properties of the available instruments, costs, ease of data collection and burden on participants (2). Selecting outcomes that are relevant to the end-users of research: patients, health care providers and policy makers is crucial. High quality research can assist these stakeholders in decision making and ensure the best care is delivered (3). There is clear evidence that the choice of outcome measures by researchers often does not align with the priorities of the end-users (4, 5). When this mismatch occurs researchers risk designing studies that overlook key factors and could interpret some interventions to be effective when they are not (and at worst cause harm) (6).

Aneurysmal subarachnoid hemorrhage (aSAH) is a devastating type of stroke triggered by the sudden rupture of an abnormal blood vessel in the brain. It affects younger patients when compared to other forms of stroke, has a distinct clinical course, and survivors are often left with long term impairment (7, 8). Our previous work has demonstrated that there is high degree of heterogeneity in the outcome measures used in aSAH research (9). We have also shown that the perspectives of patients and families members in the development of outcome measures are often overlooked (10). Additionally, there is evidence of a failure to meet the needs of aSAH survivors especially with respect to poorly-reported outcomes such as fatigue, mood and cognition (11).

Our objective is to characterize the perspectives of patients, researchers and health care providers and understand which outcomes measures in aSAH are considered the highest priority. We also aim to identify if there are clearly different viewpoints between our three stakeholder groups with respect to outcome prioritization. This work is designed to inform efforts to standardize outcome selection and ensure the selected outcomes in aSAH research align with priorities of research end users (12).

Methods

Standard protocol approvals, registrations, and patient consents

Ethical approval for the survey development work was provided by the Ottawa Health Science Network Research Ethics Board (Reference 20190312-01H) and by Northern Sydney Local Health District Reference: 2020/ETH03188 for the q-sort recruitment and administration. Reporting of this study has been conducted consistent with the Checklist for Reporting of Survey Studies (CROSS) (13).

Q methodology

Q-methodology is a valuable technique for exploring subjective opinion with respect to priorities in healthcare. It can be used to identify groups of participants who have shared viewpoints or make sense of a pool of comparable items in similar ways (14). Importantly, it requires participants to differentially value a collection of statements (in this case outcome measures) by ranking them between two extremes such as most important to least important. This ranking process is called q-sorting. The resultant rankings are then analyzed through factor analysis to identify similar viewpoints.

This process is described in detail in Figure 1. The first step is to create a concourse of statements through a variety of techniques and achieve as broad a range of statements as possible. The concourse is then reduced by the researchers into a manageable but representative list (q-set) that can be used for sorting. The participants are provided with the q-set and then rank the statements between two extremes. The pattern for the distribution is usually a quasi-normally distributed grid, although other patterns are also effective. A quantitative analysis is then performed on the q-sorts to identify shared perspectives or viewpoints called factors. There is a representative q-sort for each factor that enables qualitative interpretation of the results (15–17).

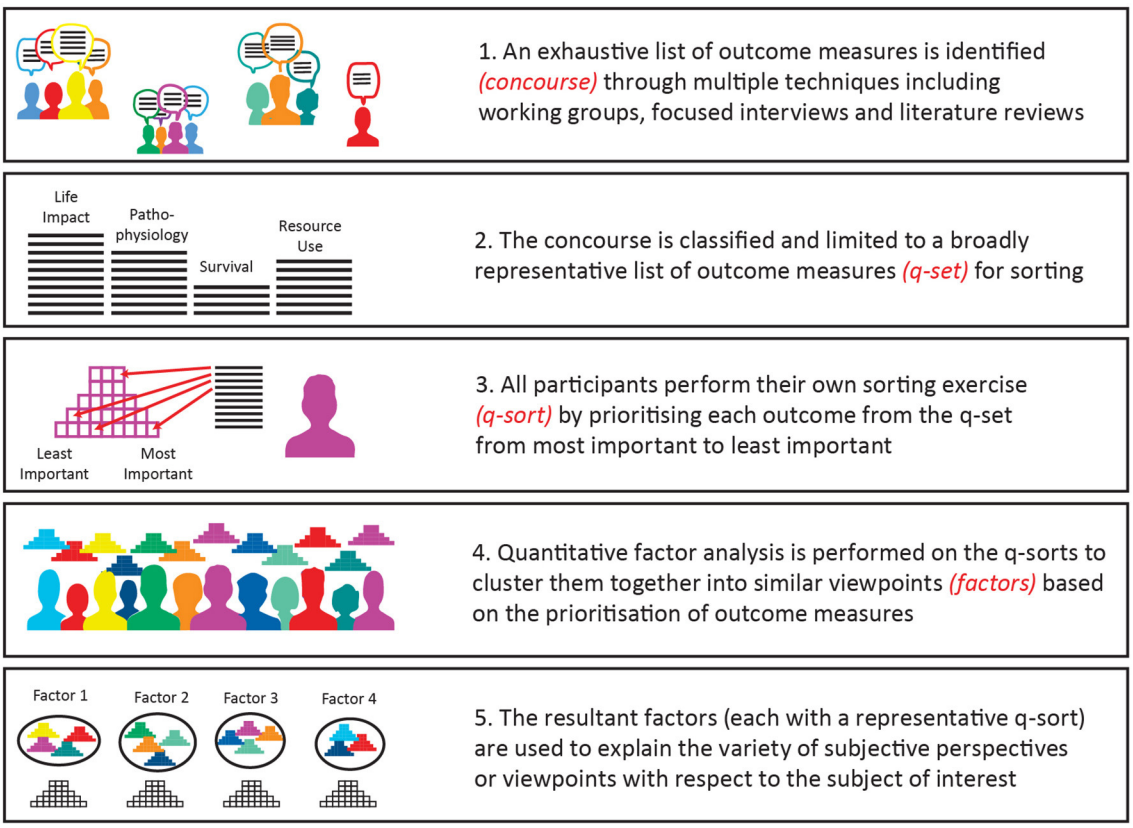

FIGURE 1
Overview of Q-methodology.

Survey development

The concourse was developed through several techniques including a working group with members of all three stakeholder groups at the International Subarachnoid Hemorrhage Conference in Amsterdam in June 2019 (18). Additionally, we ran a focus session with aSAH survivors and their families in North America, and interviews with health care providers and aSAH survivors in the UK and Australia. A final concourse of 106 outcome measures was identified (Appendix 1).

The concourse classified into 4 core areas (pathophysiological, life impact, death and resource use) consistent with the OMERACT Filter for outcome classification in clinical research (19). It has been recommended that an outcome measure from each of these core areas is included in core outcome sets (COS) used to improve the consistency of outcome measure selection (20). The research team, including patient research partners, then reduced the overall concourse to 27 items by consensus for a final q-set (Appendix 1). We used a quasi-normal grid for our q-sort with a −4 to +4 distribution (21).

We piloted the survey with members of each stakeholder group who were also part of our larger research group for clarity and ease of completion. Based on feedback, we refined the participant instructions and provided additional links for assistance.

Recruitment

In accordance with recommendations of the q-method literature, a sample size of 60 was chosen (14). Participants were recruited *via* email (Appendix 2) who had previously registered interest in improving outcome selection after being approached *via* patient, research and healthcare provider organizations. A purposive sampling technique was employed to ensure broad representation based on personal or professional involvement with aSAH, self-identified gender, and geographical location (14). All communication between the researchers and the participants was *via* email.

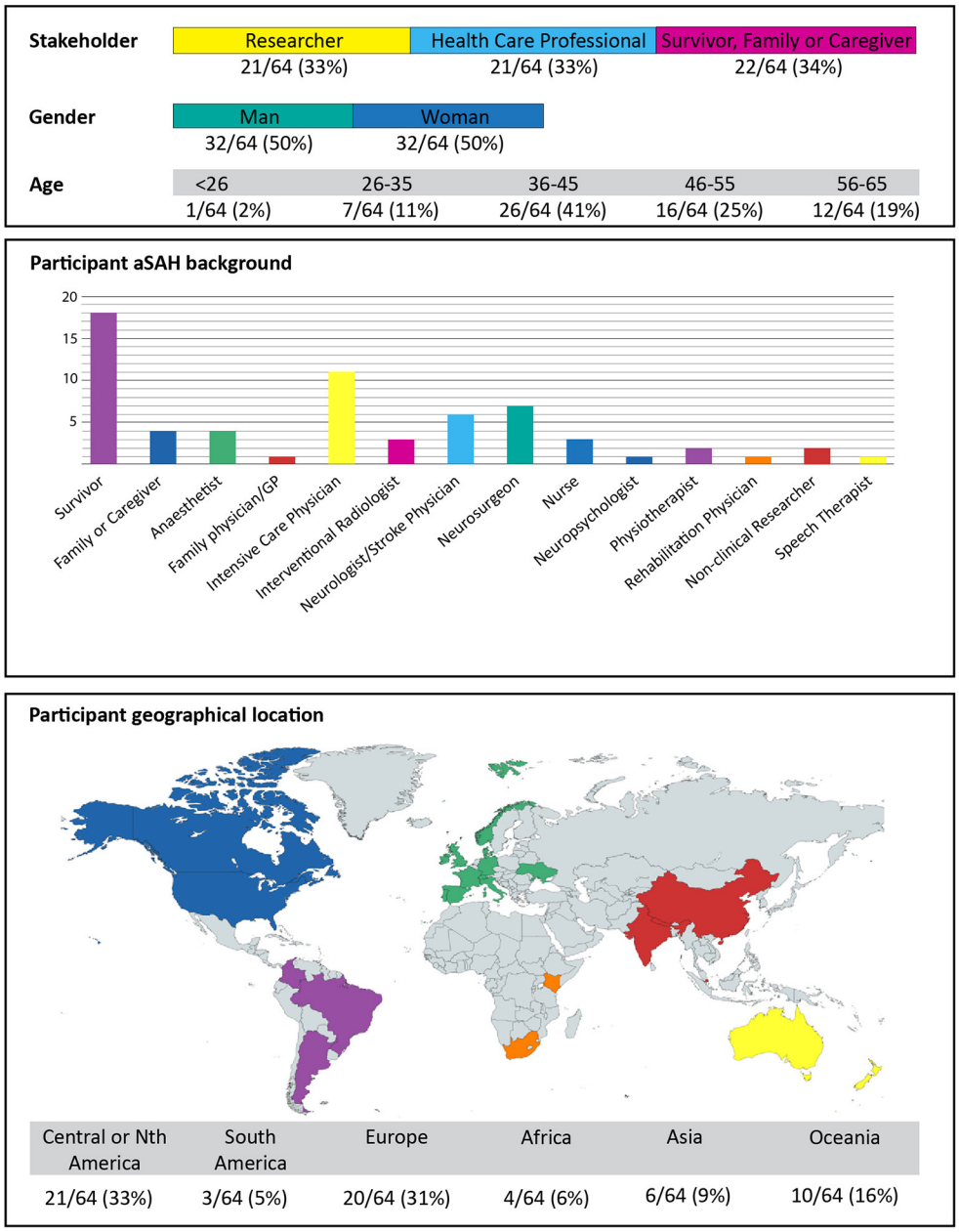

FIGURE 2
Participant demographics.

Survey administration

Invited participants were provided a randomly generated alphanumeric code and link to complete the survey to prevent multiple participations. Participants conducted the q-sort using Q-method software online platform (22). After providing informed consent and completing the demographic questions, participants were given a text explanation (Appendix 2) and video explanation (23) on how to complete a q-sort. The outcome measures in the q-set were presented randomly to participants. They were asked to prioritize the outcomes with the prompt "When we are testing a new treatment(s) for subarachnoid hemorrhage, in your personal opinion do you think measuring this domain, outcome or indicator of health is more important, neutral or less important when compared to the others in this list". After sorting the outcomes into 3

TABLE 1 Overall outcome measure rankings from all participants.

Rank	Outcome measure	Overall rating
1	The overall quality of life as reported by the SAH survivor	99
2	The ability to independently manage basic needs such as toileting, feeding, bathing and getting dressed	97
3	A measure of function or a return to baseline function	62
=4	Delayed cerebral ischemia or cerebral infarction (a common complication in the days after SAH that is associated with worse outcomes)	57
=4^	The ability to independently manage instrumental activities of daily living such as managing finances, shopping, preparing food, and doing laundry	57
6	An assessment of memory and cognitive function	49
7	The ability to walk independently	47
8	Being alive (survival) three months after the subarachnoid hemorrhage	44
=9	A subsequent bleed related to the aneurysm (rebleeding)	38
=9^	Being able to return to work	38
11	The ability to speak fluently	32
12	The ability to maintain concentration and focus	20
13	Feelings of anxiety and/or symptoms of post-traumatic stress disorder	11
14	A measure of the overall impact on family and caregivers	7
15	Being discharged from hospital alive	6
16	Symptoms of depression and/or a more general assessment of mood	3
17	The frequency and severity of pain related to the SAH including headaches	−2
18	Vasospasm (the narrowing of arteries) in the first days and weeks after SAH	−17
19	Overall energy levels and how easy it is to fatigue	−29
20	The destination after discharge from hospital (for example home, a rehabilitation facility or a residential care facility)	−52
21	The overall speed of recovery	−65
22	The ability to attend social functions such as dinners, birthdays and other gatherings	−66
23	A return to normal sexual activity and function	−68
24	The ability to return to driving	−69
25	The length of stay in intensive care or hospital	−75
=26	The overall cost of the initial hospital admission	−112
=26^	The overall cost of rehabilitation and treatment after hospital discharge	−112

categories the participant progressed to placing them on the final q-sort according to their priorities. At the completion of the q-sort, 4 optional questions were provided for participants to explain their rationale for their preferences, whether there were any missing outcomes in the q-set and their experience completing the survey. Data were stored on password protected University of Sydney servers and responses were associated with the unique code rather than identifiable information to ensure confidentiality.

Survey analysis

A quantitative analysis of the overall configurations decided by participants was conducted using Q Method Software (22). Only completed q-sorts were included in the analysis. The extraction method was performed *via* principal components analysis and eigenvalues >1 was used to determine factors to rotate. Significance loadings were set at $p < 0.01$. The rotation method was varimax. The method of factor flagging was automatic. These methods are the most commonly used in health care settings (21, 24, 25). The variance explained by each factor was calculated by the formula (eigenvalue times number of participants/100) (26). Extracted factors that explained at least 5% of the overall variance were reported (27). The reliability and standard error of the z-scores were also reported (28). There was no weighting or propensity matching performed. Additionally, an exploratory analysis of the overall outcome measure rankings across all participants was performed. The ideal q-sorts that represent each of the factors are described qualitatively following the methods described by Watts and Stenner (27).

Results

From 112 emailed invitations to take part there were 70 responses (63%) with 64 q-sorts completed (91%) over a two-month period from 3rd September 2021. Baseline demographic details are provided in Figure 2.

In the exploratory analysis the highest ranked outcome measure across all respondents was the overall quality of life (QoL) as reported by the aSAH survivor (Table 1). Independence in basic needs and instrumental activities, as well as a measure of function or return to baseline function all ranked in the top 5. The highest ranked pathophysiological outcome was delayed cerebral ischemia (a common complication after aSAH that is associated with worse outcomes) which ranked 4th out of 27. Measures of death included being alive 3 months after the aSAH and being discharged from hospital alive ranked 8th and 15th, respectively. Outcome measures of the cost of the initial hospital admission and the cost of rehabilitation and

treatment after hospital discharge were rated 26th and 27th out of 27.

Factor descriptions

Five distinct viewpoints (factors) were identified by the factor analysis, with almost half of all the participants (31/64) loading to either Factor 1 or Factor 2. The individual factors are described below with a summary of each factor provided in Figure 3. Ten participants loaded to multiple factors and eight participants loaded to factors that explained <5% of the total variance. The full 27-item prioritization for each factor is provided in Appendix 3.

Factor 1: Patient reported outcomes are best

This was the most common viewpoint overall and explained over a quarter of the total sample variance (see Figure 3). This viewpoint was shared by participants from each stakeholder group however researchers and healthcare providers predominate. The most characteristic outcome measures for this group were quality of life and independence. Almost all positively scored outcome measures in this viewpoint were related to how a patient feels, functions, or survives. Pathophysiological outcome measures including rebleeding, vasospasm and delayed cerebral were all negatively rated with cost viewed as least important. A reoccurring theme in the post q-sort statements was the primacy of patient reported outcome measures "Patient reported outcomes are best as they reflect what is important to the person that has had the aSAH" and quality of life "The most important outcomes center around the patient being able to maintain quality of life".

Factor 2: Mortality matters most

People from this viewpoint placed measures of survival in the two highest positions on the representative q-sort. Additionally, they also prioritized pathophysiological outcomes when compared to functional, psychological or measures of independence. When compared to the other perspectives this difference was marked. The other notable characteristic was cost rating in the mid-range when compared to most other perspectives that considered these outcomes least important. The post p-sort statements included the rationale for focusing on survival such as "As a neurosurgeon I am biased to protect the patient's life first".

Factor 3: Function and social engagement over survival

People from this viewpoint prioritized instrumental activities, and placed outcomes related to social interaction such as the ability to speak fluently, attend social functions and return to work notably higher than other viewpoints. This contrasted with survival which this factor placed notably lower than all other viewpoints. There were no stakeholders from the survivor, family and caregiver group that loaded to this factor. Statements included comments on 'Returning to one's prior function, activity and to be as symptom free as possible to be the most important".

Factor 4: Psychological outcomes, fatigue, and quality of life

This was the only factor where most participants were from the patient, family, and caregiver stakeholder group. Like factor 1, patient reported QoL was rated highest. This factor was notable however in the priority placed on psychological outcomes that included "feelings of anxiety and/or symptoms of post-traumatic stress disorder" and "symptoms of depression and/or a general assessment of mood". Participants also placed a much higher priority on fatigue when compared to the other factors. This was further reflected in the post q-sort statements that suggested there should be a focus on "neurofatigue, depression, anxiety and how there is an adjustment to one's previous way of functioning…" and another participant commented that "For me, the severe PTSD, depression, pain, insomnia, not knowing what was normal…" was important. A third participant made the statement "cognitive and emotional problems with clinical significance, with fatigue one of the most prominent symptoms".

Factor 5: Function, discharge destination, and length of stay

This viewpoint prioritized functional outcomes but unlike factor 3 the social engagement outcomes were not seen as important with the ability to attend social functions considered least important, as well as patient reported QoL, language fluency and overall energy levels and how easy it is to fatigue all negatively rated. Respondents in factor 5 also prioritized more outcome measures related to patient disposition (such discharge destination and length of stay in hospital/ICU) much higher when compared to other viewpoints. Respondents commented

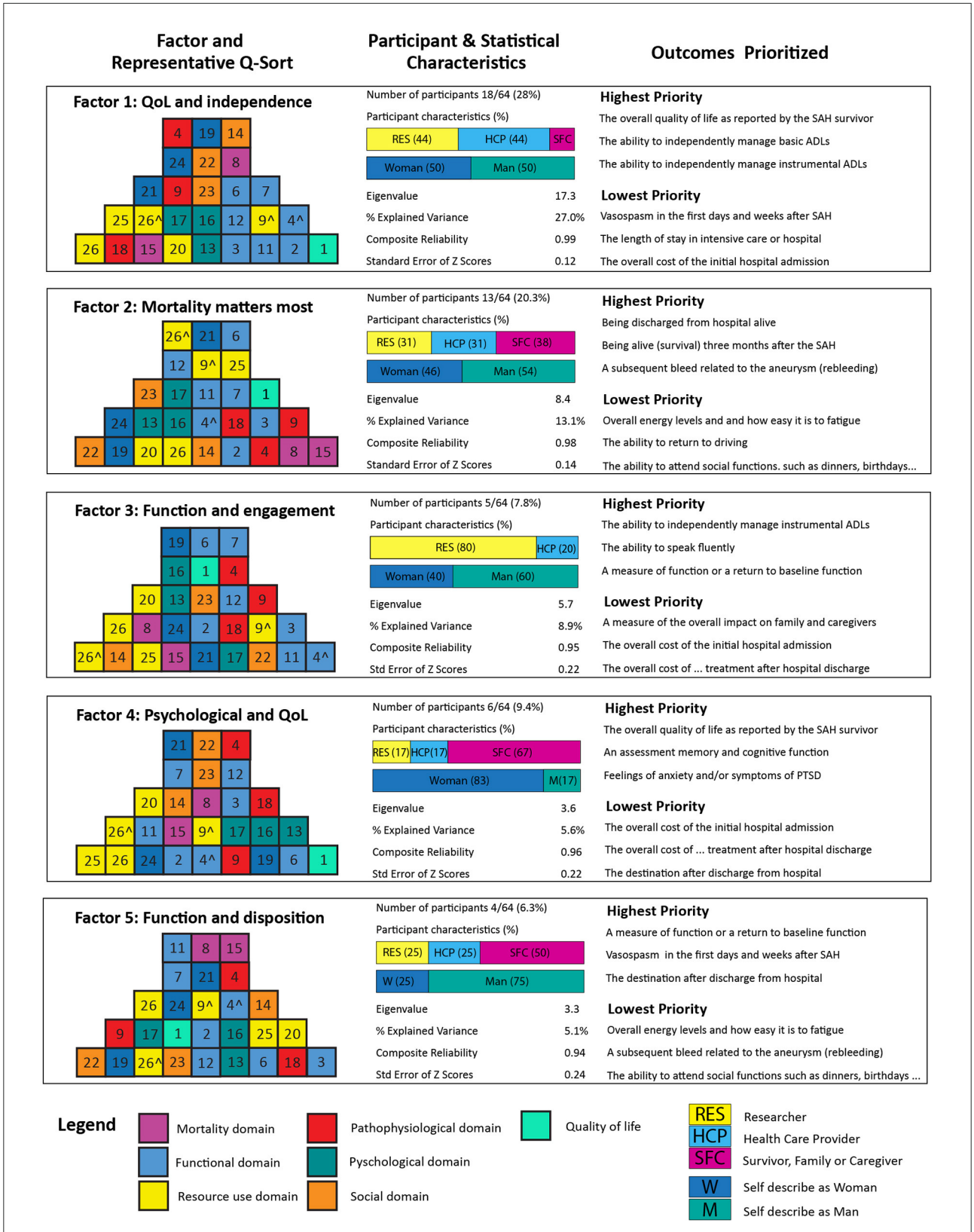

FIGURE 3
The representative q-sorts (colored pyramids) for each of the 5 identified factors are shown. The highest ranked outcome measure is in the right corner, descending in importance as you move to the left of the q-sort. In each pyramid column the higher ranked outcome measure is at the

(Continued)

FIGURE 3 (Continued)
base. The numbers for each outcome measure correspond to the overall rankings in Table 1. The number of participants loading to each factor, the demographic characteristics of these participants and the statistical characteristics are shown. In descending order, the three highest and lowest ranked outcome measures is also presented (full outcome measure rankings for each of the 5 factors is presented in the Supplemental material).

on "are you able to live in your own home? What kind of support is available post-acute hospitalization"?

Discussion

Our novel study has demonstrated that there are several distinct perspectives on the ideal outcome measures after aSAH. Overall, the respondents from this study identified patient-reported quality of life as the most important outcome measure. Measures of independence and functional outcome measures were also highly rated. Measures of survival and psychological outcomes are very important to some even if this is not reflected in the overall rankings. Indicators of resource use were generally not prioritized relative to the other outcome measures in this study.

These results support concerns that researchers in the field are not currently measuring what matters most to relevant stakeholders. Although seen as the most important outcome to respondents in this survey, patient-reported outcome measures (either as a primary or secondary outcome) have been reported in only 8.5% of randomized controlled trials in aSAH over the past 20 years (9). Psychological outcomes are also very important to some respondents but are rarely reported, which should be considered when selecting outcome measures for future studies. This research does however support measuring functional and independence outcomes that are commonly reported in aSAH research. We anticipate the results of this study will aid researchers to make more informed decisions when selecting outcome measures to test the effectiveness of future interventions.

One of the strengths of this study is the broad sample that has been achieved through purposive sampling. Participants were recruited from 25 different countries across all geographical regions representing many different health care and socio-economic settings. The recruited participants also included patients, family members as well as health care providers who are involved across all aspects of the patient experience from the acute admission through rehabilitation and care in the community. This increases the chances that we have captured a very wide range of perspectives. Our research team involved patient research partners (PT), non-clinical researchers (JP, ML and VS) and clinician researchers (CA, EF, SE, and AD) ensuring key stakeholder involvement throughout entire study process from design to write up. The use of a rigorous technique such as q-methodology also allowed us to use quantitative techniques to identify similarities of perspective in a robust way without the influence of prior assumptions.

The weakness of this study is that although we have a range of participants the purposive sampling means that we cannot assume that this is a representative sample. Efforts were made to ensure participation from not just high-income countries, but we may not have achieved equal representation of these groups. These concerns may not influence the factor analysis but there should be caution with the exploratory analysis on the overall rankings. Further investigation using more traditional quantitative analyses are required to confirm the generalizability of the overall rankings and increased representation for the survivors, family and caregiver group for this type of analysis would be prudent.

There is marked heterogeneity in outcome measures used to evaluate treatments of aSAH (9). The lack of consistent outcome measures in this area hinders comparison of trials and reduces the utility of research. The results of this study will be used to inform efforts to improve outcome measure selection in aSAH. An international consortium including patients, health care providers, journal editors, foundation representatives and leading researchers recently proposed the development of a core outcome set (COS) in SAH to address the limitations of current aSAH outcome measure selection (18). A COS is a limited set of agreed outcome measures which all studies of a particular area of medicine will report (19). Central to developing a COS is engaging the key stakeholders and ensuring consideration of a range of different viewpoints as explored in this study. Other work including an international modified Delphi study and consensus meeting will help to finalize a COS in aSAH is currently in progress.

Conclusions

We have demonstrated that there are several distinct perspectives or viewpoints with respect to outcome measure selection after aSAH. Most perspectives rated patient-reported quality of life highly or of the highest priority despite this being rarely reported in the literature. There is general support for measuring function and independence. Survival and psychological outcomes appear very important to specific groups, but this nuance may be lost when looking at overall rankings. Understanding and incorporating these perspectives when selecting outcome measures is crucial for ensuring we drive improvements in aSAH management that matter to all stakeholders.

Data availability statement

The datasets generated or analyzed during the current study are available from the corresponding author on reasonable request and may require interinstitutional data-sharing agreements to be put in place.

Ethics statement

Ethical approval for the survey development work was provided by the Ottawa Health Science Network Research Ethics Board (Reference 20190312-01H) and by Northern Sydney Local Health District Reference: 2020/ETH03188 for the q-sort recruitment and administration. The patients/participants provided their written informed consent to participate in this study.

Author contributions

CA designed and conceptualized the study, conducted recruitment, analyzed the data, and drafted and revised the manuscript for intellectual content. SE, JP, PT, and AD designed and conceptualized the study and revised the manuscript for intellectual content. VS, ML, and EF assisted with survey development and revised the manuscript for intellectual content. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by The Ottawa Hospital Academic Medical Organization Innovation Fund Grant provided to improve outcome measurement in subarachnoid hemorrhage.

Acknowledgments

The authors would like to acknowledge the contribution of Frances Bass with the ethics submissions and governance.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.1068499/full#supplementary-material

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frontiers | Frontiers in Neurology

TYPE Original Research
PUBLISHED 05 December 2022
DOI 10.3389/fneur.2022.1015304

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Endovascular and Interventional Neurology, a section of the journal Frontiers in Neurology

RECEIVED 09 August 2022
ACCEPTED 14 November 2022
PUBLISHED 05 December 2022

CITATION
Zhao X, Zhang Z, Liu J, Qin F, Hu L and Li Z (2022) Safety and effectiveness of double microcatheter technique in the treatment of ruptured aneurysms of anterior cerebral circulation. *Front. Neurol.* 13:1015304. doi: 10.3389/fneur.2022.1015304

Safety and effectiveness of double microcatheter technique in the treatment of ruptured aneurysms of anterior cerebral circulation

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Objective: To evaluate the safety and effectiveness of the double microcatheter technique in the treatment of ruptured aneurysms of the anterior cerebral circulation.

Methods: Between 2012 and 2019, 113 patients with ruptured aneurysms of the anterior cerebral circulation were treated using the double microcatheter technique. Clinical records, angiographic results, and procedure-related complications were reviewed. Clinical and angiographic follow-up was performed.

Results: Complete occlusion, neck remnant, and partial occlusion were, respectively, recorded in 56.6, 38.9, and 4.4% of the total cases. For all patients, the incidence of intraoperative complications was 5.3% (6/113), and the overall rate of morbidity was 10.6% (12/113). Before discharge, three patients (2.7%) died. There was no procedure-related mortality. At discharge, favorable outcomes were observed in 79.6% (90/113) of the patients. High Hunt-Hess grades and receiving a craniotomy or external ventricular drainage were risk factors for clinical outcomes at discharge. Clinical follow-up was performed in 91 patients at a mean interval of 14.07 ± 11.68 months. At follow-up, favorable outcomes were observed in 92.3% (84/91) of the patients. Angiographic follow-up was performed in 66 patients at an average of 11.53 ± 11.13 months. The recurrence rate was 37.9%. Of these patients, 13 (19.7%) received retreatment.

Conclusion: The double microcatheter technique can be performed in ruptured aneurysms with high technical success and low morbidity/mortality. However, recurrence remains a problem, and patients should be followed up regularly.

KEYWORDS

double microcatheter technique, stent-assisted coiling, balloon-assisted coiling, ruptured aneurysm, anterior cerebral circulation

Introduction

Since the publication of the International Subarachnoid Aneurysm Trial (ISAT) in 2002 (1), endovascular approaches have become the first choice for the treatment of intracranial aneurysms. Along with the advances in operative devices and techniques, the prognosis of ruptured aneurysms has been improved significantly. However, wide-necked and irregular aneurysms still represent a significant challenge. Stent- or balloon-assisted coiling and flow diversion can be used in these cases (2–4). However, the deployment of a stent in ruptured aneurysms may increase procedure-related complications, such as rebleeding and thrombosis (5–7). Balloon-assisted coiling requires a temporary blockage of blood flow and may also incur an increased risk of related complications (8, 9). In addition, navigating the stent- or balloon-delivery system becomes difficult in small or tortuous vessels.

Baxter et al. (10) reported the double microcatheter technique in 1998. The advantages of this approach are that there is no blockage of blood flow and that it does not recommend antiplatelet medications. Thus, the double microcatheter technique represents an alternative method to treat wide-necked and irregular aneurysms. Although some recent studies reported on the use of the double microcatheter technique (11–13), reporting on its use for the treatment of ruptured aneurysms of the anterior cerebral circulation is rarer. Here, we report the safety and effectiveness of the double microcatheter technique in anterior circulation ruptured aneurysms.

Materials and methods

Patient selection

From September 2012 to November 2019, a total of 113 patients with ruptured aneurysms of the anterior cerebral circulation were admitted to our hospital and treated with the double microcatheter technique. All patients had given their informed consent to participate. Cases of dissecting and fusiform aneurysms were excluded. Subarachnoid hemorrhage was confirmed by CT scanning. The clinical condition at admission was classified by the Hunt-Hess grade. Most patients received CT angiography (CTA), which was confirmed by digital subtraction angiography (DSA). Wide-necked aneurysms were defined as neck diameter $\geq$4 mm or dome-to-neck ratio $<$2. All procedures were performed within 48 h of being admitted to the hospital.

Endovascular procedure

All procedures were performed under general anesthesia and systemic heparinization. A 6-F guiding catheter was placed into the internal carotid artery through the right femoral artery. Frontal, lateral, and 3D angiography were performed in all patients to analyze the size and configuration of the aneurysms. The treatment strategy was determined by the operators according to the diameter of the parent artery and the characteristics of the aneurysm. Before the procedure, we verified that the guiding catheter and the parent artery could accommodate two microcatheters. Echelon-10 or Headway-17 microcatheters were mostly used during the procedures. The double microcatheter technique is usually used in wide-necked, irregular, or branch-incorporated aneurysms. Two different strategies (i.e., coil "interleaving" and "locking" techniques) were described by Durst et al. (12).

During the procedure, two microcatheters were navigated into the aneurysm under roadmap guidance after the selection of working projections. The two microcatheters should be preshaped with different tip curves to optimally reach different portions of the aneurysm. After the first microcatheter was in place, the first coil was fully or partially filled into the aneurysm. As the advancement of the second microcatheter may cause the first one to migrate, the tension of the first microcatheter should be adjusted as appropriate. Still, the possibility of rebleeding was low due to the buffering effect of the first coil, even if the tension of the first microcatheter changed.

For aneurysms with a large daughter sac (Figure 1), usually one microcatheter is navigated into the daughter sac if there was no difficulty. After the first coil was fully or partially deployed, the second coil was advanced into the aneurysm through the second microcatheter, and the two coils intertwined with each other to form a stable frame. One of the coils was then detached, while the other coil remained attached to the pusher wire. Coils were then introduced through the second catheter until the aneurysm was packed as densely as possible. If blood flow was affected during this procedure, one microcatheter was removed once a stable frame was formed. For wide-necked aneurysms with lateral growth, the double-parallel framing coil technique was first attempted. To this end, two microcatheters with different shapes were consecutively or parallelly advanced into the aneurysm so that the two framing coils form a stable structure. Then, the procedure continued as described earlier. An illustrative case is presented in Figure 2. For branch-incorporated aneurysms (Figure 3), one microcatheter was placed at the orifice of the branch to prevent its occlusion, and a second microcatheter was then used to coil the aneurysm.

In two cases with wide-necked aneurysms planned for stent-assisted coiling, the first coil formed a good frame, but this was not stable enough. Since the coil may herniate into the parent artery if it became detached, the stent-delivery catheter was removed. The other microcatheter was then navigated into the aneurysm, and a second coil was deployed to stabilize the frame.

In severe cases with a Hunt-Hess score of IV–V, ventricular drainage is usually performed first, followed by endovascular coiling, because relieving intracranial pressure is even more

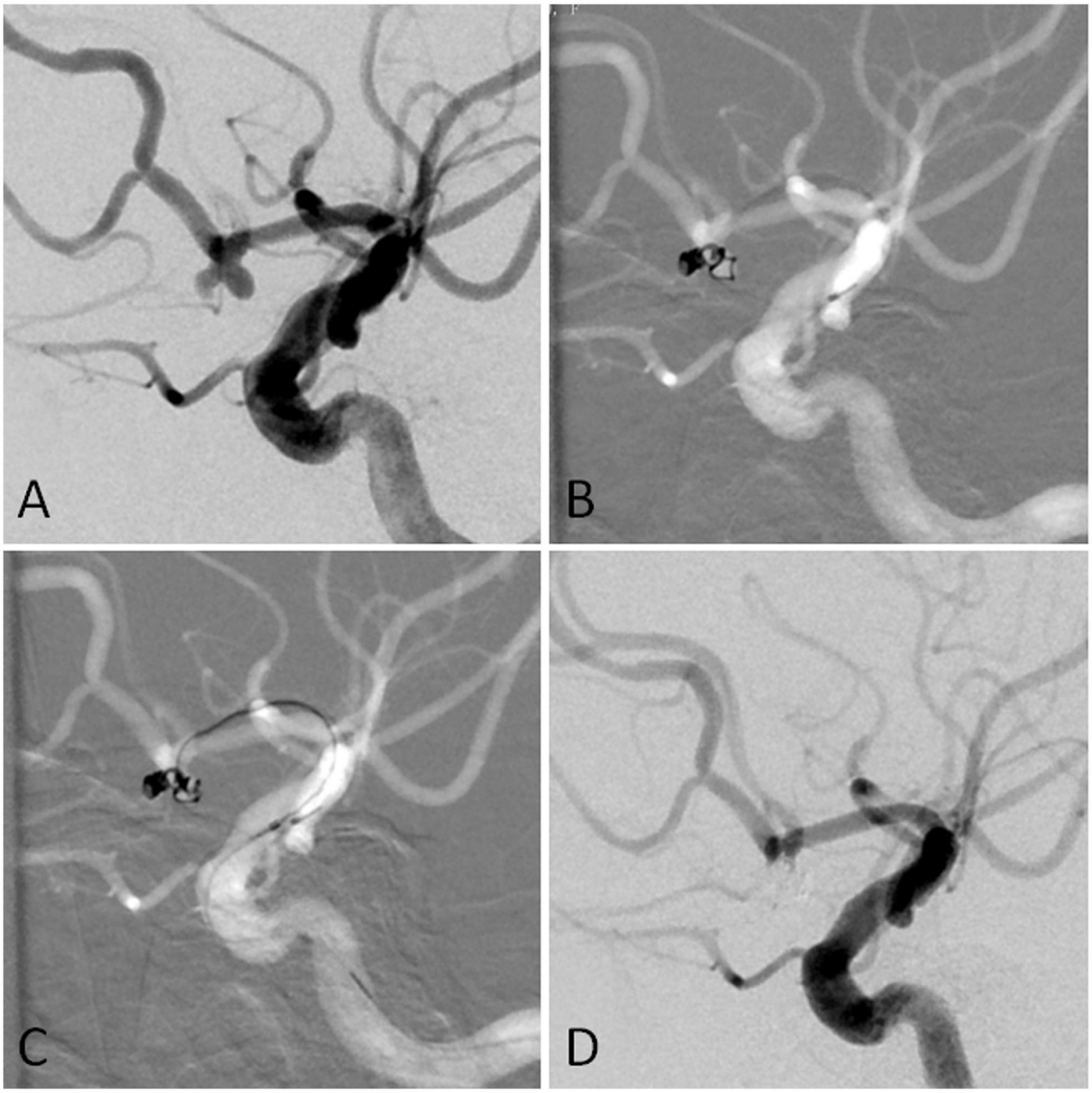

FIGURE 1
(A) The angiographic imaging showed AcomA aneurysm with the daughter sac. **(B)** The first was navigated into the left sac of the aneurysm. The first coil was fully advanced into the aneurysm. Part of the first coil and the microcatheter entered into the right sac in the end. **(C)** Another microcatheter was navigated into the aneurysm. **(D)** The aneurysm was completely occluded.

critical. For cases with a Hunt-Hess of III or below and with hydrocephalus after coiling, endovascular coiling is usually performed first, followed by EVD.

Clinical and angiographic assessment

The clinical outcomes at discharge and at the last follow-up were scored using the Glasgow Outcome Scale (GOS). Patients who attained a GOS score of 4–5 were defined as having a favorable outcome. Patients with a GOS score of 1–3 were defined as having a poor outcome. At discharge, all patients were recommended to undergo DSA at 3, 9, and 21 months after the procedure. If the patient has no recurrence after 21 months, the follow-up interval would be extended. The immediate angiographic outcomes at the end of the procedure were classified as complete obliteration, neck remnant, and partial occlusion (contrast filling in the aneurysm sac). Angiographic outcomes at follow-up were classified as stable (no change in coil configuration, obliteration grade, or contrast filling), improved (progressive occlusion or involution of the neck remnant or contrast filling in an aneurysm), and recanalized (aneurysm recurrence evident due to neck growth, coil compaction, coil extrusion by aneurysm degradation, or new sac formation) (14).

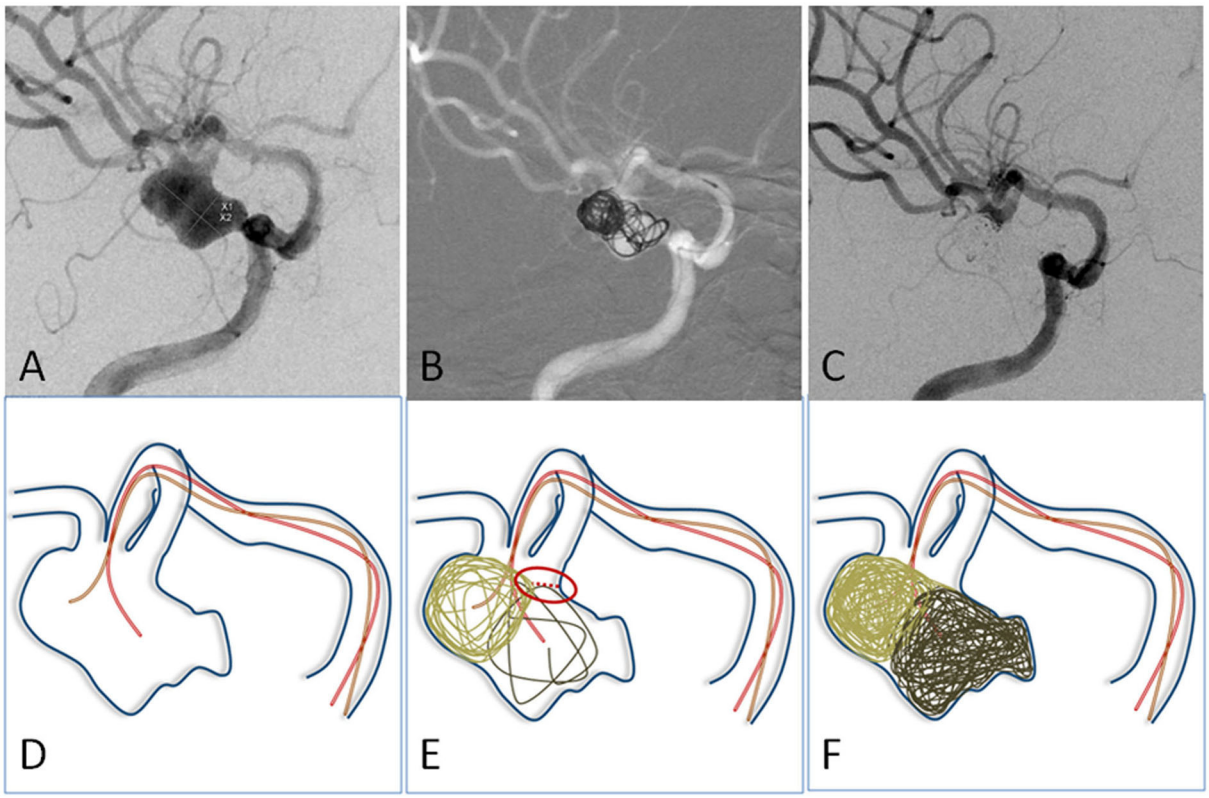

FIGURE 2
(A) The angiographic imaging showed an MCA aneurysm with lateral growth. **(D)** Illustration: Two microcatheters with different curves were navigated into different portions of the aneurysm. **(B,E)** The first two coils were advanced into aneurysms through two microcatheters to form a stable frame. They supported and embraced each other. **(C,F)** The aneurysm was embolized with neck remodeling.

Statistical analysis

Statistical analysis was performed using SPSS software, version 19.0 (IBM Inc., Chicago, IL, USA). Univariable and multivariable logistic regression were used to analyze the risk factors for procedure-related morbidities and clinical outcomes at discharge. A multivariable proportional hazards regression (Cox) model was used to analyze the risk factors for clinical and angiographic outcomes at follow-up. A $P < 0.05$ was considered to be statistically significant.

Results

Patient and aneurysm characteristics

Out of the 113 patients, 26 were men and 87 were women. The mean age was 60.12 ± 10.51 years (range, 31–82 years). The Hunt-Hess grade at admission was I in 18 patients, II in 42 patients, III in 36 patients, IV in 12 patients, and V in 5 patients. There were 40 cases of hypertension and 4 of diabetes. Seven patients had both hypertension and diabetes. Pre-procedure CT scanning showed that 14 cases had an intracranial hematoma (without brain herniation), 9 had hydrocephalus, and 4 had both.

The double microcatheter technique was used to treat one patient with bilateral posterior communicating artery aneurysms and 112 single aneurysms in the remaining 112 patients. There were 36 anterior communicating artery aneurysms, 59 posterior communicating artery aneurysms, 12 middle cerebral artery aneurysms, 3 aneurysms of an ophthalmic segment of the internal carotid artery, 3 anterior choroidal artery aneurysms, and one aneurysm at the A1 segment of the anterior cerebral artery. Of all aneurysms, 89 (78.1%) were wide-necked and 61 (53.5%) presented with a daughter sac or irregular configuration. The neck diameter ranged from 1.6 to 9 mm, with an average of 3.60 ± 1.12 mm. Maximum diameter was on average 6.30 ± 2.50 mm (range, 2.9–13 mm). The dome/neck ratio ranged from 0.7 to 3.92 with an average of 1.80 ± 0.59.

Perioperative complications

Throughout all the procedures, intraoperative bleeding occurred in 2 out of 113 patients (including a patient with rebleeding during anesthesia). In addition, thrombosis or slow

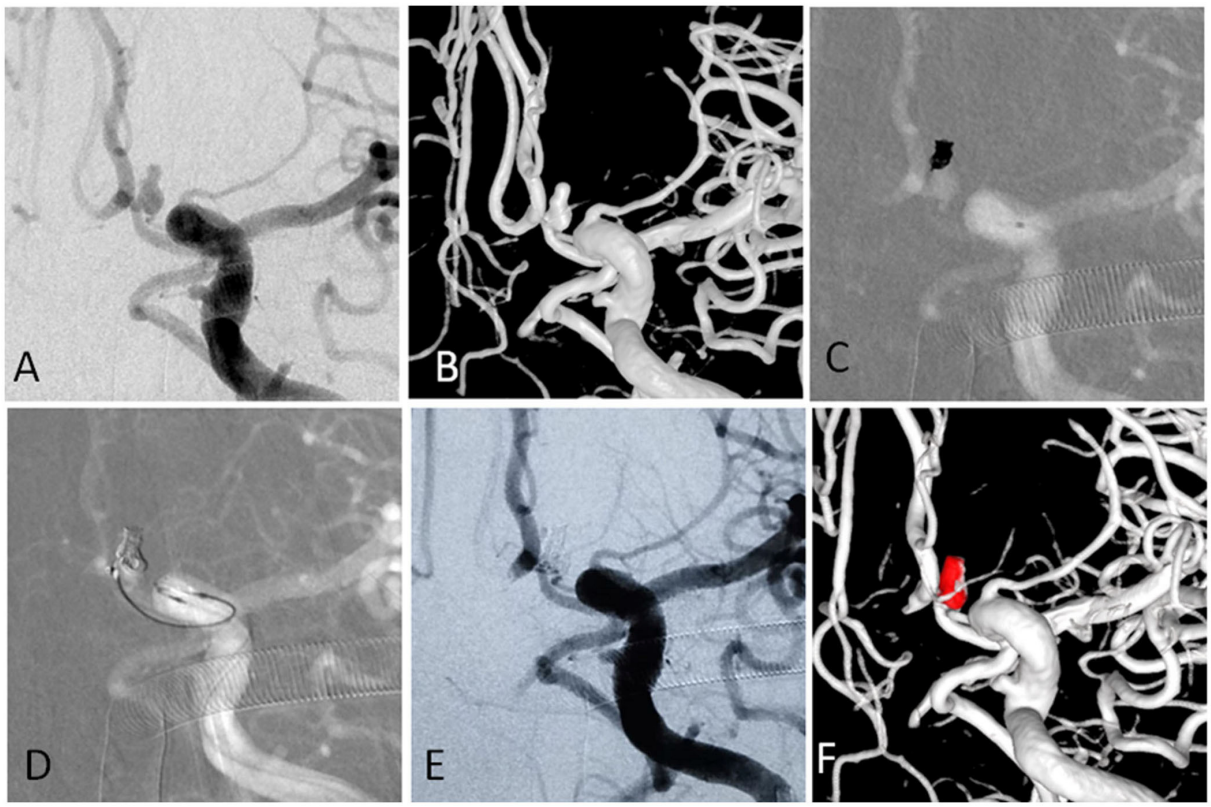

FIGURE 3
(A,B) The angiographic and 3-D imaging showed an anterior communicating artery complex aneurysm. Heubner artery originated from the neck. **(C)** The first microcatheter was navigated into the aneurysm, and the first coil was fully advanced into the aneurysm. **(D)** The second microcatheter was navigated into the aneurysm to protect the Heubner artery from being occluded. **(E,F)** The aneurysm was completely occluded, and the Heubner artery was patent.

blood flow through the parent artery was recorded in 4 cases. Once the aneurysm was packed densely, tirofiban was infused through the microcatheter until the thrombus disappeared and blood flow returned to normal. No postoperative neurological deficits were observed in any patient. The incidence of intraoperative complications was 5.3% (6/113). One patient suffered from increased bleeding and ischemic events simultaneously after the procedure, and he received a decompressive craniotomy. After the procedure, five patients suffered from ischemic events, and one of them recovered without neurological deficits after the administration of anti-thrombotic medication. The overall rate of morbidity was 10.6% (12 out of 113). Because of the low morbidity rate, there was no significant correlation between patients or aneurysm characteristics and morbidity.

Additionally, six patients underwent external ventricular drainage (EVD) for hydrocephalus. Due to hydrocephalus, hematoma, or severe vasospasm, craniotomy was performed in seven patients and craniotomy with EVD in three patients. Among the patients receiving EVD and/or craniotomy, seven had anterior communicating artery aneurysms, eight had posterior communicating artery aneurysms, and one had a middle cerebral artery aneurysm. Ventriculoperitoneal shunts were performed in six patients due to delayed hydrocephalus. An IVC filter was implanted in one patient due to deep venous thrombosis.

Clinical outcomes

In this series of patients, the clinical outcomes at discharge were as follows: a GOS score of 1 in three patients, a GOS score of 2 in three patients, a GOS score of 3 in 17 patients, a GOS score of 4 in 14 patients, and a GOS score of 5 in 76 patients. The mortality rate at discharge was 2.7% (3/113). There was no procedure-related mortality. Of the three patients who died before discharge, there were two patients with a Hunt-Hess grade of V and one patient with a Hunt-Hess grade of IV at admission. Favorable outcomes at discharge were observed in 79.6% (90/113) of patients. Table 1 shows the risk factors for clinical outcomes at discharge, based on univariable and multivariable logistic regression. High Hunt-Hess grade and

TABLE 1 Univariable and multivariable logistic analyses of risk factors for poor outcomes at discharge.

Factors	Univariable		Multivariable	
	OR (95%CI)	*P*	OR (95%CI)	*P*
Hunt-Hess grade	0.036 (0.010–0.131)	0.000	0.050 (0.008–0.328)	0.002
Craniotomy or EVD	0.027 (0.006–0.109)	0.000	0.050 (0.006–0.425)	0.006
Age	2.186 (0.821–5.823)	0.118	4.445 (0.820–24.094)	0.084
Hematoma	0.136 (0.048–0.389)	0.000	0.454 (0.088–2.353)	0.347
Hydrocephalus	0.110 (0.032–0.383)	0.001	0.668 (0.095–4.702)	0.685
Wide neck	0.692 (0.212–2.259)	0.542		
Packing density	0.713 (0.310–1.638)	0.425		

EVD, external ventricular drainage.

receiving craniotomy or EVD were risk factors for poor clinical outcomes at discharge.

Apart from three patients dying before discharge and 19 patients lost to follow-up, clinical follow-up was available in 91 patients at a mean interval of 14.07 ± 11.68 months (range, 3–71 months). Among them, seven patients had a GOS score of 3, six patients had a GOS score of 4, and 78 patients had a GOS score of 5. None of these patients suffered from rebleeding. Favorable outcomes were obtained in 92.3% (84/91) of patients. Factors influencing outcome in the multivariable proportional hazards model are shown in Table 2. Among the variables considered, a high Hunt-Hess grade was the only risk factor for clinical outcomes at follow-up.

Angiographic outcomes

Postoperative angiography demonstrated complete occlusion in 64 (56.1%), neck remnant in 44 (38.6%), and partial occlusion in six (5.3%) aneurysms. Daughter sac coiling was performed on two patients.

Angiographic follow-up was performed in 66 patients at an average of 11.53 ± 11.13 months (range: 3–71 months). In 41 aneurysms, the occlusion was stable or improved. Recurrence was found in 25 aneurysms (37.9%), and 13 of these (19.7%) received retreatment.

Discussion

Endovascular therapy has become the first choice of treatment for intracranial aneurysms. Despite its high success rate, the treatment of wide-necked and irregular aneurysms of the anterior cerebral circulation is still a challenge because of coil instability and a high recurrence rate (15). The improvement of devices and techniques expanded the usage of endovascular coiling techniques such as stent- or balloon-assisted coiling, the double microcatheter technique, and flow diversion (2–4, 12) for the treatment of wide-necked or irregular aneurysms. However, the adequacy of stent- or balloon-assisted coiling for ruptured aneurysms in the acute stage is still debated.

Stent-assisted coiling is commonly used in the treatment of unruptured, wide-necked aneurysms. The deployment of a stent prevents the coil from protruding into the parent artery and may thus reduce the recurrence rate (16, 17). However, the deployment of a stent in the acute stage may incur additional complications, such as in-stent thrombosis (7, 18, 19). Fan et al. (18) reported that thrombosis occurred in 15.9% of the patients after stent-assisted coiling vs. 3.8% of the patients after coiling alone for ruptured anterior communicating artery aneurysms. However, postoperative complications did not significantly differ between the two groups. In turn, the results of a meta-analysis of 10 retrospective cohort studies performed by Hong et al. (20) demonstrated comparable, non-significant differences in the all-complication rate associated with stent-assisted coiling (17.6%) and conventional coiling (15.9%). However, routine usage of antiplatelet medications before stent-assisted coil embolization may increase the rate of rebleeding, especially in patients who require EVD, craniotomy, or ventriculoperitoneal shunt (7, 21, 22). Additionally, it is difficult to navigate the stent-delivery catheter through tortuous and small vessels. There are several recent reports of the flow diversion treatment for intracranial aneurysms (23). However, with this technique, the occlusion of aneurysms may require weeks or months, and rebleeding is not excluded (24).

The balloon remodeling technique, described by Moret et al. (25), provided a novel approach for the treatment of wide-necked or irregular aneurysms. Once deployed into the aneurysm, the balloon is inflated, which temporarily blocks blood flow, protects the aneurysm neck, decreases the risk of rupture, and increases coil packing density. In addition, this approach does not require the recommendation of antiplatelet medications perioperatively. However, delayed coil migration (26), as well as bleeding and thrombosis events (9, 27), have been reported as potential complications of this technique. Sluzewski et al. (9) reported that procedure-related

TABLE 2 Multivariable proportional hazards model analysis for poor outcomes at follow-up.

Factors	Hazard ratio	(95%CI)	*P*
Age	76.489	0.465–12,592.967	0.096
Hunt-Hess grade	56.072	2.655–1,184.384	0.010
Hypertension	0.042	0.001–1.381	0.075
Hematoma	0.109	0.003–4.362	0.239
Hydrocephalus	0.642	0.024–17.008	0.791
Craniotomy or EVD	6.166	0.142–267.320	0.344

EVD, external ventricular drainage.

complications were higher for balloon-assisted coiling (14.1%) compared to coiling alone (3%). Additionally, as with stent-assisted coiling, navigation of the balloon catheter into tortuous and narrow vessels is often difficult. Therefore, the use of balloon-assisted coiling is not supported by some authors (9, 27).

Since the introduction by Baxter et al. (10) of the double microcatheter technique in 1998, several studies addressed its effectiveness in the treatment of intracranial aneurysms (11–13). The advantages of the double microcatheter technique are that there is no blockage of the blood flow or that antiplatelet medications are not recommended. The procedure is relatively simple compared with stent- or balloon-assisted coiling when it is used in wide-necked or irregular aneurysms. The tips of the two microcatheters must have different curves to reach different portions of the aneurysm and form a stable frame. However, as the advancement of the second microcatheter may cause the first one to migrate forward, care must be taken to properly adjust the tension of the first microcatheter. Durst et al. (12) reported three intraprocedural ruptures (3%) in 100 consecutive patients who underwent coil embolization of a wide-necked aneurysm using a dual microcatheter technique. In two of these cases, early identification of the rupture allowed successful coiling. In the remaining case, a rupture occurred because the microcatheter perforated the aneurysm dome, which led to bleeding, hydrocephalus, and patient death. In our cases, the first coil was usually advanced fully or partially into the aneurysm and remained attached before the advancement of the second microcatheter. Intraoperative bleeding occurred in two patients (including a patient with rebleeding during anesthesia). When rupture occurs, rebleeding may be controlled by rapid packing, neutralizing heparin, or lowering blood pressure. If these strategies did not work, we attempted to block the blood flow with a balloon or by compressing the internal carotid artery.

The double microcatheter technique can be used in a variety of aneurysms. First, it can be used in wide-necked aneurysms. To form a stable frame, two differently shaped microcatheters are navigated into different portions of aneurysms, as reported in several studies (11, 12). For wide-necked aneurysms with creeping growth, we first used the double parallel framing coils technique. Second, it can be used in aneurysms with a daughter sac. Some aneurysms have relatively large sacs, even larger than the aneurysm itself. The aneurysm and its daughter sac need to be coiled simultaneously in order to reduce the rate of rebleeding. If it is not difficult to insert, one microcatheter can be navigated into the daughter sac and the other one is navigated into the aneurysm sac. The daughter sac is usually the bleeding point. It can decrease the risk of rebleeding if the daughter sac can be packed densely. Kim et al. (28) reported one case of a fusiform aneurysm in the supraclinoid segment with a daughter sac. The patient received selective coiling of the daughter sac. Third, it can be used in branch-incorporated aneurysms. In order to protect the orifice of the branch from being occluded, one microcatheter was placed. Another microcatheter was used to coil the aneurysm. Kim et al. (28) reported this technique in 2018. Fourth, it can be used in elongated aneurysms (29). One microcatheter is navigated deeply into the aneurysm, and the other one is close to the neck. Additionally, it can be used in parent artery occlusion for ruptured vertebral artery aneurysms by bilateral vertebral artery approach. However, most vertebral artery aneurysms are dissecting ones. In this series of cases, the ruptured aneurysms in posterior cerebral circulation were excluded. The double microcatheter technique is associated with lower procedure-related complications compared to stent-assisted coiling (13). However, the recurrence rate may be higher. Procedure-related complications were reported to occur in ∼20% of ruptured aneurysm patients receiving stent-assisted coiling (22, 30). However, for ruptured aneurysms treated by double microcatheter, the corresponding data are scarce. Yoon et al. (11) reported 56 patients with acutely ruptured wide-necked intracranial aneurysms treated with the double microcatheter technique. Procedure-related complications and permanent complication rates were 12.5 and 1.8%, respectively. Recurrence and retreatment occurred in 21 patients (56.8%) and 5 patients (13.5%), respectively. Favorable outcome at discharge was recorded in 36 (64.3%) patients. In our series of patients, the procedure-related complication rate was 5.3%, whereas recurrence and retreatment rates were 37.9 and 19.7%, respectively.

Favorable outcomes were obtained in 79.6% (90/113) of study patients at discharge. High Hunt-Hess grade and receiving EVD and/or craniotomy were risk factors for clinical outcome at discharge. Some authors reported that there was no significant difference in recurrence rate among patients treated with the double microcatheter technique or with stent- or balloon-assisted coiling (13, 31). However, more recurrence cases may arise over extended follow-up. Upon recurrence, retreatment may be chosen in cases with fewer morbidities after addressing potential complications and the risk of recurrence.

To the best of our knowledge, this is one of the largest studies describing the use of the double microcatheter technique. There are still some limitations to this study. Because this is a retrospective and non-randomized study, there is inevitable

selection bias. Additionally, the number of patients was limited. Some patients were lost to follow-up because of changes in contact information. Some patients having poor outcomes were reluctant to follow up, especially with imaging follow-up such as DSA.

Conclusion

Based on our experience, we conclude that the double microcatheter technique is a safe and effective treatment modality for ruptured aneurysms located in the anterior cerebral circulation. However, recurrence remains a problem, and patients should be followed up regularly. A randomized controlled trial with a larger sample would be informative to further analyze the safety and effectiveness of the double microcatheter technique.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

ZL: conception and design of the manuscript. XZ: writing the original draft, reviewing, and editing. ZZ, JL, FQ, and LH: data acquisition, data analysis, and reviewed the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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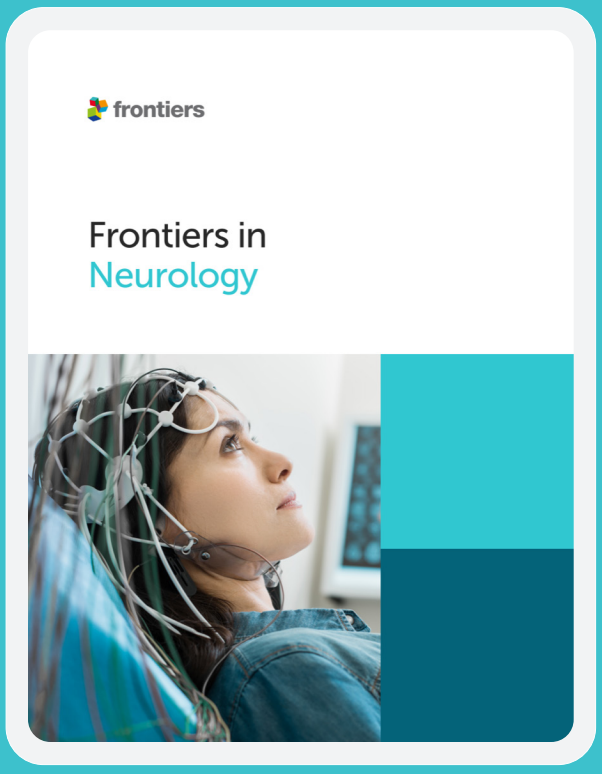

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